

Chapter 3

Structure–Activity Relationship Study of PD 404182 Derivatives for the Highly Potent Anti-HIV Agents

3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (PD 404182) (**1**, Fig. 3.1) is a promising antiviral agent because of its high therapeutic index ($CC_{50}/EC_{50} > 200$) and broad spectrum antiviral activities including against hepatitis C virus (HCV), simian immunodeficiency virus (SIV), and vesicular stomatitis virus (VSV), as well as HIV [1, 2]. In this chapter, the author describes the structure–activity relationship (SAR) studies of PD 404182 for the development of highly potent anti-HIV agents using the novel synthetic methods.

PD 404182 consists of three components, namely a 1,3-thiazin-2-imine core, and left-fused benzene and cyclic amidine moieties (Fig. 3.2). In order to obtain detailed insights into the relationships between compound structure and anti-HIV activity, the author planned to investigate substituent effects on each component: (I) derivatives with various heteroatom (N, S, and O) arrangements on the 1,3-thiazin-2-imine core; (II) pyrimido[1,2-*c*][1,3]thiazin-6-imine derivatives fused with a substituted benzene ring or a five- or six-membered aromatic heterocycle; and (III) benzo[*e*][1,3]thiazin-2-imine derivatives fused with a cyclic amidine ring with or without accessory alkyl or aryl groups.

The investigation began with the synthesis of tricyclic heterocycles with different combinations of heteroatoms on the 1,3-thiazin-2-imine core. As described in Chap. 2, the author developed synthetic methods for pyrimido[1,2-*c*][1,3]benzoxazine, pyrimido[1,2-*c*]quinazoline, and pyrimido[1,2-*c*][1,3]benzothiazine derivatives using Cu(II)-mediated C–H functionalization. This facilitates the introduction of oxygen, nitrogen, and sulfur functional groups at the *ortho*-position of 2-phenyl-1,4,5,6-tetrahydropyrimidine (**2**).

One-pot reaction for Cu(OAc)₂-mediated C–H functionalization of **2** and subsequent treatment with triphosgene provided a 1,3-oxazin-2-one derivative **4** (Scheme 3.1). The same one-pot procedure using thiophosgene produced a trace amount of the desired thiocarbonyl derivative **5**. Treatment of the purified compound **3** with thiophosgene provided the desired 1,3-oxazin-2-thione **5** in high yield. 1,3-Oxazin-2-imine **6** was obtained by the reaction of **3** with BrCN.

The Cu-mediated C–N bond formation of compound **2** with *tert*-butylcarbamate followed by spontaneous intramolecular cyclization afforded a pyrimido[1,2-*c*]quinazolin-6-one scaffold **7** (Scheme 3.1). Subsequent treatment with

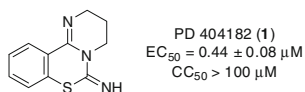


Fig. 3.1 Structure of PD 404182

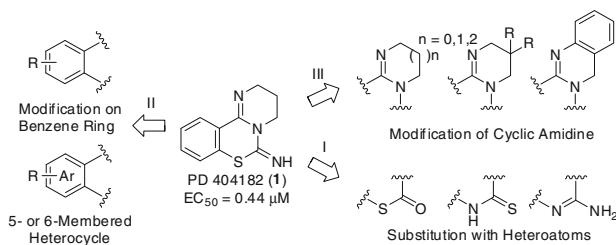
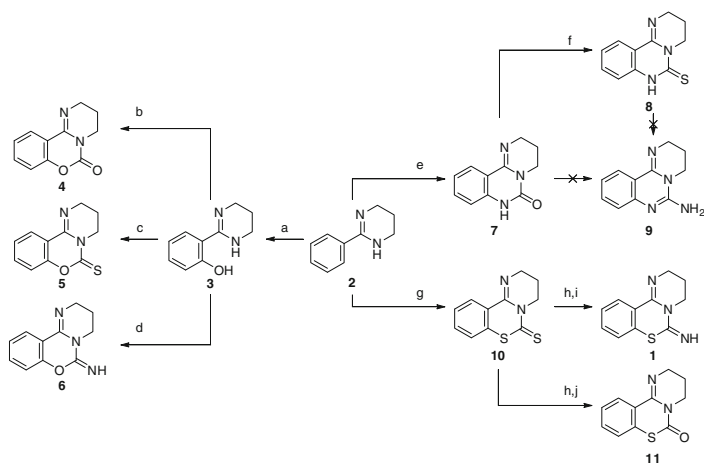
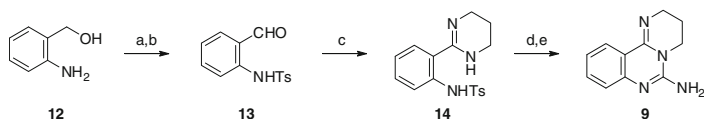


Fig. 3.2 Strategy for the SAR study of PD 404182



Scheme 3.1 Syntheses of various tricyclic heterocycles. Reagents and conditions (a) $\text{Cu}(\text{OAc})_2$, H_2O , O_2 , DMF, 130°C , 69 %; (b) triphosgene, TMEDA, CH_2Cl_2 , 0°C to rt, 70 % [2 steps (a, b)]; (c) thiophosgene, Et_3N , CH_2Cl_2 , 0°C to rt, >99 %; (d) BrCN , CH_2Cl_2 , rt, 34 %; (e) $\text{Cu}(\text{OAc})_2$, BocNH_2 , O_2 , DMF, 130°C , 53 %; (f) Lawesson's reagent, xylene, reflux, 19 %; (g) $\text{Cu}(\text{OAc})_2$, CS_2 , O_2 , 1,4-dioxane, 130°C , 11 %; (h) NaOH , MeOH , H_2O , reflux; (i) BrCN , EtOH , reflux, 61 % [2 steps (h, i)]; (j) triphosgene, Et_3N , CH_2Cl_2 , 0°C to rt, 65 % [2 steps (h, j)]



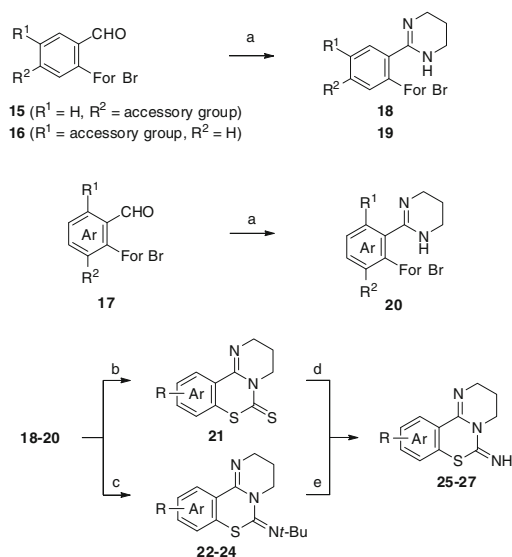
Scheme 3.2 Synthesis of 2-aminoquinazoline derivative **9**. Reagents and conditions (a) *p*-TsCl, pyridine, CHCl_3 , rt; (b) PCC, silica gel, CH_2Cl_2 , rt, 80 % [2 steps (a, b)]; (c) 1,3-propanediamine, I_2 , K_2CO_3 , *t*-BuOH, 70 °C, 98 %; (d) conc. H_2SO_4 , 100 °C, then NaOH, H_2O ; (e) BrCN, EtOH, reflux, 66 % [2 steps (d, e)]

Lawesson's reagent led to formation of the thiocarbonyl derivative **8**. Since no hydrolysis of the carbonyl or thiocarbonyl group of compound **7** or **8** for construction of the 2-aminoquinazoline structure in **9** occurred, an alternative approach starting from 2-aminobenzyl alcohol **12** was used for the synthesis the 2-aminoquinazoline derivative **9** (Scheme 3.2). After protection and PCC oxidation of **12**, oxidative amidination [3] provided 2-(*p*-tosylamino)phenyltetrahydropyrimidine (**14**). Deprotection followed by BrCN-mediated cyclization of **14** provided the expected 2-aminoquinazoline derivative **9**.

To synthesize pyrimido[1,2-*c*][1,3]benzothiazine derivatives **1** and **11** (Scheme 3.1), compound **2** was exposed to CS_2 in the presence of $\text{Cu}(\text{OAc})_2$ to directly afford a pyrimido[1,2-*c*][1,3]benzo-thiazine-6-thione scaffold **10**. Hydrolysis of the thiocarbonyl group in **10** followed by treatment with BrCN or triphosgene provided 6-imino or 6-oxo derivatives (**1** or **11**), respectively.

Pyrimido[1,2-*c*][1,3]thiazin-6-imine derivatives **25–27** with a series of fused benzene and heterocycles were prepared by consecutive heterocumulene addition and $\text{S}_\text{N}\text{Ar}$ reactions (Scheme 3.3). These reactions provide easy access to the construction of the 1,3-thiazin-2-imine derivatives more efficiently (Chap. 2.2) than the diversity-oriented C–H functionalization approach (Chap. 2.1). The oxidative amidination of aromatic aldehydes **15–17** with an accessory functional group afforded the corresponding 2-phenyltetrahydropyrimidine derivatives **18–20**. The pyrimido[1,2-*c*][1,3]thiazine-6-thione scaffold **21** was obtained by additions of **18f,g,i** or **20s,t,u** to CS_2 followed by $\text{S}_\text{N}\text{Ar}$ -type C–S bond formation. The desired 6-imino derivatives **25f,g,i** and **27s,t,u** were obtained via hydrolysis of the thiocarbonyl group of **21** followed by BrCN treatment. Alternatively, reactions of other 2-phenyltetrahydropyrimidines **18–20** with *tert*-butyl isothiocyanate afforded *N*-(*t*-Bu)-protected thiazinimine derivatives **22–24**, which were treated with TFA to provide the expected products **25–27**.

The intermediates **22e**, **22k**, and **23k** were subjected to further manipulations to obtain the functionalized derivatives (Scheme 3.4). The nitro group of **22e** was reduced by hydrogenation to form the 9-amino derivative **28**. Alkylation of **28** afforded the 9-(*N*-methylamino) derivative **22b** (eq 1). The 9-acetamide derivative **22c** was obtained by treatment of **28** with acetic anhydride (eq 2). Sandmeyer reaction of **28** gave the 9-azide derivative **22p** (eq 3). Me_2N - and MeO-substituted derivatives (**22a**, **23a**, and **23f**) were obtained by Me_2NH -mediated *N*-arylation [4, 5] of the 9-bromo **22k** and 10-bromo derivatives **23k**, and NaOMe-mediated



Scheme 3.3 Synthesis of pyrimido[1,2-*c*][1,3]thiazin-6-imine derivatives fused with substituted benzene and heterocycles (**25–27**). Reagents and conditions (a) 1,3-propanediamine, I_2 , K_2CO_3 , *t*-BuOH, 70 °C, 58–91 %; (b) NaH, CS_2 , DMF, 80 °C, 67 to >99 %; (c) NaH or *t*-BuOK, *t*-BuNCS, DMF or DMAc, rt–80 °C, 28–95 %; (d) (i) NaOH, MeOH, H_2O , reflux, (ii) BrCN, EtOH, reflux, 32–68 %; (e) TFA, MS4\AA , CHCl_3 , reflux, 63–92 %

Ullmann coupling [6] of **23k**, respectively (eq 4 and 7). The 9-acetyl derivative **22d** was obtained by Heck reaction [7] of **22k** with 2-hydroxyethyl vinyl ether (eq 5). Other derivatives with a variety of functional groups (**22**, **23**, **29**, and **30**) were synthesized by Suzuki–Miyaura coupling reactions [8, 9] of **22k** and **23k** with boronic acids or their pinacol esters (eq 6 and 7). Final deprotection of the *tert*-butyl group in **22**, **23**, **29**, and **30** afforded the 9- or 10-substituted pyrimido[1,2-*c*][1,3]benzothiazine derivatives **25**, **26**, **31**, and **32**, respectively.

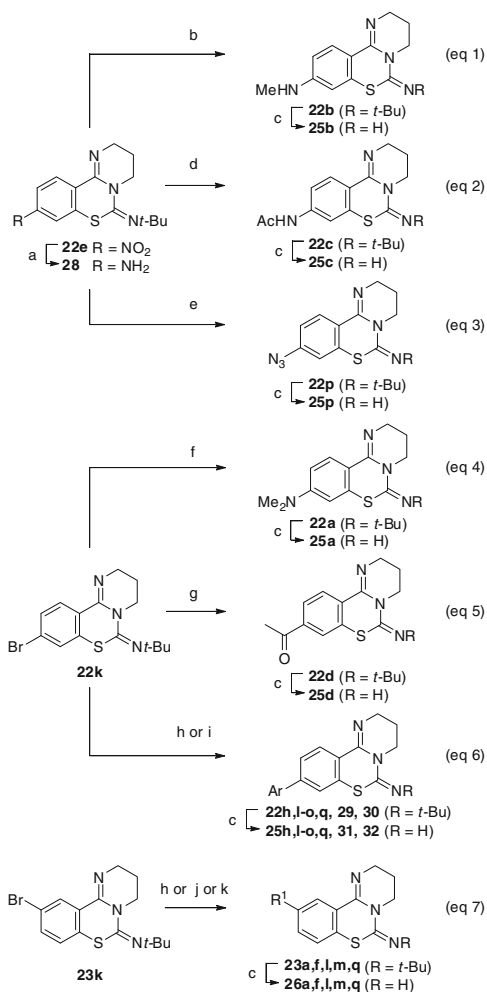
Benzo[*e*][1,3]thiazine derivatives with various ring-sized and/or modified cyclic amidine moieties **36** were synthesized using standard synthetic methods (Scheme 3.5). Oxidative addition using a number of diamines **33** proceeded efficiently to form five- or six-membered rings (**34a–d**). The same reaction for the seven-membered amidine (**34e**) was incomplete, but purification of the Boc-protected amidine **37** followed by subsequent deprotection of the Boc group gave the pure seven-membered amidine **34e**. The resulting amidines were converted to cyclic-amidine-fused benzo[*e*][1,3]thiazin-2-imines **35** via *tert*-butyl isothiocyanate addition and an $\text{S}_{\text{N}}\text{Ar}$ reaction. TFA-mediated deprotection gave the expected derivatives **36**.

The synthesis of the spiropyrimidine-fused derivatives started with the dialkylation of malononitrile with dihaloalkanes (**38**, **39**, or **41**, Scheme 3.6). BH_3 -mediated reduction of the alkylated malononitriles (**42–44**) followed by oxidative amidination with 4-bromo-2-fluorobenzaldehyde gave the 2-phenyl-1,4,5,6-tetrahydropyrimidine derivatives (**45–47**). Subsequent exposure of compounds **45–47** to *tert*-butylisothiocyanate provided the tetracyclic compounds **48**, **50**, and **52a**. Deprotection of the *tert*-butyl groups in compounds **48**, **50**, and **52a** afforded the desired spiropyrimidine-fused benzothiazinimine derivatives (**49**, **51**, and **53a**).

The substitution of the *p*-methoxybenzyl (PMB) group in compound **53a** was also attempted (Scheme 3.6). The treatment of compound **52a** with methyl chloroformate or acetyl chloride directly provided derivatives **52b** and **52c**, respectively. A two-step procedure, including the removal of the PMB group by treatment with 1-chloroethyl chloroformate followed by modification with mesyl chloride (MsCl) or trimethylsilyl isocyanate (TMSNCO) was used for the synthesis of the derivatives **52d** and **52e**, respectively, because the reaction of compound **52a** with MsCl and TMSNCO failed. Deprotection of the *tert*-butyl group in **52b–e** afforded the respective *N*-substituted derivatives **53b–e**.

SARs of the central heterocyclic core in pyrimido[1,2-*c*][1,3]benzothiazines were carried out. Initially, the structural requirements of the 1,3-thiazin-2-imine core substructure in **1** (PD 404182) for anti-HIV activity were investigated (Table 3.1). The antiviral activities against the HIV-1_{IIIB} strain were evaluated using the MAGI assay [10]. Substitution of the imino group in **1** with a carbonyl group (**11**) resulted in a significant decrease in anti-HIV activity ($\text{EC}_{50} = 8.94 \mu\text{M}$). Pyrimido[1,2-*c*][1,3]benzoxazines (**4–6**), pyrimido[1,2-*c*]quinazolines (**7–9**), and pyrimido[1,2-*c*] [1,3]benzothiazine-6-thione (**10**), in which the 1-sulfur and/or 2-imino groups in **1** were modified, showed no activity. These results suggested that both the 1-sulfur atom and the 2-imino group are indispensable functional groups for the inhibitory activity against HIV infection, and may be involved in potential interactions with the target molecules.

A series of derivatives with modification of the benzene substructure in the pyrimido[1,2-*c*][1,3]benzothiazine were evaluated for anti-HIV activity (Table 3.2). The addition of positively charged *N,N*-dimethylamino (**25a**) and *N*-methylamino groups (**25b**) at the 9-position significantly decreased the anti-HIV activity. The 9-acetamide group (**25c**), which has hydrogen bond donor/acceptor abilities, also attenuated the bioactivity. The acetyl (**25d**) and nitro (**25e**) groups, with hydrogen acceptor properties, induced slight decreases in the anti-HIV activity. In contrast, derivatives with less-polarized substituents (**25f–o** and **25q**) at this position generally reproduced the potent anti-HIV activity of **1**. In terms of the electron-donating or -withdrawing properties of the substituent groups on the benzene substructure, good correlations were not observed. For example, the electron-donating methoxy (**25f**), methyl (**25g**), and *n*-butyl groups (**25h**), and the electron-withdrawing fluoro (**25i**) and trifluoromethyl groups (**25j**) exhibited similar anti-HIV activities ($\text{EC}_{50} = 0.44\text{--}0.57 \mu\text{M}$), indicating that the antiviral activity is independent of the electronic state of the 1,3-benzothiazin-2-imine core in forming potential π -stacking interaction(s) with the target molecules. Among

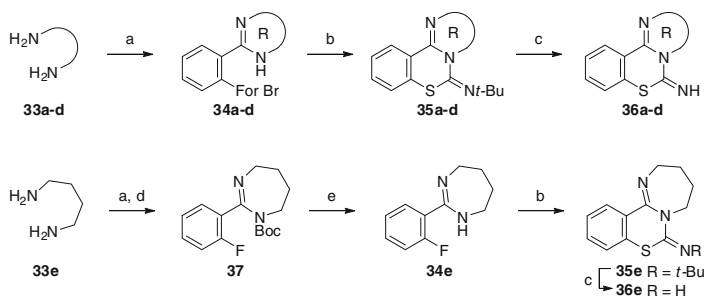


Scheme 3.4 Synthesis of 9- or 10-substituted pyrimido[1,2-*c*][1,3]benzothiazin-6-imine derivatives. Reagents and conditions (a) H_2 , 10 % Pd/C, EtOH, rt, 88 %; (b) NaOMe, $(\text{CH}_2\text{O})_n$, MeOH, reflux, then NaBH_4 , 91 %; (c) TFA, MS4Å, CHCl_3 , reflux, 37–95 %; (d) Ac_2O , DMAP, Et_3N , CH_2Cl_2 , rt, >99 %; (e) NaNO_2 , AcOH, H_2O , 0 °C, then NaN_3 , 70 %; (f) $\text{Pd}(\text{OAc})_2$, *t*- Bu_3P , NHMe₂, THF, KO*t*-Bu, toluene, reflux, >99 %; (g) 2-hydroxyethylvinylether, $\text{Pd}(\text{OAc})_2$, 1,3-bis(diphenylphosphino)propane, K_2CO_3 , H_2O , 90 °C, 13 % [2 steps (g, c)]; (h) R-B(OH)₂ or R-Bpin, $\text{Pd}(\text{PPh}_3)_4$, $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$, K_2CO_3 , toluene or 1,4-dioxane, EtOH, H_2O , reflux, 62–96 %; (i) *n*-BuB(OH)₂, $\text{Pd}_2(\text{dba})_3$, P(*t*-Bu)₃, CsCO_3 , 1,4-dioxane, reflux, 6 % (for **22h**); (j) $\text{Pd}(\text{Pr-Bu}_3)_2$, NHMe₂, THF, KO*t*-Bu, toluene, 170 °C, 67 % (for **23a**); (k) CuBr, NaOMe, MeOH, DMF, reflux, 40 % (for **23f**)

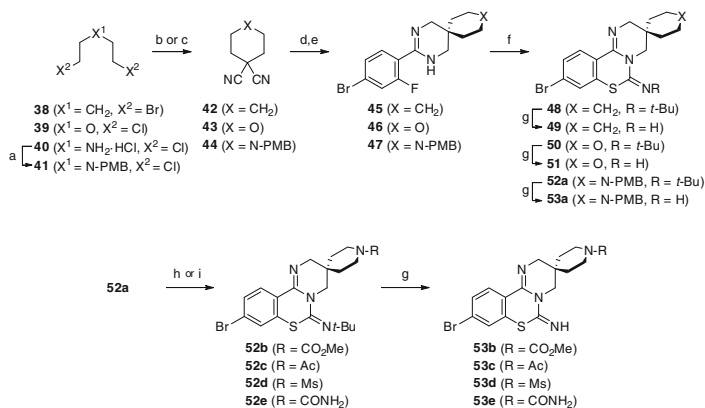
the hydrophobic substituents at this position, bromo (**25k**), phenyl (**25l**), vinyl (**25m**), styryl (**25n**), and pentenyl groups (**25o**) induced inhibitory activity two or three times greater than that of **1** ($EC_{50} = 0.18\text{--}0.25\ \mu\text{M}$). Modification with photoreactive azido (**25p**) and benzoylphenyl groups (**25q**) maintained the inhibitory activity; these could be used as probe molecules to identify the target molecule(s) of **1** [11–13].

Similar SARs were observed for modification at the 10-position of pyrimido[1,2-*c*] [1,3]benzothiazine. Addition of positively charged *N,N*-dimethylamino (**26a**) and polarized nitro groups (**26e**) reduced the anti-HIV activity ($EC_{50} = 2.12$ and $3.00\ \mu\text{M}$, respectively). Hydrophobic groups including methoxy (**26f**), methyl (**26g**), bromo (**26k**), phenyl (**26l**), vinyl (**26m**), and 4-benzoylphenyl (**26q**) had favorable effects on the bioactivity ($EC_{50} = 0.24\text{--}0.67\ \mu\text{M}$), suggesting potential hydrophobic interactions of these additional functional groups with the target molecule(s).

Further miscellaneous modifications of benzothiazine substructure were also investigated (Table 3.2). The naphtho[2,3-*e*][1,3]thiazine derivative **27r**, with a 9,10-fused benzene, exhibited anti-HIV activity equipotent to that of the parent **1** ($EC_{50} = 0.56\ \mu\text{M}$). A 6-fold decrease in the anti-HIV activity of the pyridine-fused pyrido[3,2-*e*][1,3]thiazine derivative (**27s**) was observed ($EC_{50} = 2.55\ \mu\text{M}$). In addition, introduction of 8-bromo (**27k**) and 8,9-fused benzene (**27t**, naphtho[2,1-*e*][1,3]thiazine) substituents on benzothiazine resulted in a loss of activity, suggesting that modification at the 8-position was inappropriate for favorable interactions with the target molecule(s). The 11-fluoro derivative **27i** and thio-phene-fused **27u**, the latter of which has 5-6-6 framework (thieno[2,3-*e*][1,3]thiazine), exhibited four times lower and no inhibitory potencies, respectively.



Scheme 3.5 Synthesis of benzo[*e*][1,3]thiazine derivatives with fused cyclic amidines. Reagents and conditions (a) 2-fluorobenzaldehyde or 2-bromobenzaldehyde, I_2 , K_2CO_3 , *t*-BuOH, $70\ ^\circ\text{C}$, 68–79 %; (b) NaH, *t*-BuNCS, DMF, rt – $80\ ^\circ\text{C}$, 18–50 %; (c) TFA, MS4Å, $CHCl_3$, reflux, 16–86 %; (d) Boc_2O , Et_3N , DMAP, CH_2Cl_2 , rt, 37 % [2 steps (a, d)]; (e) TFA, $CHCl_3$, reflux, 80 %



Scheme 3.6 Synthesis of spiropyrimidine-fused benzothiazinimine derivatives. Reagents and conditions (a) (i) 4-methoxybenzoyl chloride, Et_3N , CH_2Cl_2 , rt; (ii) LiAlH_4 , Et_2O , rt, 75 % (2 steps); (b) malononitrile, DBU, DMF, 50 °C, 8–60 % (for **42** and **43**); (c) malononitrile, K_2CO_3 , DMF, 65 °C, 85 % (for **44**); (d) BH_3 , THF, 0 °C to rt; (e) 4-bromo-2-fluorobenzaldehyde, I_2 , K_2CO_3 , $t\text{-BuOH}$, 70 °C, 11–62 % [2 steps (d,e)]; (f) NaH , $t\text{-BuNCS}$ DMF, rt –80 °C, 78–94 %; (g) TFA, $\text{MS4}\text{\AA}$, CHCl_3 , reflux, 65–94 %. (h) ClCO_2Me or AcCl , CH_2Cl_2 , 0 °C, 81–96 % (for **52b** or **52c**); (i) (i) 1-chloroethyl chloroformate, Et_3N , CH_2Cl_2 , 0 °C, then MeOH , reflux, (ii) MsCl or TMSNCO , (Et_3N), CH_2Cl_2 , rt, 29–82 % (2 steps, for **52d** or **52e**)

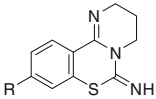
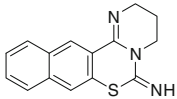
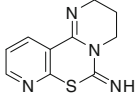
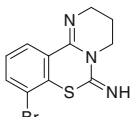
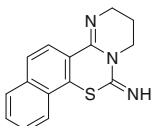
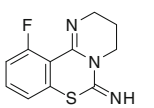
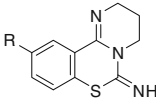
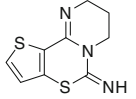
Table 3.1 SARs for 1,3-thiazin-2-imine core

Compound	X	Y	EC_{50} (μM) ^a
1	S	NH	0.44 ± 0.08
4	O	O	>10
5	O	S	>10
6	O	NH	>10
7	NH	O	>10
8	NH	S	>10
9	NH	NH	>10
10	S	S	>10
11	S	O	8.94 ± 1.07

^a EC_{50} values represent the concentration of compound required to inhibit the HIV-1 infection by 50 % and were obtained from three independent experiments

On the basis of the above SAR data for the benzene substructure in **1** (PD 404182), the author expected that introduction of a hydrophobic group at the pyrimido[1,2-*c*][1,3]benzothiazine 9-position would be the most promising. The next optimization to obtain more potent derivatives was therefore focused on

Table 3.2 SARs for benzene part

Compound	EC ₅₀ (μM) ^a	Compound	EC ₅₀ (μM) ^a
		27r	0.56 ± 0.13
1	R = H	0.44 ± 0.08	
25a	R = NMe ₂	4.74 ± 1.07	27s
25b	R = NHMe	>10	
25c	R = NHAc	>10	
25d	R = COMe	1.44 ± 0.33	27k
25e	R = NO ₂	1.13 ± 0.18	>10
25f	R = OMe	0.57 ± 0.09	
25g	R = Me	0.49 ± 0.10	
25h	R = n-butyl	0.44 ± 0.09	27t
25i	R = F	0.50 ± 0.07	>10
25j	R = CF ₃	0.53 ± 0.12	
25k	R = Br	0.25 ± 0.09	
25l	R = Ph	0.24 ± 0.04	27i
25m	R = vinyl	0.18 ± 0.05	>10
25n	R = styryl	0.25 ± 0.05	
25o	R = pentenyl	0.24 ± 0.11	
25p	R = N ₃	0.43 ± 0.06	27u
25q	R = C ₆ H ₄ (4-Bz)	0.53 ± 0.12	>10
		27i	1.68 ± 0.19
26a	R = NMe ₂	2.12 ± 0.26	
26e	R = NO ₂	3.00 ± 0.59	
26f	R = OMe	0.53 ± 0.04	
26g	R = Me	0.38 ± 0.04	
26k	R = Br	0.24 ± 0.05	
26l	R = Ph	0.24 ± 0.05	
26m	R = vinyl	0.40 ± 0.09	
26q	R = C ₆ H ₄ (4-Bz)	0.67 ± 0.16	

^a EC₅₀ values represent the concentration of compound required to inhibit the HIV-1 infection by 50 % and were obtained from three independent experiments

modification of the benzothiazine scaffold at position 9 with an additional aryl group (Tables 3.3, 3.4).

The author initially examined substituent effects at the *para*-position on the 9-phenyl group of compound **25l**. Modification with methoxycarbonyl (**31a**), cyano (**31b**), nitro (**31c**), and trifluoromethyl (**31d**) groups slightly reduced the anti-HIV activity (EC₅₀ = 0.44–0.81 μM), whereas a significant decrease in the anti-HIV activity was observed for a carbamoyl group (**31e**), with hydrogen bond donor/acceptor properties (EC₅₀ = 8.71 μM). The hydrophobic methoxy (**31f**,

Table 3.3 SARs for biphenyl-type derivatives

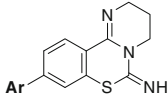
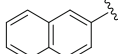

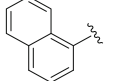

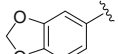

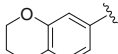
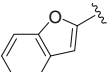
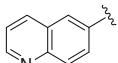

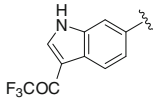
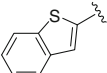
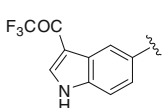


Compound	Ar	EC ₅₀ (μM) ^a	Compound	Ar	EC ₅₀ (μM) ^a
25l	R = H	0.24 ± 0.04	31s	R = OMe	0.41 ± 0.10
31a	R = CO ₂ Me	0.81 ± 0.29	31t	R = Ph	0.32 ± 0.12
31b	R = CN	0.44 ± 0.10	31u		0.27 ± 0.04
31c	R = NO ₂	0.46 ± 0.06			
31d	R = CF ₃	0.55 ± 0.16			
31e	R = CONH ₂	8.71 ± 0.82			
31f	R = OMe	0.24 ± 0.04	31v		0.25 ± 0.03
31g	R = SMe	0.20 ± 0.06			
31h	R = OCF ₃	0.38 ± 0.06	31w		0.32 ± 0.04
31i	R = CO ₂ Me	0.39 ± 0.09			
31j	R = CN	1.17 ± 0.27			
31k	R = NO ₂	1.26 ± 0.13			
31l	R = CH(OH)CH ₃	1.19 ± 0.19			
31m	R = NHAc	>10			0.48 ± 0.06
31n	R = NHMs	>10			
31o	R = OH	2.62 ± 0.26			
31p	R = OMe	0.15 ± 0.05			
31q	R = Oi-Pr	0.32 ± 0.10			
31r	R = Ph	1.35 ± 0.26			

^a EC₅₀ values represent the concentration of compound required to inhibit the HIV-1 infection by 50 % and were obtained from three independent experiments

EC₅₀ = 0.24 μM), methylthio (**31g**, EC₅₀ = 0.20 μM), and trifluoromethoxy (**31h**, EC₅₀ = 0.38 μM) groups had favorable effects on the anti-HIV activity.

Similar effects as a result of modification at the *meta*-position of the 9-phenyl group were observed. Addition of electron-withdrawing methoxycarbonyl (**31i**), cyano (**31j**), and nitro (**31k**) (EC₅₀ = 0.39–1.26 μM) groups resulted in slight decreases in anti-HIV activity. Hydrophilic (1-hydroxy)ethyl (**31l**, EC₅₀ = 1.19 μM), acetylamino (**31m**), mesylamino (**31n**), and hydroxyl (**31o**, EC₅₀ = 2.62 μM) groups induced reduction or loss of anti-HIV activity. In contrast, a methoxy group (**31p**) improved the inhibitory activity (EC₅₀ = 0.15 μM). The more hydrophobic isopropoxy group (**31q**) maintained the anti-HIV activity of 25l (EC₅₀ = 0.32 μM), whereas a phenyl group (**31r**) decreased the inhibitory activity (EC₅₀ = 1.35 μM).

Table 3.4 SARs for biaryl-type derivatives

					
Compound	Ar	EC ₅₀ (μM) ^a	Compound	Ar	EC ₅₀ (μM) ^a
32a		0.20 ± 0.06	32h		0.45 ± 0.07
32b		0.39 ± 0.12	32i		0.54 ± 0.04
32c		0.15 ± 0.03	32j		0.26 ± 0.02
32d		0.26 ± 0.07	32k		0.20 ± 0.03
32e		0.25 ± 0.04	32l		0.22 ± 0.07
32f		>1.00 ^b	32m		0.26 ± 0.06
32g		>1.00 ^b	32n		0.42 ± 0.08
			32o		5.12 ± 1.28

^a EC₅₀ values represent the concentration of compound required to inhibit the HIV-1 infection by 50 % and were obtained from three independent experiments

^b Cytotoxicity was observed at 10 μM

Similar anti-HIV activities of the *ortho*-methoxy (**31s**) and *ortho*-phenyl group (**31t**) to that of **25l** were exhibited (EC₅₀ = 0.41 and 0.32 μM, respectively), suggesting that the twisted conformations of these 9-phenyl PD 404182 derivatives might not prevent the interaction with the target molecule(s).

In order to develop more potent anti-HIV agents, the author subsequently attempted bis and tris modifications of the 9-phenyl group in **25l**. Modification with 9-(3,4-dimethoxy)phenyl (**31u**, EC₅₀ = 0.27 μM) or 9-(3,4,5-trimethoxy)phenyl (**31v**, EC₅₀ = 0.25 μM) groups of the pyrimido[1,2-*c*][1,3]benzothiazine scaffold did not alter the bioactivity. Cl-modified derivatives **31w** and **31x** exhibited similar potencies (EC₅₀ = 0.32 and 0.48 μM, respectively).

Since the 9-(2-naphthyl)-modified analog (**32a**) exhibited slightly more potent anti-HIV activity (EC₅₀ = 0.20 μM) compared with that of the 1-naphthyl congener (**32b**, EC₅₀ = 0.39 μM, Table 3.4), the author further investigated modifications with a variety of 3,4-fused phenyl groups. Compound **32c** with a

1,3-dioxolane-fused phenyl group displayed activity twice as potent as that of compound **25i** ($EC_{50} = 0.15 \mu\text{M}$), whereas the 1,4-dioxane-fused derivative **32d** and quinolin-6-yl derivative **32e** exhibited less favorable effects ($EC_{50} = 0.26$ and $0.25 \mu\text{M}$, respectively). Introduction of an indolyl group (**32f** and **32g**) resulted in no anti-HIV activity and unexpected cytotoxicity.

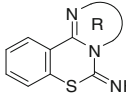
Substitutions of the 9-phenyl group by various heterocyclic substructures were also investigated. Six-membered heterocycles such as pyridine (**32h** and **32i**) slightly reduced the anti-HIV activity ($EC_{50} = 0.45$ and $0.54 \mu\text{M}$, respectively). The five-membered furan (**32j**), benzofuran (**32k**), thiophene (**32l**), benzothio-*phene* (**32m**), and pyrazole (**32n**) derivatives maintained the original activity of **25i** ($EC_{50} = 0.20$ – $0.42 \mu\text{M}$). Notably, reduced anti-HIV activity was observed for the basic imidazole derivative (**32o**, $EC_{50} = 5.12 \mu\text{M}$).

A SAR study of the top-right cyclic amidine substructure was carried out. The five-membered dihydroimidazole derivative **36a** had no anti-HIV activity (Table 3.5), suggesting that the five-membered ring may impair the critical interactions with the target molecule(s) via its small-sized ring strain or indirect effects on the thiazinimine core with a possibly altered conformation. Similarly, compound **36b** with the phenyl-fused dihydropyrimidine substructure showed lower inhibitory activity ($EC_{50} = 3.78 \mu\text{M}$). Appending one or two methyl groups on the six-membered pyrimidine (**36c** and **36d**) induced 1.5- to 2-fold higher inhibitory potencies ($EC_{50} = 0.35$ and $0.24 \mu\text{M}$, respectively) compared with that of the parent compound **1**. In addition, compound **36e** with a seven-membered tetrahydro-1,3-diazepine substructure exhibited similar anti-HIV activity to that of **1** ($EC_{50} = 0.31 \mu\text{M}$).

Above optimization studies indicated that the introduction of a hydrophobic group on the cyclic amidine substructures effectively improved the antiviral activity (compound **36c–e**) by generating a potentially favorable interaction(s) with the target molecule(s). Therefore, anti-HIV activities of several spiro-pyrimidine fused derivatives were evaluated (Table 3.6).¹ Cyclohexane (**49**) and *N*-methoxycarbonylpiperidine (**53b**) derivatives exhibited the similar levels of anti-HIV activity ($EC_{50} = 0.25$ and $0.44 \mu\text{M}$, respectively) to that of the dimethyl derivative **36d** ($EC_{50} = 0.24 \mu\text{M}$). In contrast, the tetrahydropyran (**51**) and *N*-(*p*-methoxybenzyl)piperidine (**53a**) derivatives exerted inhibitory activities that were 5–7-fold lower ($EC_{50} = 1.73$ and $1.45 \mu\text{M}$, respectively) than that of the parent dimethyl derivative **36d**. The *N*-acetyl- (**53c**), *N*-methanesulfonyl- (**53d**), and *N*-carbamoyl- (**53e**) piperidine derivatives also provided reduced levels of antiviral activity ($EC_{50} = 1.81$ to $>10 \mu\text{M}$). With this in mind, the *N*-alkoxycarbonyl piperidine group was identified as a linkage for the introduction of additional functional group(s) to PD 404182 with potent anti-HIV activity (**53b**).

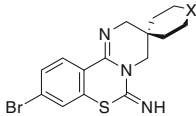
To investigate the mechanism of action of PD 404182 derivatives, a time of drug addition study was carried out (Fig. 3.3). In this experiment, the anti-HIV

¹ Because a 9-brominated derivative **25k** exhibited more potent anti-HIV activity than compound **1** in the SAR study, the author employed compound **25k** as a lead.

Table 3.5 SARs for cyclic amidine core


Compound	EC ₅₀ (μM) ^a	Compound	EC ₅₀ (μM) ^a
1	0.44 ± 0.08	36c	0.35 ± 0.09
36a	>10	36d	0.24 ± 0.04
36b	3.78 ± 1.39	36e	0.31 ± 0.06

^a EC₅₀ values represent the concentration of compound required to inhibit the HIV-1 infection by 50 % and were obtained from three independent experiments

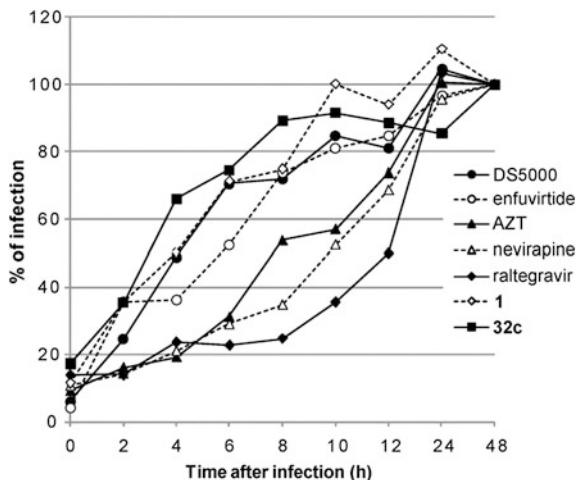
Table 3.6 SARs for spiroimidine-fused derivatives


Compound	X	EC ₅₀ (μM) ^a
49	CH ₂	0.25 ± 0.01
51	O	1.73 ± 0.35
53a	N-PMB	1.45 ± 0.05
53b	N-CO ₂ Me	0.44 ± 0.02
53c	N-Ac	2.74 ± 0.15
53d	N-Ms	1.81 ± 0.43
53e	N-CONH ₂	>10

^a EC₅₀ values represent the concentration of compound required to inhibit the HIV-1 infection by 50 % and were obtained from three independent experiments

activity profiles of **1** and its derivatives **32c** were compared with those of well-known anti-HIV agents such as an adsorption inhibitor (DS 5000) [14], fusion inhibitor (enfuvirtide) [15–17], NRTI (AZT) [18], NNRTI (nevirapine) [19], and integrase inhibitor (raltegravir) [20]. After inoculation of HeLa-CD4/CCR5-LTR/ β -gal cells with HIV-1_{IIIB}, each anti-HIV-1 drug was added at a 90 % inhibitory effect concentration at the indicated time points. The inhibitory effects on the infection were determined by counting the blue cells 48 h later. This investigation revealed that compound **1** (PD 404182) had an inhibitory profile in the early stage

Fig. 3.3 Time of drug addition profiles in the presence of Anti-HIV agents for infection of a HIV-1_{IIB} strain of HeLa-CD4/CCR5-LTR/ β -gal cells



of viral infection similar to those of DS 5000 and enfuvirtide (Fig. 3.3). Identical profiles were observed for **1** and the most potent derivative **32c**, indicating that the bioactivity profile is independent of the appended functional group(s).

To gain additional insights into the mechanism of action of PD 404182 derivatives, the antiviral activities against other HIV subtypes were evaluated (Table 3.7). Compound **1** was effective against not only HIV-1_{IIB} but also other two HIV-1 strains (HIV-1_{NL4-3} and HIV-1_{BaL}) with similar potency. Both HIV-1_{IIB} and HIV-1_{NL4-3} strains utilize CXCR4 as a coreceptor for entry, while HIV-1_{BaL} strain does CCR5, indicating that chemokine receptors CXCR4 and CCR5 are not the molecular targets of PD 404182 derivatives. The similar level of antiviral activity of **1** against HIV-2 (HIV-2_{EHO} and HIV-2_{ROD}), which is mainly distributed in West Africa, was observed. Highly potent inhibitory activities of derivatives **32c** and **36d**² against these HIV strains were observed, as in the case of the SAR study of the HIV-1_{IIB} strain discussed above. It has been well-known that NNRTIs are not effective against HIV-2, highlighting that PD 404182 derivatives do not act as NNRTIs. Although PD 404182 derivatives and enfuvirtide showed similar anti-HIV-1 profile in the time of drug addition assay, HIV-2_{EHO} and HIV-2_{ROD} infection were affected by PD 404182 derivatives, in contrast with the less effective enfuvirtide [21], suggesting that PD 404182 derivatives may not be directed at the HIV gp41 envelope protein. Recent reports have suggested that the antiviral activities of compound **1** against HIV, HCV, and pseudotype lentiviruses were derived from disruption of the structural integrities of virions [2]. Although the mechanism of action of PD 404182 derivatives is not fully understood at this

² The cytotoxicity of compounds **1**, **32c** and **36d** was not observed at 10 μ M in the MAGI assay. Further toxicity studies such as hemolytic activity or renal/liver accumulation may be needed to take a drug for long periods of time.

Table 3.7 Anti-HIV activity of compounds **1**, **32c**, and **36d** against other HIV strains

Strains	EC ₅₀ (μM) ^a		
	1	32c	36d
HIV-1 _{NL4-3}	0.38 ± 0.06	0.25 ± 0.03	0.23 ± 0.09
HIV-1 _{BaL}	0.37 ± 0.06	0.16 ± 0.02	0.13 ± 0.05
HIV-2 _{EHO}	0.31 ± 0.06	0.17 ± 0.03	0.14 ± 0.02
HIV-2 _{ROD}	0.30 ± 0.06	0.11 ± 0.03	0.10 ± 0.04

^a EC₅₀ values represent the concentration of compound required to inhibit the HIV-1 infection by 50 % and were obtained from three independent experiments

stage, the unidentified biomolecule(s) in viruses or host cells could be promising molecular targets for this new class of anti-HIV agents.

In conclusion, the author have designed and synthesized PD 404182 derivatives for a novel series of anti-HIV agents. Comprehensive SAR studies demonstrated that the 6-6-6 fused pyrimido[1,2-*c*][1,3]benzothiazine scaffold and the heteroatom arrangement in the thiazinimine moiety are indispensable for the inhibitory activity of **1** (PD 404182) against HIV infection. Optimization studies of the benzene and cyclic amidine rings indicate that the introduction of a hydrophobic group on the benzene ring is more effective in improving the antiviral activity, giving potential favorable interaction(s) with the target molecule(s). The most potent compound, **32c**, had anti-HIV activity three times higher than that of the parent **1**. In addition, PD 404182 derivatives could be promising agents for treatment of HIV-2 infection. The author also revealed, using a time of drug addition experiment, that PD 404182 derivatives prevent the HIV infection process at a fusion or binding process.

3.1 Experimental Section

3.1.1 General Methods

All moisture-sensitive reactions were performed using syringe-septum cap techniques under an Ar atmosphere and all glasswares were dried in an oven at 80 °C for 2 h prior to use. Melting points were measured by a hot stage melting point apparatus (uncorrected). For flash chromatography, Wakogel C-300E (Wako) or aluminum oxide 90 standardized (Merck) was employed. For preparative TLC, TLC silica gel 60 F254 (Merck) or TLC aluminum oxide 60 F254 basic (Merck), or NH₂ Silica Gel 60 F254 Plate (Wako) were employed. For analytical HPLC, a COSMOSIL 5C18-ARII column (4.6 × 250 mm, Nacalai Tesque, Inc., Kyoto, Japan) was employed with method A [a linear gradient of CH₃CN containing 0.1 % (v/v) TFA] or method B [a linear gradient of CH₃CN containing 0.1 % (v/v) NH₃] at a flow rate of 1 mL/min on a Shimadzu LC-10ADvp (Shimadzu Corp., Ltd., Kyoto, Japan), and eluting products were detected by UV at 254 nm.

Preparative HPLC was performed using a COSMOSIL 5C18-ARII column (20 × 250 mm, Nacalai Tesque Inc.) with a linear gradient of MeCN containing 0.1 % (v/v) NH₃ at a flow rate of 8 mL/min on Shimadzu LC-6AD (Shimadzu corporation, Ltd). ¹H-NMR spectra were recorded using a JEOL AL-400 or a JEOL ECA-500 spectrometer, and chemical shifts are reported in δ (ppm) relative to Me₄Si (CDCl₃) or DMSO (DMSO-*d*₆) as internal standards. ¹³C-NMR spectra were recorded using a JEOL AL-400 or JEOL ECA-500 spectrometer and referenced to the residual solvent signal. ¹⁹F-NMR spectra were recorded using a JEOL ECA-500 and referenced to the internal CFCl₃ (δ_F 0.00 ppm). ¹H-NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s), and number of protons. Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 FT-IR spectrometer with JASCO ATR PRO410-S. The purity of the compounds was determined by combustion analysis or HPLC analysis as >95 % unless otherwise stated. Synthesis and characterization data of compounds **2**, **4**, **7**, and **10** are shown in Chap. 2. Synthesis and characterization data of compounds **1**, **18e-g**, **18i**, **19e**, **20s**, **20t**, **21f**, **21g**, **21i**, **21s**, **21t**, **34a** and **35a** are shown in Chap. 2.

3.1.2 Synthesis of 3,4-Dihydro-2H,6H-pyrimido [1,2-*c*][1,3]benzoxazine-6-thione (**5**)

2-(2-Hydroxyphenyl)tetrahydropyrimidine (3). DMF (0.83 mL) and water (4.5 μ L, 0.25 mmol) were added to a flask 2-phenyl-1,4,5,6-tetrahydropyrimidine **2** (40.1 mg, 0.25 mmol) and Cu(OAc)₂ (45.4 mg, 0.25 mmol) under an O₂ atmosphere. After being stirred at 130 °C for 20 min, mixture was concentrated. The residue was purified by flash chromatography over aluminum oxide with CHCl₃–MeOH (95:5) to give the title compound **3** as brown solid (30.3 mg, 69 %): IR (neat) cm⁻¹: 3257–3041 (OH), 1613 (C=N); ¹H-NMR (500 MHz, DMSO-*d*₆) δ : 1.84–1.88 (2H, m, CH₂), 3.40 (4H, t, *J* = 5.7 Hz, 2 × CH₂), 6.27–6.30 (1H, m, Ar), 6.47 (1H, d, *J* = 8.6 Hz, Ar), 7.04–7.08 (1H, m, Ar), 7.45 (1H, dd, *J* = 8.0, 1.7 Hz, Ar), 12.09 (1H, br s); ¹³C-NMR (125 MHz, CD₃OD) δ : 20.0, 39.3 (2C), 111.2, 114.5, 124.4, 126.3, 135.1, 161.0, 172.4; MS (FAB) *m/z* (%): 177 (MH⁺, 100).

Compound 5. To a suspension of **3** (33.0 mg, 0.19 mmol) and Et₃N (0.068 mL, 0.47 mmol) in CH₂Cl₂ (10.0 mL) was added dropwise a solution of thiophosgene (0.016 mL, 0.21 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C. After being stirred at rt for 1 h, the mixture was quenched with sat. NaHCO₃. The whole was extracted with EtOAc. The extract was washed with sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to give the title compound **5** as yellow solid (41.9 mg, >99 %): mp 135–136 °C (from CHCl₃–*n*-hexane); IR

(neat) cm^{-1} : 1655 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 2.03–2.08 (2H, m, CH_2), 3.68 (2H, t, $J = 5.5$ Hz, CH_2), 4.30 (2H, t, $J = 6.1$ Hz, CH_2), 7.21 (1H, d, $J = 8.5$ Hz, Ar), 7.25–7.29 (1H, m, Ar), 7.50–7.52 (1H, m, Ar), 8.00 (1H, d, $J = 7.8$ Hz, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.1, 44.5, 49.2, 115.9, 116.9, 125.4, 125.7, 133.0, 139.7, 150.9, 180.8; *Anal.* calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{OS}$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.23; H, 4.72; N, 12.62.

3.1.3 Synthesis of 3,4-Dihydro-2H,6H-pyrimido [1,2-*c*][1,3]benzoxazin-6-imine (6)

2-(2-Hydroxyphenyl)tetrahydropyrimidine **3** (5.4 mg, 0.03 mmol) was suspended with CH_2Cl_2 (0.3 mL) and added the solution of BrCN (3.3 mg, 0.06 mmol) in CH_2Cl_2 (0.3 mL). After being stirred for 1 h at rt, the additional portion of BrCN (3.3 mg, 0.06 mmol) in CH_2Cl_2 (0.3 mL) was added. After being stirred for 1 h at rt, the mixture was concentrated. The residue was purified by preparative TLC over NH_2 silica gel with *n*-hexane–EtOAc (1:1) to give the title compound **6** as colorless solid (2.1 mg, 34 %): mp 104–105 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1639 (C=N), 1611 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.98–2.03 (2H, m, CH_2), 3.64 (2H, t, $J = 5.4$ Hz, CH_2), 3.93 (2H, t, $J = 6.0$ Hz, CH_2), 5.83 (1H, br s, NH), 6.99 (1H, d, $J = 8.0$ Hz, Ar), 7.15 (1H, t, $J = 8.0$ Hz, Ar), 7.42 (1H, td, $J = 8.0, 1.7$ Hz, Ar), 7.99 (1H, dd, $J = 8.0, 1.7$ Hz, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 20.6, 43.4, 44.1, 115.2, 116.2, 123.9, 125.5, 132.3, 142.5, 150.4, 150.7; *Anal.* calcd for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.55; H, 5.40; N, 20.70.

3.1.4 Synthesis of 3,4-Dihydro-2H,6H-pyrimido [1,2-*c*]quinazolin-6(7H)-thione (8)

Xylene (4.0 mL) was added to a flask containing 3,4-dihydro-2H,6H-pyrimido[1,2-*c*]quinazolin-6(7H)-one **7** (50.3 mg, 0.25 mmol) and Lawesson's reagent (202.2 mg, 0.50 mmol). After being stirred under reflux for 24 h, xylene (2 mL) and additional amount of Lawesson's reagent (101.1 mg, 0.25 mmol) were added. After being stirred under reflux for additional 12 h, the mixture was cooled to rt. The residue was dissolved in CHCl_3 and washed with sat. NaHCO_3 and brine and dried over MgSO_4 . After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) to give the title compound **8** as colorless solid (10.4 mg, 19 %): mp 258–259 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1618 (C=N); $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$) δ : 1.85–1.90 (2H, m, CH_2), 3.52 (2H, t, $J = 5.4$ Hz, CH_2), 4.19 (2H, t, $J = 6.0$ Hz, CH_2), 7.12–7.19 (2H, m, Ar), 7.46 (1H, t, $J = 7.7$ Hz, Ar), 7.92 (1H, d, $J = 6.9$ Hz, Ar), 12.00 (1H,

s, NH); ^{13}C -NMR (100 MHz, DMSO- d_6) δ : 20.6, 44.0, 46.7, 114.8, 117.6, 123.8, 125.1, 132.1, 135.9, 142.1, 174.0; HRMS (FAB): m/z calcd for $\text{C}_{11}\text{H}_{12}\text{N}_3\text{S}$ $[\text{M} + \text{H}]^+$ 218.0752; found: 218.0757.

3.1.5 Synthesis of 3,4-Dihydro-2H,6H-pyrimido [1,2-*c*]quinazolin-6-amine (9)

2-[*N*-(*p*-Toluenesulfonyl)amino]benzaldehyde (13). To a solution of 2-aminobenzylalcohol **12** (2.0 g, 16.2 mmol) and pyridine (1.6 mL, 19.4 mmol) in CHCl_3 (60 mL) was added a solution of *p*-TsCl (3.4 g, 18.0 mmol) in CHCl_3 (17 mL), and the mixture was stirred at rt for 3 h. After concentration, EtOAc and sat. NH_4Cl were added to the residue. The organic phase was separated and dried over MgSO_4 . After concentration, the resulting solid was added to a suspension of PCC (5.2 g, 24.3 mmol) and silica gel (10.6 g) in CHCl_3 (70 mL). After being stirred at rt for 2 h, the mixture was filtered and concentrated. The residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (9:1) to give the title compound **13** as colorless solid (3.6 g, 80 %): mp 134–136 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1672 (C=O), 1492 (NSO₂), 1157 (NSO₂); ^1H -NMR (400 MHz, CDCl_3) δ : 2.36 (3H, s, CH₃), 7.16 (1H, t, $J = 7.6$ Hz, Ar), 7.24 (2H, d, $J = 8.5$ Hz, Ar), 7.49–7.53 (1H, m, Ar), 7.59 (1H, dd, $J = 7.6, 1.5$ Hz, Ar), 7.69 (1H, d, $J = 8.3$ Hz, Ar), 7.77 (2H, d, $J = 8.5$ Hz, Ar), 9.83 (1H, s, CHO), 10.78 (1H, br s, NH); ^{13}C -NMR (100 MHz, CDCl_3) δ : 21.5, 117.8, 121.9, 122.9, 127.3 (2C), 129.7 (2C), 135.8, 136.1, 136.5, 140.0, 144.1, 194.9; Anal. calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_3\text{S}$: C, 61.07; H, 4.76; N, 5.09. Found: C, 60.97; H, 4.46; N, 5.05.

2-[2-*N*-(*p*-Toluenesulfonylamino)phenyl]-1,4,5,6-tetrahydropyrimidine (14). To a solution of **13** (2.75 g, 10 mmol) in *t*-BuOH (94 mL) was added propylendiamine (969 mg, 11 mmol). The mixture was stirred at 70 °C for 30 min, and then K_2CO_3 (4.15 g, 30 mmol) and I_2 (3.17 g, 12.5 mmol) were added. After being stirred at same temperature for 3 h, the mixture was quenched with sat. Na_2SO_3 until the iodine color disappeared. The organic layer was separated and concentrated. The resulting solid was dissolved in H_2O . The whole was extracted with CHCl_3 , and dried over MgSO_4 . After concentration, the resulting solid was recrystallized from CHCl_3 – Et_2O –*n*-hexane to give the title compound **14** as pale yellow crystals (3.23 g, 98 %): mp 211–213 °C; IR (neat) cm^{-1} : 1630 (C=N); 1478 (NSO₂), 1124 (NSO₂); ^1H -NMR (400 MHz, CDCl_3) δ : 1.77–1.82 (2H, m, CH₂), 2.34 (3H, s, CH₃), 3.36 (4H, t, $J = 5.7$ Hz, 2 × CH₂), 6.53–6.57 (1H, m, Ar), 7.04–7.08 (1H, m, Ar), 7.16–7.22 (3H, m, Ar), 7.58 (1H, dd, $J = 8.2, 1.3$ Hz, Ar), 7.76 (2H, d, $J = 8.3$ Hz, Ar), 10.75 (1H, br s, NH); ^{13}C -NMR (100 MHz, CDCl_3) δ : 18.4, 21.3, 38.8 (2C), 112.4, 117.7, 121.2, 126.3 (2C), 126.5, 129.2 (2C), 133.0, 140.9, 142.0, 150.3, 158.9; HRMS (FAB): m/z calcd for $\text{C}_{17}\text{H}_{20}\text{N}_3\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$ 330.1276; found: 330.1273.

Compound 9. To a flask containing **14** (164.7 mg, 0.5 mmol) was added conc. H₂SO₄ (5.0 mL). After being stirred at 100 °C for 30 min, the mixture was cooled to 0 °C, and then pH was adjusted to 12–14 with 2 N NaOH. The whole was extracted with CHCl₃, and dried over MgSO₄. After concentration, the residue was dissolved in anhydrous EtOH (2 mL). Then, BrCN (105.9 mg, 1.0 mmol) was added to the mixture under an Ar atmosphere. After being stirred under reflux for 2 h, the reaction was quenched with 2N NaOH. The whole was extracted with CHCl₃, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over aluminum oxide with EtOAc–MeOH (95:5) to give the title compound **9** as colorless solid (66.0 mg, 66 %): mp 259–260 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1620 (C=N), 1603 (C=N); ¹H-NMR (400 MHz, DMSO-*d*₆) δ: 1.81–1.87 (2H, m, CH₂), 3.44 (2H, t, *J* = 5.4 Hz, CH₂), 3.70 (2H, t, *J* = 6.1 Hz, CH₂), 6.49 (2H, br s, NH₂), 6.87–6.95 (2H, m, Ar), 7.27–7.31 (1H, m, Ar), 7.87 (1H, dd, *J* = 7.9, 1.1 Hz, Ar); ¹³C-NMR (100 MHz, DMSO-*d*₆) δ: 20.0, 42.8, 42.9, 118.9, 120.7, 122.7, 124.3, 131.1, 145.6, 146.6, 151.6; HRMS (FAB): *m/z* calcd for C₁₁H₁₃N₄ [M + H]⁺ 201.1140; found: 201.1138.

3.1.6 Synthesis of 3,4-Dihydro-2H,6H-pyrimido [1,2-*c*][1,3]benzothiazin-6-one (**11**)

3,4-Dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazine-6-thione **10** (58.6 mg, 0.25 mmol) was suspended into a 0.1 M NaOH in MeOH–H₂O (9:1, 5 mL). After being stirred under reflux for 12 h, the mixture was concentrated. To a stirring solution of the residue and Et₃N (0.029 mL, 2.0 mmol) in CH₂Cl₂ (16.6 mL) was added dropwise a solution of triphosgene (155.8 mg, 0.52 mmol) in CH₂Cl₂ (1.7 mL) at 0 °C. After being stirred at rt for 1 h, the mixture was quenched with sat. NaHCO₃. The whole was extracted with CHCl₃. The extract was washed with sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (9:1) to give the title compound **11** as colorless solid (35.3 mg, 65 %): mp 102–103 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1639 (C=O) 1612 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.95–1.99 (2H, m, CH₂), 3.73 (2H, t, *J* = 5.7 Hz, CH₂), 4.00 (2H, t, *J* = 6.0 Hz, CH₂), 7.13 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.27–7.30 (1H, m, Ar), 7.40 (1H, td, *J* = 8.0, 1.1 Hz, Ar), 8.28 (1H, dd, *J* = 8.0, 1.1 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 20.8, 42.4, 45.2, 124.4, 125.8, 126.8, 128.9, 129.2, 130.9, 146.1, 162.8; HRMS (FAB): *m/z* calcd for C₁₁H₁₁N₂OS [M + H]⁺ 219.0592; found: 219.0592.

3.1.7 Synthesis of 9-(*N,N*-Dimethylamino)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25a)

N-(*tert*-Butyl)-9-(*N'*,*N'**H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (22a). To a mixture of *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (88.1 mg, 0.25 mmol) and Pd(OAc)₂ (5.6 mg, 0.025 mmol) and KO^tBu (84.2 mg, 0.75 mmol) in toluene (2.0 mL) were added P(*tert*-Bu)₃ (0.009 mL, 0.038 mmol) and 2 N Me₂NH in THF (0.38 mL, 0.75 mmol). After being stirred at reflux for 1 h, the mixture was filtered through a Celite pad and concentrated. The residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) to give the title compound **22a** as colorless solid (80.9 mg, >99 %): mp 161–162 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1587 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.38 (9H, s, 3 × CH₃), 1.86–1.92 (2H, m, CH₂), 2.97 (6H, s, 2 × CH₃), 3.58 (2H, t, *J* = 5.5 Hz, CH₂), 3.85 (2H, t, *J* = 6.1 Hz, CH₂), 6.28 (1H, d, *J* = 2.7 Hz, Ar), 6.55 (1H, dd, *J* = 9.0, 2.7 Hz, Ar), 8.04 (1H, d, *J* = 9.0 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 22.0, 30.0 (3C), 40.0 (2C), 44.9, 45.5, 54.0, 105.5, 110.6, 115.7, 129.7, 130.0, 139.2, 148.0, 151.2; HRMS (FAB): *m/z* calcd for C₁₇H₂₅N₄S [M + H]⁺ 317.1800; found: 317.1803.

Compound 25a. TFA (2.0 mL) was added to a mixture of **22a** (63.3 mg, 0.2 mmol) in small amount of CHCl₃ and MS4 Å (300 mg, powder, activated by heating with Bunsen burner). After being stirred under reflux for 1 h, the mixture was concentrated. To a stirring mixture of the residue in CHCl₃ was added dropwise Et₃N at 0 °C to adjust pH to 8–9. The whole was extracted with EtOAc. The extract was washed with sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) to give the title compound 25a as colorless solid (38.2 mg, 73 %): mp 150–151 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1600 (C=N), 1562 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.93–1.98 (2H, m, CH₂), 2.98 (6H, s, 2 × CH₃), 3.64 (2H, t, *J* = 5.7 Hz, CH₂), 4.00 (2H, t, *J* = 6.3 Hz, CH₂), 6.17 (1H, d, *J* = 2.3 Hz, Ar), 6.55 (1H, dd, *J* = 9.2, 2.3 Hz, Ar), 7.01 (1H, br s, NH), 8.05 (1H, d, *J* = 9.2 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.1, 40.0 (2C), 43.8, 44.7, 104.4, 110.7, 114.4, 129.8, 129.9, 146.7, 151.3, 154.2; HRMS (FAB): *m/z* calcd for C₁₃H₁₇N₄S [M + H]⁺ 261.1174; found: 261.1173.

3.1.8 Synthesis of 3,4-Dihydro-9-(*N*-methylamino)-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25b)

9-Amino-*N*-(*tert*-butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28). To a suspension of *N*-(*tert*-Butyl)-3,4-dihydro-9-nitro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22e** (477.0 mg, 1.5 mmol) in EtOH (10 mL)

was added 10 % Pd/C (ca. 55 % in water, 400 mg) under a H₂ atmosphere. After being stirred at rt overnight, the mixture was filtered through a Celite pad. After concentration, the resulting solid was recrystallized from CHCl₃-*n*-hexane to give the title compound **28** as colorless crystals (381.1 mg, 88 %): mp 152–155 °C; IR (neat) cm⁻¹: 1589 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.37 (9H, s, 3 × CH₃), 1.86–1.92 (2H, m, CH₂), 3.57 (2H, t, *J* = 5.4 Hz, CH₂), 3.84 (2H, t, *J* = 6.0 Hz, CH₂), 3.88 (2H, br s, NH₂), 6.33 (1H, d, *J* = 2.2 Hz, Ar), 6.49 (1H, dd, *J* = 8.5, 2.2 Hz, Ar), 7.99 (1H, d, *J* = 8.5 Hz, Ar); ¹³C-NMR (100 MHz, CD₃OD) δ: 22.7, 30.2 (3C), 45.2, 46.8, 55.2, 109.1, 114.4, 116.4, 130.7, 131.4, 140.5, 151.8, 152.4; HRMS (FAB): *m/z* calcd for C₁₅H₂₁N₄S [M + H]⁺ 289.1487; found: 289.1489.

***N*-(*tert*-Butyl)-3,4-dihydro-9-(*N*-methylamino)-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (22b)**. To a flask containing **28** (108.5 mg, 0.38 mmol), MeONa (30.6 mg, 0.57 mmol), and paraformaldehyde (34.2 mg, 1.1 mmol) was added anhydrous MeOH (2.5 mL) under an Ar atmosphere, and stirring was continued for 5 h under reflux. Then, NaBH₄ (28.8 mg, 0.76 mmol) was added to the mixture and stirring was continued for additional 30 min under reflux. After concentration, the residue was dissolved in EtOAc, and washed with sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was purified by flash column chromatography over aluminum oxide with *n*-hexane–EtOAc (1:1) to give the title compound **22b** as yellow solid (104.9 mg, 91 %): mp 156–158 °C (from CHCl₃-*n*-hexane); IR (neat) cm⁻¹: 1590 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.38 (9H, s, 3 × CH₃), 1.87–1.92 (2H, m, CH₂), 2.83 (3H, s, CH₃), 3.57 (2H, t, *J* = 5.4 Hz, CH₂), 3.85 (2H, t, *J* = 6.0 Hz, CH₂), 4.04 (1H, br s, NH), 6.20 (1H, d, *J* = 2.4 Hz, Ar), 6.43 (1H, dd, *J* = 8.8, 2.4 Hz, Ar), 8.01 (1H, d, *J* = 8.8 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.9, 30.0 (3C), 30.2, 44.7, 45.5, 54.0, 104.9, 111.8, 116.3, 129.7, 130.4, 139.0, 148.3, 150.6; HRMS (FAB): *m/z* calcd for C₁₆H₂₃N₄S [M + H]⁺ 303.1643; found: 303.1638.

Compound 25b. Using the general procedure as described for **25a**, compound **22b** (30.7 mg, 0.1 mmol) was allowed to react for 1 h with TFA (1.0 mL) and MS4Å (200 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:1 to 0:1) gave the title compound **25b** as pale yellow solid (9.0 mg, 37 %): mp 129–131 °C (from CHCl₃-*n*-hexane); IR (neat) cm⁻¹: 1602 (C=N), 1555 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.92–1.98 (2H, m, CH₂), 2.84 (3H, d, *J* = 4.1 Hz, CH₃), 3.64 (2H, t, *J* = 5.6 Hz, CH₂), 4.00 (2H, t, *J* = 6.2 Hz, CH₂), 4.03 (1H, br s, NH), 6.11 (1H, d, *J* = 2.4 Hz, Ar), 6.44 (1H, dd, *J* = 8.8, 2.4 Hz, Ar), 8.01 (1H, d, *J* = 8.8 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.1, 30.2, 43.9, 44.6, 104.0, 111.9, 129.2, 130.1, 130.3, 146.9, 150.8, 154.1; *Anal.* calcd for C₁₂H₁₄N₄S: C, 58.51; H, 5.73; N, 22.74. Found: C, 58.30; H, 5.62; N, 22.45.

3.1.9 Synthesis of 9-(*N*-Acetylamino)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25c)

9-(*N*-Acetylamino)-*N*-(*tert*-butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (22c). To a mixture of 9-amino-*N*-(*tert*-butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **28** (100.9 mg, 0.35 mmol), Et₃N (0.015 mL, 1.05 mmol), DMAP (4.3 mg, 0.04 mmol) in CH₂Cl₂ (3.5 mL) was added Ac₂O (0.066 mL, 0.70 mmol) under an Ar atmosphere. After being stirred under reflux for 1 h, sat. NaHCO₃ was added to the mixture. The whole was extracted with EtOAc. The extract was washed with brine, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:1 to 0:1) to give the title compound **22c** as colorless solid (120.1 mg, > 99 %): mp 213–214 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1680 (C=O), 1596 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.37 (9H, s, 3 × CH₃), 1.88–1.93 (2H, m, CH₂), 2.15 (3H, s, CH₃), 3.59 (2H, t, *J* = 5.4 Hz, CH₂), 3.86 (2H, t, *J* = 6.1 Hz, CH₂), 6.99 (1H, dd, *J* = 8.7, 2.1 Hz, Ar), 7.74 (1H, d, *J* = 2.1 Hz, Ar), 7.96 (1H, br s, NH), 8.08 (1H, d, *J* = 8.7 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.8, 24.6, 29.9 (3C), 44.9, 45.4, 54.2, 114.4, 116.8, 123.1, 129.1, 130.4, 138.2, 139.7, 147.8, 168.6; HRMS (FAB): *m/z* calcd for C₁₇H₂₃N₄OS [M + H]⁺ 331.1593; found: 331.1590.

Compound 25c. Using the general procedure as described for **28a**, compound **25c** (120.1 mg, 0.36 mmol) was allowed to react for 10 h. Purification by recrystallization from MeOH–CHCl₃–Et₂O gave the title compound **25c** as pale yellow crystals (64.9 mg, 65 %): mp 214 °C (decomp.); IR (neat) cm⁻¹: 1681 (C=O), 1619 (C=N), 1550 (C=N); ¹H-NMR (400 MHz, DMSO-*d*₆) δ: 1.85–1.91 (2H, m, CH₂), 2.07 (3H, s, CH₃), 3.55 (2H, t, *J* = 5.5 Hz, CH₂), 3.92 (2H, t, *J* = 6.0 Hz, CH₂), 7.32 (1H, dd, *J* = 8.9, 1.8 Hz, Ar), 7.61 (1H, d, *J* = 1.8 Hz, Ar), 8.10 (1H, d, *J* = 8.9 Hz, Ar), 9.14 (1H, br s, NH), 10.27 (1H, s, NH); ¹³C-NMR (100 MHz, DMSO-*d*₆) δ: 20.3, 24.1, 43.3, 43.6, 112.2, 116.7, 119.3, 129.2, 129.9, 141.7, 146.3, 149.5, 169.0; HRMS (FAB): *m/z* calcd for C₁₃H₁₅N₄OS [M + H]⁺ 275.0967; found: 275.0967.

3.1.10 Synthesis of 9-Acetyl-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25d)

To a mixture of *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (100 mg, 0.284 mmol), Pd(OAc)₂ (6.4 mg, 0.0284 mmol), K₂CO₃ (120 mg, 0.852 mmol) and dppp (23.7 mg, 0.0568 mmol) in H₂O (0.57 mL) was added ethylene glycol monovinyl ether (0.13 mL, 1.42 mmol). After being stirred at reflux for 12 h, the whole was extracted with CHCl₃. The extract was washed with brine, and dried over Na₂SO₄. After concentration, TFA (2.84 mL) was added to resulting residue. After being stirred under reflux for 1.5 h, the mixture was added dropwise to Et₃N at 0 °C to adjust

pH to 8–9. The whole was extracted with EtOAc. The extract was washed with brine, and dried over Na₂SO₄. After concentration, the residue was purified by preparative TLC over aluminum oxide with *n*-hexane–EtOAc (7:3) to give the title compound **25d** as pale yellow solid (9.7 mg, 13 %): mp 148.4 °C; IR (neat) cm⁻¹: 1678 (C=O), 1616 (C=N), 1567 (C=N); ¹H-NMR (300 MHz, CDCl₃) δ: 1.95–2.03 (2H, m, CH₂), 2.60 (3H, s, CH₃), 3.72 (2H, t, *J* = 5.7 Hz, CH₂), 4.03 (2H, t, *J* = 6.3 Hz, CH₂), 7.63 (1H, d, *J* = 1.8 Hz, Ar), 7.74 (1H, dd, *J* = 8.3, 1.7 Hz, Ar), 8.32 (1H, d, *J* = 7.8 Hz, Ar); ¹³C-NMR (75 MHz, CDCl₃) δ: 20.9, 26.7, 43.8, 45.1, 123.6, 125.7, 129.3, 129.6, 130.4, 138.3, 146.0, 152.6, 196.7; *Anal.* calcd for C₁₃H₁₃N₃OS: C, 60.21; H, 5.05; N, 16.20. Found: C, 60.16; H, 5.02; N, 15.94.

3.1.11 Synthesis of 3,4-Dihydro-9-nitro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25e)

N-(*tert*-Butyl)-3,4-dihydro-9-nitro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**22e**). To a mixture of 2-(2-fluoro-4-nitrophenyl)-1,4,5,6-tetrahydropyrimidine **18e** (2.0 g, 9.0 mmol) and NaH (716.8 mg, 17.9 mmol; 60 % oil suspension) in DMF (29.8 mL) was added *tert*-butylisothiocyanate (2.28 mL, 17.9 mmol) under an Ar atmosphere, and the mixture was stirred at –20 °C to rt for 2 days. The whole was extracted with EtOAc, and the extract was washed with sat. NaHCO₃, brine, and dried over Na₂SO₄. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) to give the title compound **22e** as pale yellow solid (1.77 g, 62 %): mp 152–153 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1591 (NO₂), 1581 (C=N), 1523 (NO₂); ¹H-NMR (500 MHz, CDCl₃) δ: 1.39 (9H, s, 3 × CH₃), 1.91–1.96 (2H, m, CH₂), 3.66 (2H, t, *J* = 5.2 Hz, CH₂), 3.88 (2H, t, *J* = 5.7 Hz, CH₂), 7.97 (1H, dd, *J* = 9.7, 2.3 Hz, Ar), 8.01 (1H, d, *J* = 2.3 Hz, Ar), 8.39 (1H, d, *J* = 9.2 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.7, 30.0 (3C), 45.3, 45.5, 54.5, 119.9, 120.3, 130.0, 131.1, 132.8, 136.1, 146.5, 148.5; HRMS (FAB): *m/z* calcd for C₁₅H₁₉N₄O₂S [M + H]⁺ 319.1229; found: 319.1229.

Compound 25e. Using the general procedure as described for **25a**, compound **22e** (47.8 mg, 0.15 mmol) was allowed to react for 1 h with TFA (1.5 mL) and MS4Å (225 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (19:1 to 1:1) gave the title compound **25e** as pale yellow solid (24.9 mg, 63 %): mp 170–172 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1620 (C=N), 1587 (NO₂), 1568 (C=N), 1523 (NO₂); ¹H-NMR (400 MHz, CDCl₃) δ: 1.97–2.03 (2H, m, CH₂), 3.74 (2H, t, *J* = 5.6 Hz, CH₂), 4.04 (2H, t, *J* = 6.2 Hz, CH₂), 7.41 (1H, br s, NH), 7.93 (1H, d, *J* = 2.2 Hz, Ar), 8.00 (1H, dd, *J* = 9.0, 2.2 Hz, Ar), 8.42 (1H, d, *J* = 9.0 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 20.8, 43.8, 45.2, 118.9, 120.5, 130.4, 130.8, 131.7, 145.1, 148.7, 151.3; *Anal.* calcd for C₁₁H₁₀N₄O₂S: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.29; H, 4.03; N, 21.08.

3.1.12 Synthesis of 3,4-Dihydro-9-methoxy-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (25f)

3,4-Dihydro-9-methoxy-2H,6H-pyrimido[1,2-c][1,3]benzothiazine-6-thione **21f** (66.1 mg, 0.25 mmol) was suspended into a 0.1 M NaOH in MeOH-H₂O (9:1) (5 mL), and the mixture was stirred for 12 h under reflux. After concentration, the residue was suspended in anhydrous EtOH (1 mL). BrCN (53.0 mg, 0.50 mmol) was added under an Ar atmosphere, and the mixture was stirred for 2 h under reflux. The reaction was quenched with 2 N NaOH, and the whole was extracted with CHCl₃, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) to give the title compound **25f** as colorless solid (37.6 mg, 61 %): mp 106 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1620 (C=N), 1572 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.94–1.98 (2H, m, CH₂), 3.66 (2H, t, *J* = 5.7 Hz, CH₂), 3.81 (3H, s, CH₃), 4.01 (2H, t, *J* = 6.0 Hz, CH₂), 6.50 (1H, d, *J* = 2.3 Hz, Ar), 6.76 (1H, dd, *J* = 9.0, 2.3 Hz, Ar), 7.15 (1H, br s, NH), 8.15 (1H, d, *J* = 9.0 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.0, 43.8, 44.8, 55.5, 107.3, 113.3, 119.5, 130.2, 130.6, 146.2, 153.4, 161.2; *Anal.* calcd for C₁₂H₁₃N₃OS: C, 58.28; H, 5.30; N, 16.99. Found: C, 58.15; H, 5.23; N, 16.79.

3.1.13 Synthesis of 3,4-Dihydro-9-methyl-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (25g)

3,4-Dihydro-9-methyl-2H,6H-pyrimido[1,2-c][1,3]benzothiazine-6-thione **21g** (62.1 mg, 0.25 mmol) was subjected to the general procedure as described for **25f** to give the title compound **25g** as colorless solid (39.2 mg, 68 %): mp 121 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1620 (C=N), 1569 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.94–1.99 (2H, m, CH₂), 2.32 (3H, s, CH₃), 3.67 (2H, t, *J* = 5.7 Hz, CH₂), 4.01 (2H, t, *J* = 6.3 Hz, CH₂), 6.84 (1H, s, Ar), 7.02 (1H, d, *J* = 8.6 Hz, Ar), 7.16 (1H, br s, NH), 8.10 (1H, d, *J* = 8.6 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.1, 21.1, 43.8, 44.9, 123.6, 124.1, 127.4, 128.6, 128.8, 141.1, 146.6, 153.6; HRMS (FAB): *m/z* calcd for C₁₂H₁₄N₃S [M + H]⁺ 232.0908; found: 232.0912.

3.1.14 Synthesis of 9-(*n*-Butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (25h)

9-(*n*-Butyl)-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (**22h**). To a mixture of *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (352.3 mg, 1.0 mmol),

n-butylboronic acid (152.9 mg, 1.5 mmol), Pd₂(dba)₃·CHCl₃ (51.8 mg, 0.05 mmol) and Cs₂CO₃ (391.0 mg, 1.2 mmol) in 1,4-dioxane (2.5 mL) was added P(*tert*-Bu)₃ (0.024 mL, 0.1 mmol) under an Ar atmosphere, the mixture was stirred for 19 h under reflux. The mixture was filtered through a Celite pad, and concentrated. The residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 19:1) to give the title compound **22h** as a colorless oil (21.0 mg, 6 %): IR (neat) cm⁻¹: 1593 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 0.91 (3H, t, *J* = 7.3 Hz, CH₃), 1.29–1.36 (2H, m, CH₂), 1.38 (9H, s, 3 × CH₃), 1.54–1.62 (2H, m, CH₂), 1.87–1.93 (2H, m, CH₂), 2.57 (2H, t, *J* = 7.7 Hz, CH₂), 3.60 (2H, t, *J* = 5.4 Hz, CH₂), 3.86 (2H, t, *J* = 6.0 Hz, CH₂), 6.91 (1H, d, *J* = 1.2 Hz, Ar), 7.01 (1H, dd, *J* = 8.3, 1.2 Hz, Ar), 8.08 (1H, d, *J* = 8.3 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 13.8, 21.9, 22.2, 30.0 (3C), 33.0, 35.2, 45.0, 45.4, 54.1, 123.9, 125.3, 126.5, 128.3, 128.7, 138.6, 145.4, 147.9; HRMS (FAB): *m/z* calcd for C₁₉H₂₈N₃S [M + H]⁺ 330.2004; found: 330.1999.

Compound 25h. Using the general procedure as described for **25a**, compound **22h** (10.3 mg, 0.03 mmol) was allowed to react for 1 h with TFA (1.0 mL) and MS4 Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) gave the title compound **25h** as colorless solid (5.2 mg, 61 %): mp 52–55 °C (from *n*-hexane); IR (neat) cm⁻¹: 1621 (C=N), 1571 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 0.91 (3H, t, *J* = 7.3 Hz, CH₃), 1.29–1.38 (2H, m, CH₂), 1.54–1.61 (2H, m, CH₂), 1.93–1.99 (2H, m, CH₂), 2.58 (2H, t, *J* = 7.7 Hz, CH₂), 3.67 (2H, t, *J* = 5.6 Hz, CH₂), 4.01 (2H, t, *J* = 6.2 Hz, CH₂), 6.84 (1H, d, *J* = 1.5 Hz, Ar), 7.03–7.05 (1H, m, Ar), 8.11 (1H, d, *J* = 8.3 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 13.8, 21.1, 22.2, 33.0, 35.2, 43.8, 44.9, 123.0, 124.4, 126.8, 128.6, 128.8, 146.1, 146.6, 153.7; HRMS (FAB): *m/z* calcd for C₁₅H₂₀N₃S [M + H]⁺ 274.1378; found: 274.1372.

3.1.15 Synthesis of 9-Fluoro-3,4-dihydro-2H, 6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25i)

9-Fluoro-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazine-6-thione **21i** (63.1 mg, 0.25 mmol) was subjected to the general procedure as described for **25f** to give the title compound **25i** as colorless solid (30.4 mg, 52 %): mp 123–124 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1624 (C=N), 1585 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.94–2.00 (2H, m, CH₂), 3.67 (2H, t, *J* = 5.7 Hz, CH₂), 4.01 (2H, t, *J* = 6.3 Hz, CH₂), 6.75 (1H, dd, *J* = 8.0, 2.9 Hz, Ar), 6.91 (1H, ddd, *J* = 8.6, 8.0, 2.9 Hz, Ar), 7.22 (1H, br s, NH), 8.24 (1H, dd, *J* = 8.6, 5.7 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.0, 43.8, 44.8, 110.0 (d, *J* = 25.2 Hz), 113.9 (d, *J* = 21.6 Hz), 123.1, 130.9 (d, *J* = 8.4 Hz), 131.5 (d, *J* = 8.4 Hz), 146.4 (d, *J* = 155.9 Hz), 152.6, 163.7 (d, *J* = 254.3 Hz); ¹⁹F-NMR (500 MHz, CDCl₃) δ: –109.1; *Anal.* calcd for C₁₁H₁₀FN₃S: C, 56.15; H, 4.28; N, 17.86. Found: C, 56.13; H, 4.44; N, 17.78.

3.1.16 Synthesis of 3,4-Dihydro-9-trifluoromethyl-2H, 6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (25j)

2-(2-Fluoro-4-trifluoromethylphenyl)-1,4,5,6-tetrahydropyrimidine (18j). To a solution of 2-fluoro-4-trifluoromethylbenzaldehyde **15j** (1.00 g, 5.21 mmol) in *t*-BuOH (49 mL) was added propylenediamine (424.7 mg, 5.73 mmol). The mixture was stirred at 70 °C for 30 min, and then K₂CO₃ (2.16 g, 15.6 mmol) and I₂ (1.65 g, 6.51 mmol) were added. After being stirred at same temperature for 3 h, the mixture was quenched with sat. Na₂SO₃. The organic layer was separated and concentrated. The resulting solid was dissolved with H₂O, and then pH was adjusted to 12–14 with 2 N NaOH. The whole was extracted with CHCl₃, and the extract was dried over MgSO₄. After concentration, the resulting solid was recrystallized from CHCl₃–*n*-hexane to give the title compound **18j** as colorless crystals (0.84 g, 65 %): mp 108–110 °C; IR (neat) cm⁻¹: 1620 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.86–1.90 (2H, m, CH₂), 3.52 (4H, t, *J* = 5.2 Hz, 2 × CH₂), 5.34 (1H, br s, NH), 7.33 (1H, d, *J* = 11.5 Hz, Ar), 7.42 (1H, d, *J* = 8.6 Hz, Ar), 7.96 (1H, dd, *J* = 8.6, 8.0 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 20.5, 42.2 (2C), 113.4 (dq, *J* = 26.9, 3.9 Hz), 120.9–121.0 (m), 123.0 (dq, *J* = 273.0, 2.5 Hz), 128.0 (d, *J* = 13.2 Hz), 131.5 (d, *J* = 4.1 Hz), 132.8 (dq, *J* = 33.7, 9.1 Hz), 150.4, 159.6 (d, *J* = 249.1 Hz); ¹⁹F-NMR (500 MHz, CDCl₃) δ: -115.1, -63.4; *Anal.* calcd for C₁₁H₁₀F₄N₂: C, 53.66; H, 4.09; N, 11.38. Found: C, 53.82; H, 4.06; N, 11.43.

***N*-(*tert*-Butyl)-3,4-dihydro-9-trifluoromethyl-2H, 6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (22j).** Using the general procedure as described for **22e**, compound **18j** (246.2 mg, 1.0 mmol) was allowed to react at 80 °C for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **22j** as colorless solid (219.4 mg, 64 %): mp 82 °C (from *n*-hexane); IR (neat) cm⁻¹: 1601 (C=N), 1569 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.39 (9H, s, 3 × CH₃), 1.90–1.95 (2H, m, CH₂), 3.64 (2H, t, *J* = 5.4 Hz, CH₂), 3.88 (2H, t, *J* = 6.3 Hz, CH₂), 7.38 (1H, s, Ar), 7.41 (1H, d, *J* = 8.6 Hz, Ar), 8.31 (1H, d, *J* = 8.6 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.8, 29.9 (3C), 45.2, 45.4, 54.3, 121.6 (q, *J* = 4.0 Hz), 122.4 (q, *J* = 3.6 Hz), 123.5 (q, *J* = 272.7 Hz), 129.2, 130.1, 130.7, 132.0 (q, *J* = 33.2 Hz), 136.9, 146.9; ¹⁹F-NMR (500 MHz, CDCl₃) δ: -63.6; HRMS (FAB): *m/z* calcd for C₁₆H₁₉F₃N₃S [M + H]⁺ 342.1252; found: 342.1252.

Compound 25j. Using the general procedure as described for **25a**, compound **22j** (68.3 mg, 0.20 mmol) was allowed to react for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (8:2) gave the title compound **25j** as colorless solid (48.2 mg, 84 %): mp 91.5 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1625 (C=N), 1561 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.96–2.01 (2H, m, CH₂), 3.71 (2H, t, *J* = 5.7 Hz, CH₂), 4.03 (2H, t, *J* = 6.3 Hz, CH₂), 7.27 (2H, m, Ar, NH), 7.44 (1H, dd, *J* = 8.3, 1.4 Hz, Ar), 8.35 (1H, d, *J* = 8.6 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 20.9, 43.8, 45.0, 120.7 (q, *J* = 4.0 Hz), 122.7 (q, *J* = 3.2 Hz), 123.3 (q, *J* = 272.7 Hz), 129.6, 129.7,

129.9, 132.5 (q, $J = 33.2$ Hz), 145.6, 152.1; ^{19}F -NMR (500 MHz, CDCl_3) δ : -63.8; *Anal.* calcd for $\text{C}_{12}\text{H}_{10}\text{F}_3\text{N}_3\text{S}$: C, 50.52; H, 3.53; N, 14.73. Found: C, 50.51; H, 3.50; N, 14.69.

3.1.17 Synthesis of 9-Bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (25k)

2-(4-Bromo-2-fluorophenyl)-1,4,5,6-tetrahydropyrimidine (18k). 4-Bromo-2-fluorobenzaldehyde 15k (1.02 g, 5.0 mmol) was subjected to the general procedure as described for **18j** to give the title compound **18k** as colorless crystals (0.80 g, 62 %): mp 135–137 °C (from CHCl_3 -*n*-hexane); IR (neat) cm^{-1} : 1622 (C=N); ^1H -NMR (400 MHz, CDCl_3) δ : 1.83–1.89 (2H, m, CH_2), 3.49 (4H, t, $J = 5.9$ Hz, $2 \times \text{CH}_2$), 4.88 (1H, br s, NH), 7.24 (1H, dd, $J = 11.2$, 2.0 Hz, Ar), 7.30 (1H, dd, $J = 8.5$, 2.0 Hz, Ar), 7.71 (1H, dd, $J = 8.5$, 8.3 Hz, Ar); ^{13}C -NMR (100 MHz, CDCl_3) δ : 20.6, 42.3 (2C), 119.5 (d, $J = 27.3$ Hz), 123.4 (d, $J = 3.3$ Hz), 123.6 (d, $J = 5.0$ Hz), 127.7 (d, $J = 3.3$ Hz), 131.6 (d, $J = 4.1$ Hz), 150.7, 159.8 (d, $J = 251.6$ Hz); ^{19}F -NMR (500 MHz, CDCl_3) δ : -114.7; *Anal.* calcd for $\text{C}_{10}\text{H}_{10}\text{BrFN}_2$: C, 46.72; H, 3.92; N, 10.90. Found: C, 46.66; H, 3.82; N, 10.87.

9-Bromo-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (22k). Using the general procedure as described for **22e**, compound **18k** (257.1 mg, 1.00 mmol) was allowed to react at rt overnight. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **22k** as colorless solid (295.6 mg, 84 %): mp 107–108 °C (from *n*-hexane); IR (neat) cm^{-1} : 1596 (C=N); ^1H -NMR (400 MHz, CDCl_3) δ : 1.38 (9H, s, $3 \times \text{CH}_3$), 1.87–1.93 (2H, m, CH_2), 3.60 (2H, t, $J = 5.6$ Hz, CH_2), 3.85 (2H, t, $J = 6.1$ Hz, CH_2), 7.26–7.31 (2H, m, Ar), 8.05 (1H, d, $J = 8.5$ Hz, Ar); ^{13}C -NMR (100 MHz, CDCl_3) δ : 21.8, 30.0 (3C), 45.0, 45.4, 54.3, 124.4, 126.7, 126.8, 129.1, 130.1, 130.9, 137.2, 147.2; *Anal.* calcd for $\text{C}_{15}\text{H}_{18}\text{BrN}_3\text{S}$: C, 51.14; H, 5.15; N, 11.93. Found: C, 51.30; H, 5.07; N, 11.82.

Compound 25k. Using the general procedure as described for **25a**, compound **22k** (52.8 mg, 0.15 mmol) was allowed to react for 2 h with TFA (1.5 mL) and MS4Å (225 mg). Purification by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) gave the title compound **25k** as colorless solid (40.2 mg, 91 %): mp 104–105 °C (from CHCl_3 -*n*-hexane); IR (neat) cm^{-1} : 1620 (C=N), 1569 (C=N); ^1H -NMR (400 MHz, CDCl_3) δ : 1.94–1.99 (2H, m, CH_2), 3.67 (2H, t, $J = 5.5$ Hz, CH_2), 4.00 (2H, t, $J = 6.0$ Hz, CH_2), 7.19–7.34 (3H, m, NH, Ar), 8.08 (1H, d, $J = 8.8$ Hz, Ar); ^{13}C -NMR (100 MHz, CDCl_3) δ : 20.9, 43.8, 44.9, 125.0, 125.6, 125.9, 129.5, 130.4, 130.7, 145.8, 152.4; *Anal.* calcd for $\text{C}_{11}\text{H}_{10}\text{BrN}_3\text{S}$: C, 44.61; H, 3.40; N, 14.19. Found: C, 44.37; H, 3.28; N, 13.93.

3.1.18 Synthesis of 3,4-Dihydro-9-phenyl-2H, 6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (25l)

N-(*tert*-Butyl)-3,4-dihydro-9-phenyl-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (**22l**). To a solution of *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) and phenylboronic acid (21.9 mg, 0.18 mmol) in a mixture of toluene (1.5 mL), EtOH (0.9 mL) and 1 M aq. K₂CO₃ (1.5 mL) was added Pd(PPh₃)₄ (6.9 mg, 4 mol %) and PdCl₂(dppf)·CH₂Cl₂ (3.7 mg, 3 mol %). After being stirred at reflux for 1 h, the mixture was extracted with CHCl₃. The extract was dried over MgSO₄ and concentrated. The residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) to give the title compound **22l** as colorless solid (44.8 mg, 85 %): mp 122.5–124 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1592 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.40 (9H, s, 3 × CH₃), 1.90–1.95 (2H, m, CH₂), 3.64 (2H, t, *J* = 5.4 Hz, CH₂), 3.89 (2H, t, *J* = 6.0 Hz, CH₂), 7.33–7.37 (2H, m, Ar), 7.41–7.44 (3H, m, Ar), 7.58 (2H, d, *J* = 6.9 Hz, Ar), 8.25 (1H, d, *J* = 8.6 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 122.7, 124.8, 126.5, 127.0 (2C), 128.0, 128.8 (2C), 128.9, 129.5, 138.3, 139.4, 142.9, 147.7; HRMS (FAB): *m/z* calcd for C₂₁H₂₄N₃S [M + H]⁺ 350.1691; found: 350.1683.

Compound 25l. Using the general procedure as described for **25a**, compound **22l** (25.1 mg, 0.07 mmol) was allowed to react for 1 h with TFA (1.0 mL) and MS4Å (105 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (8:2) gave the title compound **25l** as pale yellow solid (19.4 mg, 92 %): mp 122–124 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1619 (C=N), 1567 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.97–2.02 (2H, m, CH₂), 3.72 (2H, t, *J* = 5.4 Hz, CH₂), 4.04 (2H, t, *J* = 6.3 Hz, CH₂), 7.25–7.26 (1H, m, Ar), 7.37–7.40 (1H, m, Ar), 7.43–7.47 (3H, m, Ar), 7.58 (2H, d, *J* = 7.4 Hz, Ar), 8.29 (1H, d, *J* = 8.6 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.1, 43.8, 45.0, 121.8, 121.8, 125.1, 125.5, 127.0 (2C), 128.2, 128.9 (2C), 129.4, 139.2, 143.5, 146.5, 153.4; HRMS (FAB): *m/z* calcd for C₁₇H₁₆N₃S [M + H]⁺ 294.1065; found: 294.1069.

3.1.19 Synthesis of 3,4-Dihydro-9-vinyl-2H, 6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (25m)

N-(*tert*-Butyl)-3,4-dihydro-9-vinyl-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (**22m**). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (528.4 mg, 1.5 mmol) was allowed to react with vinylboronic acid pinacol ester (0.305 mL, 1.8 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **22m** as

colorless solid (455.7 mg, > 99 %): mp 67–68 °C (from *n*-hexane); IR (neat) cm^{-1} : 1589 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.39 (9H, s, $3 \times \text{CH}_3$), 1.88–1.94 (2H, m, CH_2), 3.62 (2H, t, $J = 5.6$ Hz, CH_2), 3.87 (2H, t, $J = 6.1$ Hz, CH_2), 5.33 (1H, d, $J = 11.0$ Hz, CH), 5.79 (1H, d, $J = 17.6$ Hz, CH), 6.64 (1H, dd, $J = 17.6, 11.0$ Hz, CH), 7.12 (1H, d, $J = 1.7$ Hz, Ar), 7.23 (1H, dd, $J = 8.3, 1.7$ Hz, Ar), 8.14 (1H, d, $J = 8.3$ Hz, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.1, 45.4, 54.1, 115.9, 122.1, 123.7, 127.0, 128.6, 129.3, 135.4, 138.3, 139.3, 147.7; HRMS (FAB): m/z calcd for $\text{C}_{17}\text{H}_{22}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 300.1534; found: 300.1536.

Compound 25m. Using the general procedure as described for **25a**, compound **22m** (60.4 mg, 0.2 mmol) was allowed to react for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (8:2) gave the title compound **25m** as colorless solid (42.1 mg, 87 %): mp 76–77 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1618 (C=N), 1564 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.95–2.01 (2H, m, CH_2), 3.69 (2H, t, $J = 5.4$ Hz, CH_2), 4.02 (2H, t, $J = 6.1$ Hz, CH_2), 5.36 (1H, d, $J = 10.9$ Hz, CH), 5.81 (1H, d, $J = 17.7$ Hz, CH), 6.65 (1H, dd, $J = 17.7, 10.9$ Hz, CH), 7.04 (1H, s, Ar), 7.20 (1H, br s, NH), 7.26–7.28 (1H, m, Ar), 8.17 (1H, d, $J = 8.5$ Hz, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 21.0, 43.8, 44.9, 116.4, 121.1, 124.0, 125.8, 129.0 (2C), 135.2, 139.8, 146.4, 153.3; HRMS (FAB): m/z calcd for $\text{C}_{13}\text{H}_{14}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 244.0908; found: 244.0911.

3.1.20 Synthesis of 3,4-Dihydro-9-styryl-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (25n)

***N*-(*tert*-Butyl)-3,4-dihydro-9-styryl-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (22n).** Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with styrylboronic acid pinacol ester (41.4 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **22n** as colorless solid (50.9 mg, 90 %): mp 124.5–125 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1590 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.40 (9H, s, $3 \times \text{CH}_3$), 1.88–1.94 (2H, m, CH_2), 3.63 (2H, t, $J = 5.5$ Hz, CH_2), 3.87 (2H, t, $J = 6.1$ Hz, CH_2), 7.01 (1H, d, $J = 16.3$ Hz, CH), 7.14 (1H, d, $J = 16.3$ Hz, CH), 7.22 (1H, d, $J = 1.7$ Hz, Ar), 7.27–7.38 (4H, m, Ar), 7.50 (2H, d, $J = 7.3$ Hz, Ar), 8.17 (1H, d, $J = 8.3$ Hz, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 122.2, 124.0, 126.6, 126.7 (2C), 127.0, 128.1, 128.7 (2C), 128.8, 129.4, 130.7, 136.8, 138.3, 139.2, 147.7; HRMS (FAB): m/z calcd for $\text{C}_{23}\text{H}_{26}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 376.1847; found: 376.1845.

Compound 25n. Using the general procedure as described for **25a**, compound **22n** (31.7 mg, 0.084 mmol) was allowed to react for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title

compound **25n** as colorless solid (20.2 mg, 75 %): mp 111–113 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1618 (C=N), 1567 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.94–2.00 (2H, m, CH₂), 3.69 (2H, t, *J* = 5.6 Hz, CH₂), 4.02 (2H, t, *J* = 6.2 Hz, CH₂), 7.00 (1H, d, *J* = 16.3 Hz, CH), 7.12–7.16 (2H, m, CH, Ar), 7.20 (1H, br s, NH), 7.26–7.30 (1H, m, Ar), 7.34–7.38 (3H, m, Ar), 7.50 (2H, d, *J* = 7.6 Hz, Ar), 8.20 (1H, d, *J* = 8.5 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.0, 43.8, 45.0, 121.2, 124.2, 125.5, 126.6, 126.7 (2C), 128.2, 128.7 (2C), 129.1, 129.2, 131.1, 136.6, 139.7, 146.4, 153.3; *Anal.* calcd for C₁₉H₁₇N₃S: C, 71.44; H, 5.36; N, 13.15. Found: C, 71.17; H, 5.24; N, 13.07.

3.1.21 Synthesis of 3,4-Dihydro-9-pentenyl-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**25o**)

N-(*tert*-Butyl)-3,4-dihydro-9-pentenyl-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**22o**). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with pentenylboronic acid pinacol ester (35.2 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **22o** as a colorless oil (44.2 mg, 86 %): IR (neat) cm⁻¹: 1590 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 0.95 (t, *J* = 7.4 Hz, 3H, CH₃), 1.38 (9H, s, 3 × CH₃), 1.46–1.54 (2H, m, CH₂), 1.87–1.93 (2H, m, CH₂), 2.16–2.21 (2H, m, CH₂), 3.61 (2H, t, *J* = 5.6 Hz, CH₂), 3.86 (2H, t, *J* = 6.2 Hz, CH₂), 6.29–6.30 (2H, m, 2 × CH), 7.05 (1H, d, *J* = 1.7 Hz, Ar), 7.17 (1H, dd, *J* = 8.3, 1.7 Hz, Ar), 8.10 (1H, d, *J* = 8.3 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 13.7, 21.9, 22.3, 30.0 (3C), 35.1, 45.1, 45.4, 54.1, 121.6, 123.6, 126.0, 128.5, 128.6, 129.1, 133.4, 138.5, 139.8, 147.8; HRMS (FAB): *m/z* calcd for C₂₀H₂₈N₃S [M + H]⁺ 342.2004; found: 342.2007.

Compound 25o. Using the general procedure as described for **25a**, compound **22o** (40.0 mg, 0.12 mmol) was allowed to react for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (8:2) gave the title compound **25o** as a colorless oil (31.9 mg, 95 %): IR (neat) cm⁻¹: 1619 (C=N), 1568 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 0.95 (3H, t, *J* = 7.4 Hz, CH₃), 1.45–1.54 (2H, m, CH₂), 1.93–1.99 (2H, m, CH₂), 2.17–2.22 (2H, m, CH₂), 3.68 (2H, t, *J* = 5.5 Hz, CH₂), 4.01 (2H, t, *J* = 6.2 Hz, CH₂), 6.29–6.31 (2H, m, 2 × CH), 6.96 (1H, d, *J* = 1.7 Hz, Ar), 7.16 (1H, br s, NH), 7.19 (1H, dd, *J* = 8.5, 1.7 Hz, Ar), 8.13 (1H, d, *J* = 8.5 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 13.7, 21.0, 22.3, 35.1, 43.8, 44.9, 120.6, 123.8, 124.9, 128.3, 128.9, 129.0, 133.9, 140.3, 146.5, 153.5; HRMS (FAB): *m/z* calcd for C₁₆H₂₀N₃S [M + H]⁺ 286.1378; found: 286.1376.

3.1.22 Synthesis of 9-Azido-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (25p)

9-Azido-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (22p). To a solution of 9-amino-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **28** (100.9 mg, 0.35 mmol) in AcOH (2 mL) and H₂O (1 mL) was added NaNO₂ (33.8 mg, 0.49 mmol) at 0 °C, and the stirring was continued for 1 h. NaN₃ (34.1 mg, 0.53 mmol) was added to the reaction mixture, and stirring was continued for 30 min at rt. Reaction mixture was neutralized with K₂CO₃, and the whole was extracted with CHCl₃, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) to give the title compound **22p** as pale yellow solid (77.3 mg, 70 %): mp 79–80 °C (from *n*-hexane); IR (neat) cm⁻¹: 2104 (N₃), 1592 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.38 (9H, s, 3 × CH₃), 1.88–1.94 (2H, m, CH₂), 3.60 (2H, t, *J* = 5.6 Hz, CH₂), 3.86 (2H, t, *J* = 6.2 Hz, CH₂), 6.74 (1H, d, *J* = 2.3 Hz, Ar), 6.84 (1H, dd, *J* = 8.5, 2.3 Hz, Ar), 8.19 (1H, d, *J* = 8.5 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.8, 30.0 (3C), 45.0, 45.4, 54.2, 114.2, 116.8, 124.5, 130.3, 130.9, 137.4, 142.0, 147.1; HRMS (FAB): *m/z* calcd for C₁₅H₁₉N₆S [M + H]⁺ 315.1392; found: 315.1398.

Compound 25p. Using the general procedure as described for **25a**, compound **22p** (77.3 mg, 0.25 mmol) was allowed to react for 2 h with TFA (3.5 mL) and MS4 Å (525 mg). Purification by recrystallization from MeOH–Et₂O gave the title compound **25p** as pale yellow crystals (27.0 mg, 42 %): mp 120–121 °C; IR (neat) cm⁻¹: 2107 (N₃), 1615 (C=N), 1569 (C=N); ¹H-NMR (400 MHz, DMSO-*d*₆) δ: 1.82–1.88 (2H, m, CH₂), 3.56 (2H, t, *J* = 5.5 Hz, CH₂), 3.89 (2H, t, *J* = 5.4 Hz, CH₂), 6.97 (1H, dd, *J* = 8.8, 2.4 Hz, Ar), 7.03 (1H, d, *J* = 2.4 Hz, Ar), 8.17 (1H, d, *J* = 8.8 Hz, Ar), 8.76 (1H, s, NH); ¹³C-NMR (100 MHz, DMSO-*d*₆) δ: 20.6, 43.1, 44.2, 113.7, 117.0, 122.6, 130.2, 130.8, 141.9, 144.7, 150.0; *Anal.* calcd for C₁₁H₁₀N₆S: C, 51.15; H, 3.90; N, 32.54. Found: C, 51.07; H, 3.88; N, 32.28.

3.1.23 Synthesis of 9-(4-Benzoylphenyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (25q)

9-(4-Benzoylphenyl)-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (22q). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 4-benzoylphenylboronic acid (40.7 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (8:2) gave the title compound **22q** as colorless solid (55.6 mg, 82 %): mp 187–189 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1656 (C=O), 1593 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.41 (9H, s, 3 × CH₃), 1.91–1.97 (2H, m, CH₂), 3.65 (2H, t, *J* = 5.5 Hz, CH₂), 3.90 (2H, t, *J* = 6.1 Hz, CH₂), 7.39 (1H, d, *J* = 1.7 Hz, Ar), 7.46–7.53 (3H, m, Ar), 7.60 (1H,

t, $J = 7.4$ Hz, Ar), 7.70 (2H, d, $J = 8.0$ Hz, Ar), 7.82 (2H, d, $J = 7.3$ Hz, Ar), 7.88 (2H, d, $J = 8.0$ Hz, Ar), 8.30 (1H, d, $J = 8.3$ Hz, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.2, 45.4, 54.2, 123.0, 124.8, 126.9 (2C), 127.4, 128.3 (2C), 129.1, 129.9, 130.0 (2C), 130.7 (2C), 132.5, 136.9, 137.6, 137.9, 141.7, 143.3, 147.6, 196.1; HRMS (FAB): m/z calcd for $\text{C}_{28}\text{H}_{28}\text{N}_3\text{OS}$ $[\text{M} + \text{H}]^+$ 454.1953; found: 454.1954.

Compound 25q. Using the general procedure as described for **25a**, compound **22q** (30.4 mg, 0.067 mmol) was allowed to react for 1 h with TFA (1.0 mL) and MS4 Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **25q** as colorless solid (16.7 mg, 63 %): mp 155–156 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1655 (C=O), 1619 (C=N), 1561 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.97–2.03 (2H, m, CH_2), 3.72 (2H, t, $J = 5.5$ Hz, CH_2), 4.05 (2H, t, $J = 6.1$ Hz, CH_2), 7.30 (1H, d, $J = 1.7$ Hz, Ar), 7.48–7.52 (3H, m, Ar), 7.59–7.63 (1H, m, Ar), 7.68 (2H, d, $J = 8.3$ Hz, Ar), 7.81–7.83 (2H, m, Ar), 7.89 (2H, d, $J = 8.3$ Hz, Ar), 8.32 (1H, d, $J = 8.5$ Hz, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.0, 43.8, 45.0, 122.0, 125.1, 126.2, 126.9 (2C), 128.3 (2C), 129.5, 129.6, 130.0 (2C), 130.7 (2C), 132.5, 137.1, 137.5, 142.2, 143.0, 146.3, 153.0, 196.0; HRMS (FAB): m/z calcd for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{OS}$ $[\text{M} + \text{H}]^+$ 398.1327; found: 398.1333.

3.1.24 Synthesis of 10-(*N,N*-Dimethylamino)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (26a)

***N*-(*tert*-Butyl)-10-(*N,N*-dimethylamino)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (23a).** To a mixture of 10-bromo-*N*-(*tert*-butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **23k** (600.2 mg, 1.70 mmol) and $\text{Pd}(\text{Pt-Bu}_3)_2$ (174.2 mg, 0.341 mmol) and $\text{KO}t\text{-Bu}$ (573.3 mg, 5.11 mmol) in toluene (1.7 mL) was added 2.0 M Me_2NH in THF (2.55 mL, 5.11 mmol). The reaction was heated using a microwave reactor (standard mode) for 10 min at 170 °C. The whole was extracted with EtOAc. The extract was washed with brine, and dried over Na_2SO_4 . After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (6:4 to 5:5) to give the title compound **23a** as pale yellow solid (363.3 mg, 67.4 %): mp 86.1 °C; IR (neat) cm^{-1} : 1583 (C=N); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.38 (9H, s, 3 \times CH_3), 1.86–1.94 (2H, m, CH_2), 2.97 (6H, s, 2 \times CH_3), 3.61 (2H, t, $J = 5.3$ Hz, CH_2), 3.86 (2H, t, $J = 6.3$ Hz, CH_2), 6.78 (1H, dd, $J = 9.0$, 3.0 Hz, Ar), 6.98 (1H, d, $J = 8.4$ Hz, Ar), 7.56 (1H, d, $J = 2.4$ Hz, Ar); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : 22.0, 29.9 (3C), 40.8 (2C), 45.1, 45.5, 54.0, 111.6, 115.4, 115.8, 125.3, 128.7, 139.7, 148.8, 149.3; HRMS (FAB): m/z calcd for $\text{C}_{17}\text{H}_{25}\text{N}_4\text{S}$ $[\text{M} + \text{H}]^+$ 317.1800; found: 317.1796.

Compound 26a. TFA (0.63 mL) was added to a mixture of **23a** (20 mg, 0.063 mmol) and MS4Å (110 mg, powder, activated by heating with Bunsen burner) in small amount of CHCl₃. After being stirred under reflux for 40 min, the mixture was added dropwise to Et₃N at 0 °C to adjust pH to 8–9. The whole was extracted with EtOAc. The extract was washed with sat. NaHCO₃, brine, and dried over Na₂SO₄. After concentration, the residue was purified by preparative TLC over aluminum oxide with *n*-hexane–EtOAc (7:3) to give the title compound **26a** as yellow solid (11.4 mg, 68.3 %): mp 134.5 °C; IR (neat) cm⁻¹: 1617 (C=N), 1552 (C=N); ¹H-NMR (300 MHz, CDCl₃) δ: 1.92–2.00 (2H, m, CH₂), 2.97 (6H, s, 2 × CH₃), 3.68 (2H, t, *J* = 5.7 Hz, CH₂), 4.01 (2H, t, *J* = 6.3 Hz, CH₂), 6.79 (1H, dd, *J* = 8.7, 3.3 Hz, Ar), 6.89 (1H, d, *J* = 8.7 Hz, Ar), 7.08 (1H, br s, NH), 7.58 (1H, d, *J* = 2.7 Hz, Ar); ¹³C-NMR (75 MHz, CDCl₃) δ: 20.8, 40.6 (2C), 44.1, 44.3, 111.8, 114.6, 116.3, 124.6, 126.3, 148.7, 149.4, 154.4; *Anal.* calcd for C₁₃H₁₆N₄S: C, 59.97; H, 6.19; N, 21.52. Found: C, 59.91; H, 6.19; N, 21.41.

3.1.25 Synthesis of 3,4-Dihydro-10-nitro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**26e**)

***N*-(*tert*-Butyl)-3,4-dihydro-10-nitro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**23e**).** To a mixture of 2-(2-bromo-5-nitrophenyl)-1,4,5,6-tetrahydropyrimidine **19e** (50 mg, 0.209 mmol) in DMAc (0.70 mL) were added *tert*-butylisothiocyanate (0.053 mL, 0.418 mmol) and KO^{*t*}-Bu (46.9 mg, 0.418 mmol) at 0 °C under an N₂ atmosphere. After being stirred at 0 °C for 1 h, sat. NH₄Cl was added. The whole was extracted with EtOAc. The extract was washed with brine, and dried over Na₂SO₄. After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (1:0 to 9:1) to give the title compound **23e** as pale yellow solid (39.1 mg, 58.9 %): mp 123.8 °C; IR (neat) cm⁻¹: 1593 (NO₂), 1520 (NO₂); ¹H-NMR (300 MHz, CDCl₃) δ: 1.40 (s, 9H, 3 × CH₃), 1.90–1.98 (2H, m, CH₂), 3.67 (2H, t, *J* = 5.6 Hz, CH₂), 3.89 (2H, t, *J* = 6.3 Hz, CH₂), 7.23 (1H, m, Ar), 8.13 (1H, dd, *J* = 8.7, 2.7 Hz, Ar), 9.11 (1H, d, *J* = 2.7 Hz, Ar); ¹³C-NMR (75 MHz, CDCl₃) δ: 21.7, 30.0 (3C), 45.1, 45.5, 54.5, 124.1, 124.3, 125.3, 128.5, 135.6, 137.1, 145.8, 146.1; HRMS (FAB): *m/z* calcd for C₁₅H₁₉N₄O₂S [M + H]⁺ 319.1229; found: 319.1232.

Compound 26e. TFA (3.2 mL) was added to compound **23e** (100 mg, 0.314 mmol). After being stirred under reflux for 1.5 h, the mixture was added dropwise to Et₃N at 0 °C to adjust pH to 8–9. The whole was extracted with EtOAc. The extract was washed with sat. NaHCO₃, brine, and dried over Na₂SO₄. After concentration, the residue was purified by preparative TLC over aluminum oxide with *n*-hexane–EtOAc (7:3) to give the title compound **26e** as orange solid (15.9 mg, 19.3 %): mp 167.9 °C; IR (neat) cm⁻¹: 1614 (C=N), 1576 (NO₂), 1557 (C=N), 1519 (NO₂); ¹H-NMR (300 MHz, CDCl₃) δ: 1.97–2.04 (2H, m, CH₂), 3.74 (2H, t, *J* = 5.6 Hz, CH₂), 4.05 (2H, t, *J* = 6.2 Hz, CH₂), 7.19 (1H, d, *J* = 9.0 Hz,

Ar), 7.38 (1H, br s, NH), 8.17 (1H, dd, $J = 8.7, 2.7$ Hz, Ar), 9.13 (1H, d, $J = 2.7$ Hz, Ar); ^{13}C -NMR (75 MHz, CDCl_3) δ : 20.8, 44.1, 44.9, 124.5 (2C), 124.8, 127.6, 136.7, 144.5, 146.3, 151.0; HRMS (FAB): m/z calcd for $\text{C}_{11}\text{H}_{11}\text{N}_4\text{O}_2\text{S} [\text{M} + \text{H}]^+$ 263.0603; found: 263.0606. The purity of the compound was 75 % by HPLC.

3.1.26 Synthesis of 3,4-Dihydro-10-methoxy-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (26f)

***N*-(*tert*-Butyl)-3,4-dihydro-10-methoxy-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (23f).** To a mixture of *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (500.3 mg, 1.42 mmol) and NaOMe (767 mg, 14.2 mmol, 28 % solution in MeOH,) in DMF (2.5 mL) was added CuBr (20.4 mg, 0.142 mmol). The mixture was stirred at 110 °C for 2.5 h. The whole was extracted with CH_2Cl_2 . The extract was washed with brine, and dried over Na_2SO_4 . After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (6:4 to 4:6) to give the title compound **23f** as colorless solid (171.5 mg, 39.8 %): mp 87.1 °C; IR (neat) cm^{-1} : 1588 (C=N); ^1H -NMR (300 MHz, CDCl_3) δ : 1.38 (9H, s, 3 \times CH_3), 1.87–1.95 (2H, m, CH_2), 3.62 (2H, t, $J = 5.6$ Hz, CH_2), 3.86 (5H, m, CH_3 , CH_2), 6.92 (1H, dd, $J = 8.7, 2.7$ Hz, Ar), 7.00 (1H, d, $J = 8.4$ Hz, Ar), 7.75 (1H, d, $J = 3.3$ Hz, Ar); ^{13}C -NMR (75 MHz, CDCl_3) δ : 21.9, 29.9 (3C), 45.1, 45.5, 54.1, 55.6, 111.3, 118.9, 120.2, 125.7, 128.9, 138.8, 148.1, 158.1; *Anal.* calcd for $\text{C}_{16}\text{H}_{21}\text{N}_3\text{OS}$: C, 63.33; H, 6.98; N, 13.85. Found: C, 63.04; H, 6.97; N, 13.68.

Compound 26f. TFA (0.88 mL) was added to compound **23f** (26.7 mg, 0.088 mmol). After being stirred under reflux for 3 h, the mixture was added dropwise to Et_3N at 0 °C to adjust pH to 8–9. The whole was extracted with EtOAc. The extract was washed with sat. NaHCO_3 , brine, and dried over Na_2SO_4 . After concentration, the residue was purified by preparative TLC over aluminum oxide with *n*-hexane–EtOAc (7:3) to give the title compound **26f** as colorless solid (9.6 mg, 44 %): mp 89.0 °C; IR (neat) cm^{-1} : 1614 (C=N), 1562 (C=N); ^1H -NMR (300 MHz, CDCl_3) δ : 1.93–2.00 (2H, m, CH_2), 3.69 (2H, t, $J = 5.4$ Hz, CH_2), 3.85 (3H, s, CH_3), 4.02 (2H, t, $J = 6.2$ Hz, CH_2), 6.92–6.98 (2H, m, Ar), 7.15 (1H, br s, NH), 7.78 (1H, s, Ar); ^{13}C -NMR (75 MHz, CDCl_3) δ : 21.0, 43.9, 44.9, 55.6, 111.9, 119.3, 119.9, 124.8, 127.9, 146.7, 153.9, 158.3; *Anal.* calcd for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{OS}$: C, 58.28; H, 5.30; N, 16.99. Found: C, 58.24; H, 5.36; N, 16.46. The purity of the compound was 92 % by HPLC.

3.1.27 Synthesis of 3,4-Dihydro-10-methyl-2H, 6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (26g)

2-(2-Fluoro-5-methylphenyl)-1,4,5,6-tetrahydropyrimidine (19g). 2-Fluoro-5-methylbenzaldehyde 16g (3.0 g, 21.7 mmol) was subjected to the general procedure as described for **18j** to give the title **19g** as colorless crystals (3.1 g, 75 %): mp 119–121 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1626 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.84–1.89 (2H, m, CH₂), 2.31 (3H, s, CH₃), 3.51 (4H, t, *J* = 5.7 Hz, 2 × CH₂), 5.01 (1H, s, NH), 6.92 (1H, dd, *J* = 11.7, 8.3 Hz, Ar), 7.09–7.12 (1H, m, Ar), 7.63 (1H, dd, *J* = 7.4, 2.3 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 20.5, 20.7, 42.3 (2C), 115.6 (d, *J* = 24.0 Hz), 123.7 (d, *J* = 12.0 Hz), 130.6 (d, *J* = 3.6 Hz), 131.3 (d, *J* = 9.6 Hz), 133.9 (d, *J* = 3.6 Hz), 151.7, 158.4 (d, *J* = 244.7 Hz); ¹⁹F-NMR (500 MHz, CDCl₃) δ: -122.4; HRMS (FAB): *m/z* calcd for C₁₁H₁₄FN₂ [M + H]⁺ 193.1141; found: 193.1140.

***N*-(*tert*-Butyl)-3,4-dihydro-10-methyl-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (23g).** To a mixture of compound **19g** (0.50 g, 2.6 mmol) and KO^{*t*}-Bu (0.58 g, 5.2 mmol) in DMAc (8.7 mL) was added *tert*-butylisothiocyanate (0.66 mL, 5.2 mmol) under an Ar atmosphere. After being stirred at 80 °C for 3 h, the whole was extracted with EtOAc. The whole was washed with sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (1:1) to give the title compound **23g** as colorless solid (0.21 g, 28 %): mp 76–77 °C (from *n*-hexane); IR (neat) cm⁻¹: 1597 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.38 (9H, s, 3 × CH₃), 1.88–1.94 (2H, m, CH₂), 2.33 (3H, s, CH₃), 3.62 (2H, t, *J* = 5.6 Hz, CH₂), 3.87 (2H, t, *J* = 6.2 Hz, CH₂), 7.00 (1H, d, *J* = 8.0 Hz, Ar), 7.13 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 8.01 (1H, d, *J* = 1.3 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.0, 22.0, 29.9 (3C), 45.1, 45.4, 54.1, 124.4, 125.7, 127.6, 128.6, 131.1, 135.9, 138.7, 148.2; HRMS (FAB): *m/z* calcd for C₁₆H₂₂N₃S [M + H]⁺ 288.1534; found: 288.1535.

Compound 26g. Using the general procedure as described for **25a**, compound **23g** (200 mg, 0.7 mmol) was allowed to react for 1 h with TFA (3.0 mL) and MS4Å (450 mg). Purification by preparative TLC over aluminum oxide with *n*-hexane–EtOAc (9:1) gave the title compound **26g** as colorless solid (150 mg, 92 %): mp 116 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1623 (C=N), 1556 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.94–2.00 (2H, m, CH₂), 2.34 (3H, s, CH₃), 3.69 (2H, t, *J* = 5.6 Hz, CH₂), 4.01 (2H, t, *J* = 6.1 Hz, CH₂), 6.94 (1H, d, *J* = 8.0 Hz, Ar), 7.15–7.17 (2H, m, Ar, NH), 8.04 (1H, s, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.0, 21.1, 43.8, 44.9, 123.5, 125.4, 126.5, 129.0, 131.6, 136.3, 146.9, 153.7; HRMS (FAB): *m/z* calcd for C₁₂H₁₄N₃S [M + H]⁺ 232.0908; found: 232.0913.

3.1.28 Synthesis of 10-Bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (26k)

2-(5-Bromo-2-fluorophenyl)-1,4,5,6-tetrahydropyrimidine (19k). 5-Bromo-2-fluorobenzaldehyde 16k (1.02 g, 5.0 mmol) was subjected to the general procedure as described for **18j** to give the title compound **19k** as colorless crystals (1.02 g, 79 %): mp 121–122 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1623 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.83–1.89 (2H, m, CH₂), 3.50 (4H, t, *J* = 5.7 Hz, 2 × CH₂), 5.28 (1H, br s, NH), 6.94 (1H, dd, *J* = 11.1, 8.8 Hz, Ar), 7.42 (1H, ddd, *J* = 8.8, 4.4, 2.7 Hz, Ar), 7.97 (1H, dd, *J* = 6.8, 2.7 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 20.6, 42.1 (2C), 117.1 (d, *J* = 3.3 Hz), 117.7 (d, *J* = 25.7 Hz), 126.2 (d, *J* = 13.2 Hz), 133.3 (d, *J* = 3.3 Hz), 133.6 (d, *J* = 9.1 Hz), 150.3, 159.1 (d, *J* = 247.5 Hz); ¹⁹F-NMR (500 MHz, CDCl₃) δ: –119.5; *Anal.* calcd for C₁₀H₁₀BrFN₂: C, 46.72; H, 3.92; N, 10.90. Found: C, 46.59; H, 3.87; N, 10.89.

10-Bromo-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (23k). Using the general procedure as described for 22e, compound 19k (257.1 mg, 1.00 mmol) was allowed to react at rt overnight. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **23k** as colorless solid (111.6 mg, 32 %): mp 93–94 °C (from *n*-hexane); IR (neat) cm⁻¹: 1599 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.38 (9H, s, 3 × CH₃), 1.88–1.93 (2H, m, CH₂), 3.62 (2H, t, *J* = 5.6 Hz, CH₂), 3.86 (2H, t, *J* = 6.1 Hz, CH₂), 6.97 (1H, d, *J* = 8.5 Hz, Ar), 7.41 (1H, dd, *J* = 8.5, 2.2 Hz, Ar), 8.36 (1H, d, *J* = 2.2 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.8, 29.9 (3C), 45.1, 45.4, 54.2, 119.7, 125.9, 128.1, 129.3, 131.2, 133.0, 137.4, 146.7; *Anal.* calcd for C₁₅H₁₈BrN₃S: C, 51.14; H, 5.15; N, 11.93. Found: C, 51.09; H, 4.98; N, 11.89.

Compound 26k. Using the general procedure as described for 25a, compound 23k (52.8 mg, 0.15 mmol) was allowed to react for 2 h with TFA (1.5 mL) and MS4Å (225 mg). Purification by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) gave the title compound **26k** as colorless crystals (39.7 mg, 89 %): mp 106–107 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1621 (C=N), 1571 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.94–1.99 (2H, m, CH₂), 3.69 (2H, t, *J* = 5.4 Hz, CH₂), 4.01 (2H, t, *J* = 6.3 Hz, CH₂), 6.91 (1H, d, *J* = 8.6 Hz, Ar), 7.20 (1H, br s, NH), 7.44 (1H, dd, *J* = 8.6, 2.3 Hz, Ar), 8.39 (1H, d, *J* = 2.3 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 20.9, 43.8, 44.9, 120.0, 125.0, 127.8, 128.3, 131.6, 133.5, 145.4, 152.5; *Anal.* calcd for C₁₁H₁₀BrN₃S: C, 44.61; H, 3.40; N, 14.19. Found: C, 44.51; H, 3.66; N, 14.06.

3.1.29 Synthesis of 3,4-Dihydro-10-phenyl-2H, 6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (26l)

N-(*tert*-Butyl)-3,4-dihydro-10-phenyl-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**23l**). Using the general procedure as described for **22l**, 10-bromo-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **23k** (52.8 mg, 0.15 mmol) was allowed to react for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **23l** as colorless solid (32.6 mg, 62 %): mp 101–103 °C (from *n*-hexane); IR (neat) cm^{-1} : 1594 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.40 (9H, s, 3 \times CH_3), 1.90–1.95 (2H, m, CH_2), 3.64 (2H, t, $J = 5.4$ Hz, CH_2), 3.89 (2H, t, $J = 6.0$ Hz, CH_2), 7.18 (1H, d, $J = 8.0$ Hz, Ar), 7.32 (1H, t, $J = 7.4$ Hz, Ar), 7.41 (2H, t, $J = 7.4$ Hz, Ar), 7.55 (1H, dd, $J = 8.0, 2.0$ Hz, Ar), 7.61 (2H, d, $J = 7.4$ Hz, Ar), 8.47 (1H, d, $J = 2.0$ Hz, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.1, 45.5, 54.2, 125.0, 126.9, 127.0 (2C), 127.4, 127.9, 128.1, 128.7 (2C), 128.7, 138.2, 139.1, 140.0, 147.9; HRMS (FAB): m/z calcd for $\text{C}_{21}\text{H}_{24}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 350.1691; found:350.1683.

Compound 26l. Using the general procedure as described for **25a**, compound **23l** (13.1 mg, 0.037 mmol) was allowed to react for 2 h with TFA (1.0 mL) and MS4\AA (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) gave the title compound **26l** as colorless solid (8.4 mg, 77 %): mp 82 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1621 (C=N), 1550 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.95–2.01 (2H, m, CH_2), 3.71 (2H, t, $J = 5.6$ Hz, CH_2), 4.03 (2H, t, $J = 6.2$ Hz, CH_2), 7.10–7.44 (5H, m, Ar), 7.56–7.64 (3H, m, Ar), 8.50 (1H, d, $J = 2.2$ Hz, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.1, 43.9, 45.0, 124.0, 126.9, 127.1 (2C), 127.3, 127.6, 128.8 (2C), 129.2, 139.4, 139.8, 146.6, 152.1, 153.3; *Anal.* calcd for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{S}$: C, 69.59; H, 5.15; N, 14.32. Found: C, 69.61; H, 5.13; N, 14.22.

3.1.30 Synthesis of 3,4-Dihydro-10-vinyl-2H, 6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (26m)

N-(*tert*-Butyl)-3,4-dihydro-10-vinyl-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**23m**). Using the general procedure as described for **22l**, 10-bromo-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **23k** (52.8 mg, 0.15 mmol) was allowed to react with vinylboronic acid pinacol ester (0.031 mL, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **23m** as a colorless oil (30.5 mg, 68 %): IR (neat) cm^{-1} : 1595 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.38 (9H, s, 3 \times CH_3), 1.89–1.94 (2H, m, CH_2), 3.63 (2H, t, $J = 5.4$ Hz, CH_2), 3.87 (2H, t, $J = 6.0$ Hz, CH_2), 5.24 (1H, d, $J = 11.0$ Hz, CH), 5.77 (1H, d, $J = 17.6$ Hz, CH), 6.69 (1H, dd, $J = 17.6, 11.0$ Hz, CH), 7.07 (1H, d,

$J = 8.3$ Hz, Ar), 7.40 (1H, dd, $J = 8.3, 2.0$ Hz, Ar), 8.20 (1H, d, $J = 2.0$ Hz, Ar); ^{13}C -NMR (100 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.1, 45.4, 54.1, 114.1, 124.7, 126.6, 127.4, 127.8, 128.2, 135.7, 135.9, 138.2, 147.9; HRMS (FAB): m/z calcd for $\text{C}_{17}\text{H}_{22}\text{N}_3\text{S}$ $[\text{M} + \text{H}]^+$ 300.1534; found: 300.1532.

Compound 26m. Using the general procedure as described for **25a**, compound **23m** (7.3 mg, 0.024 mmol) was allowed to react for 1 h with TFA (1.0 mL) and $\text{MS4}\text{\AA}$ (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) gave the title compound **26m** as colorless solid (3.7 mg, 62 %): mp 69–70 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1622 (C=N), 1550 (C=N); ^1H -NMR (400 MHz, CDCl_3) δ : 1.95–2.01 (2H, m, CH_2), 3.70 (2H, t, $J = 5.7$ Hz, CH_2), 4.02 (2H, t, $J = 6.2$ Hz, CH_2), 5.27 (1H, dd, $J = 10.7, 0.6$ Hz, CH), 5.79 (1H, dd, $J = 17.7, 0.6$ Hz, CH), 6.69 (1H, dd, $J = 17.7, 10.7$ Hz, CH), 7.00 (1H, d, $J = 8.3$ Hz, Ar), 7.19 (1H, br s, NH), 7.42 (1H, dd, $J = 8.3, 2.0$ Hz, Ar), 8.23 (1H, d, $J = 2.0$ Hz, Ar); ^{13}C -NMR (100 MHz, CDCl_3) δ : 21.0, 43.8, 44.9, 114.5, 123.8, 126.8, 126.9, 127.8, 127.9, 135.6, 135.9, 146.5, 153.2; HRMS (FAB): m/z calcd for $\text{C}_{13}\text{H}_{14}\text{N}_3\text{S}$ $[\text{M} + \text{H}]^+$ 244.0908; found: 244.0902.

3.1.31 Synthesis of 10-(4-Benzoylphenyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (26q)

10-(4-Benzoylphenyl)-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (23q). Using the general procedure as described for **22l**, 10-bromo-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **23k** (52.8 mg, 0.15 mmol) was allowed to react with 4-benzoylphenylboronic acid (40.7 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (8:2) gave the title compound **23q** as colorless solid (65.1 mg, 96 %): mp 192–193 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1654 (C=O), 1592 (C=N); ^1H -NMR (400 MHz, CDCl_3) δ : 1.41 (9H, s, $3 \times \text{CH}_3$), 1.91–1.96 (2H, m, CH_2), 3.65 (2H, t, $J = 5.5$ Hz, CH_2), 3.90 (2H, t, $J = 6.1$ Hz, CH_2), 7.39 (1H, d, $J = 1.7$ Hz, Ar), 7.46–7.52 (3H, m, Ar), 7.58–7.62 (1H, m, Ar), 7.70 (2H, d, $J = 8.5$ Hz, Ar), 7.82 (2H, dd, $J = 8.3, 1.2$ Hz, Ar), 7.88 (2H, d, $J = 8.5$ Hz, Ar), 8.30 (1H, d, $J = 8.5$ Hz, Ar); ^{13}C -NMR (125 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 123.0, 124.8, 126.9 (2C), 127.3, 128.3 (2C), 129.1, 129.8, 130.0 (2C), 130.7 (2C), 132.5, 136.9, 137.6, 137.9, 141.6, 143.3, 147.5, 196.1; HRMS (FAB): m/z calcd for $\text{C}_{28}\text{H}_{28}\text{N}_3\text{OS}$ $[\text{M} + \text{H}]^+$ 454.1953; found: 454.1952.

Compound 26q. Using the general procedure as described for **25a**, compound **23q** (36.2 mg, 0.08 mmol) was allowed to react for 1 h with TFA (1.0 mL) and $\text{MS4}\text{\AA}$ (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **26q** as colorless solid (23.4 mg, 74 %): mp 163–165 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1654 (C=O),

1622 (C=N), 1561 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.97–2.03 (2H, m, CH_2), 3.72 (2H, t, $J = 5.6$ Hz, CH_2), 4.05 (2H, t, $J = 6.2$ Hz, CH_2), 7.15 (1H, d, $J = 8.0$ Hz, Ar), 7.48–7.52 (2H, m, Ar), 7.58–7.64 (2H, m, Ar), 7.73 (2H, d, $J = 8.5$ Hz, Ar), 7.82 (2H, dd, $J = 8.2, 1.3$ Hz, Ar), 7.88 (2H, d, $J = 8.5$ Hz, Ar), 8.57 (1H, d, $J = 2.0$ Hz, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.0, 43.9, 45.0, 124.3, 126.7 (2C), 127.2, 127.6, 128.3 (2C), 128.8, 129.2, 130.0 (2C), 130.7 (2C), 132.4, 136.5, 137.7, 138.0, 143.7, 146.3, 152.9, 196.1; HRMS (FAB): m/z calcd for $\text{C}_{24}\text{H}_{20}\text{N}_3\text{OS}$ [$\text{M} + \text{H}$] $^+$ 398.1327; found: 398.1327.

3.1.32 Synthesis of 11-Fluoro-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (27i)

2-(2,6-Difluorophenyl)-1,4,5,6-tetrahydropyrimidine (20i). 2,6-Difluorobenzaldehyde **17i** (1.00 g, 7.04 mmol) was subjected to the general procedure as described for **18j** to give the title compound **20i** as colorless crystals (1.08 g, 78 %): mp 165–166 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1620 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.85–1.90 (2H, m, CH_2), 3.47 (4H, t, $J = 5.7$ Hz, $2 \times \text{CH}_2$), 4.77 (1H, br s, NH), 6.86–6.91 (2H, m, Ar), 7.24–7.30 (1H, m, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 20.5, 42.2 (2C), 111.4–111.6 (m, 2C), 115.9 (t, $J = 20.3$ Hz), 130.1 (t, $J = 9.9$ Hz), 146.8, 160.3 (dd, $J = 250.3, 7.0$ Hz, 2C). $^{19}\text{F-NMR}$ (500 MHz, CDCl_3) δ : –114.4; *Anal.* calcd for $\text{C}_{10}\text{H}_{10}\text{F}_2\text{N}_2$: C, 61.22; H, 5.14; N, 14.28. Found: C, 61.23; H, 5.13; N, 14.26.

***N*-(*tert*-Butyl)-11-fluoro-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (24i).** Using the general procedure as described for **22e**, compound **20i** (196.2 mg, 1.0 mmol) was allowed to react at rt overnight. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **24i** as colorless solid (212.6 mg, 73 %): mp 81 °C (from *n*-hexane); IR (neat) cm^{-1} : 1592 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.37 (9H, s, $3 \times \text{CH}_3$), 1.90–1.95 (2H, m, CH_2), 3.66 (2H, t, $J = 5.7$ Hz, CH_2), 3.80 (2H, t, $J = 6.6$ Hz, CH_2), 6.94–6.99 (2H, m, Ar), 7.23–7.26 (1H, m, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 22.5, 30.1 (3C), 45.3, 45.5, 54.2, 115.0 (d, $J = 24.0$ Hz), 118.7, 120.9 (d, $J = 3.6$ Hz), 130.6 (d, $J = 10.8$ Hz), 131.9, 137.6, 146.1 (d, $J = 8.4$ Hz), 160.2 (d, $J = 260.3$ Hz); $^{19}\text{F-NMR}$ (500 MHz, CDCl_3) δ : –110.8; HRMS (FAB): m/z calcd for $\text{C}_{15}\text{H}_{19}\text{FN}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 292.1284; found: 292.1288.

Compound 27i. Using the general procedure as described for **25a**, compound **24i** (58.3 mg, 0.20 mmol) was allowed to react for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) gave the title compound **27i** as colorless solid (42.3 mg, 90 %): mp 142.5 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1624 (C=N), 1585 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.97–2.02 (2H, m, CH_2), 3.73 (2H, t, $J = 5.2$ Hz, CH_2), 3.94 (2H, t, $J = 6.6$ Hz, CH_2), 6.91 (1H, d, $J = 8.0$ Hz, Ar), 6.97–7.01 (1H, m, Ar), 7.22 (1H, br s, NH), 7.27–7.31 (1H, m, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 21.7, 44.0,

45.5, 115.3 (d, $J = 24.0$ Hz), 117.4 (d, $J = 8.4$ Hz), 120.0 (d, $J = 3.6$ Hz), 131.2 (d, $J = 9.6$ Hz), 131.5, 144.8 (d, $J = 9.6$ Hz), 152.6 (d, $J = 4.8$ Hz), 160.5 (d, $J = 261.5$ Hz); ^{19}F -NMR (500 MHz, CDCl_3) δ : -110.0 . *Anal.* calcd for $\text{C}_{11}\text{H}_{10}\text{FN}_3\text{S}$: C, 56.15; H, 4.28; N, 17.86. Found: C, 56.05; H, 4.28; N, 17.71.

3.1.33 Synthesis of 8-Bromo-3,4-dihydro-2H, 6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (27k)

2-(3-Bromo-2-fluorophenyl)-1,4,5,6-tetrahydropyrimidine (20k). 3-Bromo-2-fluorobenzaldehyde 17k (0.71 g, 3.5 mmol) was subjected to the general procedure as described for **18j** to give the title compound **20k** as colorless crystals (0.62 g, 69 %): mp 99 °C; IR (neat) cm^{-1} : 1624 (C=N); ^1H -NMR (400 MHz, CDCl_3) δ : 1.84–1.89 (2H, m, CH_2), 3.50 (4H, t, $J = 5.7$ Hz, $2 \times \text{CH}_2$), 5.13 (1H, br s, NH), 7.03 (1H, td, $J = 8.0, 0.9$ Hz, Ar), 7.54 (1H, ddd, $J = 8.0, 6.4, 1.3$ Hz, Ar), 7.69 (1H, ddd, $J = 8.0, 6.5, 1.3$ Hz, Ar); ^{13}C -NMR (100 MHz, CDCl_3) δ : 20.6, 42.1 (2C), 109.6 (d, $J = 22.3$ Hz), 125.1 (d, $J = 4.1$ Hz), 126.3 (d, $J = 13.2$ Hz), 129.8 (d, $J = 3.3$ Hz), 134.3, 150.8, 156.3 (d, $J = 248.3$ Hz); ^{19}F -NMR (500 MHz, CDCl_3) δ : -110.7 ; *Anal.* calcd for $\text{C}_{10}\text{H}_{10}\text{BrFN}_2$: C, 46.72; H, 3.92; N, 10.90. Found: C, 46.64; H, 4.10; N, 10.93.

8-Bromo-N-(tertH,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (24k). Using the general procedure as described for **22e**, compound **20k** (257.1 mg, 1.00 mmol) was allowed to react at rt overnight. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **24k** as colorless solid (335.3 mg, 95 %): mp 89 °C (from *n*-hexane); IR (neat) cm^{-1} : 1595 (C=N); ^1H -NMR (500 MHz, CDCl_3) δ : 1.42 (9H, s, $3 \times \text{CH}_3$), 1.87–1.92 (2H, m, CH_2), 3.62 (2H, t, $J = 5.4$ Hz, CH_2), 3.86 (2H, t, $J = 6.0$ Hz, CH_2), 7.07 (1H, dd, $J = 8.0, 7.4$ Hz, Ar), 7.55 (1H, d, $J = 7.4$ Hz, Ar), 8.19 (1H, d, $J = 8.0$ Hz, Ar); ^{13}C -NMR (125 MHz, CDCl_3) δ : 21.7, 30.1 (3C), 45.3, 45.3, 54.3, 118.6, 126.5, 127.5, 129.9, 130.7, 133.8, 137.4, 147.5; *Anal.* calcd for $\text{C}_{15}\text{H}_{18}\text{BrN}_3\text{S}$: C, 51.14; H, 5.15; N, 11.93. Found: C, 50.89; H, 5.06; N, 11.83.

Compound 27k. Using the general procedure as described for **25a**, compound **24k** (52.8 mg, 0.15 mmol) was allowed to react for 2 h with TFA (1.5 mL) and MS4Å (225 mg). Purification by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) gave the title compound **27k** as colorless solid (31.6 mg, 71 %): mp 138–139 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1567 (C=N); ^1H -NMR (500 MHz, CDCl_3) δ : 1.94–1.98 (2H, m, CH_2), 3.69 (2H, t, $J = 5.7$ Hz, CH_2), 4.02 (2H, t, $J = 6.0$ Hz, CH_2), 7.10 (1H, dd, $J = 8.3, 7.7$ Hz, Ar), 7.33 (1H, br s, NH), 7.56 (1H, dd, $J = 7.7, 1.4$ Hz, Ar), 8.23 (1H, dd, $J = 8.3, 1.4$ Hz, Ar); ^{13}C -NMR (125 MHz, CDCl_3) δ : 20.8, 43.7, 45.0, 117.6, 126.8, 127.9, 128.8, 130.5, 134.1, 146.2, 152.7; *Anal.* calcd for $\text{C}_{11}\text{H}_{10}\text{BrN}_3\text{S}$: C, 44.61; H, 3.40; N, 14.19. Found: C, 44.36; H, 3.64; N, 13.96.

3.1.34 Synthesis of 3,4-Dihydro-2H,6H-pyrimido[1,2-c]naphtho[2,3-e][1,3]thiazin-6-imine (27r)

2-(3-Fluoronaphthalen-2-yl)-1,4,5,6-tetrahydropyrimidine (20r). 1-Fluoro-2-naphthaldehyde **17r** (0.96 g, 5.52 mmol) was subjected to the general procedure as described for **18j** to give the title compound **20r** as pale yellow crystals (0.85 g, 67 %): mp 128–130 °C (from CHCl₃–EtOAc–Et₂O); IR (neat) cm⁻¹: 1619 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.86–1.91 (2H, m, CH₂), 3.52 (4H, t, *J* = 5.7 Hz, 2 × CH₂), 5.21 (1H, br s, NH), 7.41–7.44 (2H, m, Ar), 7.49 (1H, t, *J* = 7.4 Hz, Ar), 7.73 (1H, d, *J* = 8.6 Hz, Ar), 7.83 (1H, d, *J* = 8.6 Hz, Ar), 8.27 (1H, d, *J* = 8.0 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 20.5, 42.2 (2C), 111.7 (d, *J* = 22.8 Hz), 124.5 (d, *J* = 16.8 Hz), 125.6 (d, *J* = 2.4 Hz), 126.7 (d, *J* = 4.8 Hz), 127.5, 128.6, 130.1, 130.9 (d, *J* = 4.8 Hz), 134.2 (d, *J* = 9.6 Hz), 151.9, 157.8 (d, *J* = 247.1 Hz); ¹⁹F-NMR (500 MHz, CDCl₃) δ: -119.8; HRMS (FAB) *m/z* calcd for C₁₄H₁₄FN₂ [M + H]⁺ 229.1141; found: 229.1143.

***N*-(*tert*-Butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*]naphtho[2,3-*e*][1,3]thiazin-6-imine (24r).** Using the general procedure as described for **22e**, compound **20r** (228.3 mg, 1.00 mmol) was allowed to react at rt overnight. Purification by flash chromatography over silica gel with *n*-hexane–EtOAc (1:1) gave the title compound **24r** as colorless solid (284.8 mg, 88 %): mp 82.5–83.5 °C, IR (neat) cm⁻¹: 1594 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.42 (9H, s, 3 × CH₃), 1.92–1.98 (2H, m, CH₂), 3.69 (2H, t, *J* = 5.6 Hz, CH₂), 3.91 (2H, t, *J* = 6.2 Hz, CH₂), 7.38–7.43 (1H, m, Ar), 7.45–7.49 (1H, m, Ar), 7.60 (1H, s, Ar), 7.69 (1H, d, *J* = 7.8 Hz, Ar), 7.87 (1H, d, *J* = 8.0 Hz, Ar), 8.70 (1H, s, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 22.0, 30.1 (3C), 45.3, 45.5, 54.3, 122.5, 125.8, 125.9, 126.3, 126.5, 127.8, 128.5, 129.2, 131.7, 133.9, 138.4, 148.5; HRMS (FAB) *m/z* calcd for C₁₉H₂₂N₃S [M + H]⁺ 324.1534; found: 324.1526.

Compound 27r. Using the general procedure as described for **25a**, compound **24r** (64.7 mg, 0.2 mmol) was allowed to react for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (4:1) gave the title compound **27r** as colorless solid (36.6 mg, 68 %): mp 180–181 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1627 (C=N), 1572 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.98–2.04 (2H, m, CH₂), 3.75 (2H, t, *J* = 5.5 Hz, CH₂), 4.06 (2H, t, *J* = 6.2 Hz, CH₂), 7.40–7.51 (3H, m, Ar), 7.68 (1H, d, *J* = 8.3 Hz, Ar), 7.87 (1H, d, *J* = 8.3 Hz, Ar), 8.74 (1H, s, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.1, 43.9, 45.1, 121.6, 125.0, 125.4, 126.1, 126.3, 128.1, 129.2, 129.2, 131.6, 133.9, 147.1, 153.4; HRMS (FAB) *m/z* calcd for C₁₅H₁₄N₃S [M + H]⁺ 268.0908; found: 268.0909.

3.1.35 Synthesis of 3,4-Dihydro-2H,6H-pyrimido[1,2-c]pyrido[3,2-e][1,3]thiazin-6-imine (27s)

Using general procedure as described for **25f**, reaction of 2-(2-bromopyridin-3-yl)-1,4,5,6-tetrahydropyrimidine **21s** (58.8 mg, 0.25 mmol) and purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **27s** as colorless solid (17.4 mg, 32 %): mp 181–183 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1624 (C=N), 1582 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.96–2.01 (2H, m, CH₂), 3.70 (2H, t, *J* = 5.7 Hz, CH₂), 4.05 (2H, t, *J* = 6.3 Hz, CH₂), 7.17 (1H, dd, *J* = 8.0, 4.6 Hz, Ar), 7.39 (1H, br s, NH), 8.46–8.50 (2H, m, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 20.8, 43.8, 45.2, 121.4, 123.7, 136.3, 145.3, 151.2, 151.3, 153.5; HRMS (FAB): *m/z* calcd for C₁₀H₁₁N₄S [M + H]⁺ 219.0704; found: 219.0703.

3.1.36 Synthesis of 2,3-Dihydronaphtho[2,1-*e*]pyrimido[1,2-*c*][1,3]thiazin-12(1H)-imine (27t)

2,3-Dihydronaphtho[2,1-*e*]pyrimido[1,2-*c*][1,3]thiazine-12(1H)-thione **21t** (71.1 mg, 0.25 mmol) was subjected to the general procedure as described for **25f** to give the title compound **27t** as colorless solid (42.3 mg, 63 %): mp 157 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1615 (C=N), 1572 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.99–2.03 (2H, m, CH₂), 3.75 (2H, t, *J* = 5.4 Hz, CH₂), 4.07 (2H, t, *J* = 6.0 Hz, CH₂), 7.33 (1H, br s, NH), 7.53–7.57 (2H, m, Ar), 7.66 (1H, d, *J* = 8.6 Hz, Ar), 7.80–7.90 (2H, m, Ar), 8.30 (1H, d, *J* = 9.2 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 20.9, 43.7, 45.1, 123.2, 124.0, 125.1, 125.9, 126.7, 126.7, 127.5, 127.8, 128.5, 133.9, 147.1, 152.7; HRMS (FAB): *m/z* calcd for C₁₅H₁₄N₃S [M + H]⁺ 268.0908; found: 268.0906.

3.1.37 Synthesis of 3,4-Dihydro-2H,6H-pyrimido[1,2-*c*]thieno[2,3-*e*][1,3]thiazin-6-imine (27u)

2-(3-Bromothiophen-2-yl)-1,4,5,6-tetrahydropyrimidine (20u). 3-Bromothiophene-2-carbaldehyde **17u** (1.29 g, 6.75 mmol) was subjected to the general procedure as described for **18j** to give the title compound **20u** as pale yellow crystals (1.11 g, 67 %): mp 61–63 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1611 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.83–1.88 (2H, m, CH₂), 3.48 (4H, t, *J* = 5.9 Hz, 2 × CH₂), 6.07 (1H, br s, NH), 6.92 (1H, d, *J* = 5.4 Hz, Ar), 7.24 (1H, d, *J* = 5.4 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 20.5, 42.0 (2C), 105.8, 127.3, 131.4, 135.6, 149.3; HRMS (FAB): *m/z* calcd for C₈H₁₀BrN₂S [M + H]⁺ 244.9748; found: 244.9742.

3,4-Dihydro-2H,6H-pyrimido[1,2-c]thieno[2,3-e][1,3]thiazin-6-thione (21u).

To a mixture of **20u** (122.6 mg, 0.50 mmol) and NaH (40.0 mg, 1.0 mmol; 60 % oil suspension) in DMF (1.7 mL) was added CS₂ (0.060 mL, 1.0 mmol) under an Ar atmosphere. After being stirred at 80 °C for 12 h, the mixture was concentrated. The residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (8:2) to give the title compound **21u** as pale yellow solid (80.5 mg, 67 %): mp 167 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1624 (C=N); ¹³C-NMR (400 MHz, CDCl₃) δ: 2.04–2.10 (2H, m, CH₂), 3.68 (2H, t, *J* = 5.5 Hz, CH₂), 4.42 (2H, t, *J* = 6.1 Hz, CH₂), 6.76 (1H, d, *J* = 5.4 Hz, Ar), 7.49 (1H, d, *J* = 5.4 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.5, 45.0, 48.5, 122.3, 128.4, 130.8, 131.0, 141.7, 189.7; HRMS (FAB): *m/z* calcd for C₉H₉N₂S₃ [M + H]⁺ 240.9928; found: 240.9936.

Compound 27u. Compound **21u** (60.1 mg, 0.25 mmol) was subjected to general procedure as described for 25f to give the title compound **27u** as colorless solid (19.4 mg, 35 %): mp 100–101 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1616 (C=N), 1567 (C=N); ¹³C-NMR (400 MHz, CDCl₃) δ: 1.99–2.05 (2H, m, CH₂), 3.62 (2H, t, *J* = 5.6 Hz, CH₂), 3.99 (2H, t, *J* = 6.1 Hz, CH₂), 6.74 (1H, d, *J* = 5.4 Hz, Ar), 7.28 (1H, br s, NH), 7.41 (1H, d, *J* = 5.4 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.2, 43.5, 44.5, 123.3, 125.9, 127.0, 129.9, 143.7, 153.7; *Anal.* calcd for C₉H₉N₃S₂: C, 48.40; H, 4.06; N, 18.82. Found: C, 48.38; H, 3.98; N, 18.75.

3.1.38 Synthesis of 3,4-Dihydro-9-(4-methoxycarbonylphenyl)-2H,6H-pyrimido [1,2-c][1,3]benzothiazin-6-imine (31a)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(4-methoxycarbonylphenyl)-2H,6H-pyrimido [1,2-c][1,3]benzothiazin-6-imine (29a).** Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 4-(methoxycarbonyl)phenylboronic acid (32.4 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29a** as colorless solid (47.3 mg, 77 %): mp 201–202 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1719 (C=O), 1593 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.40 (s, 9H, 3 × CH₃), 1.90–1.96 (m, 2H, CH₂), 3.65 (t, *J* = 5.5 Hz, 2H, CH₂), 3.89 (t, *J* = 6.1 Hz, 2H, CH₂), 3.94 (s, 3H, CH₃), 7.36 (d, *J* = 1.7 Hz, 1H, Ar), 7.44 (dd, *J* = 8.5, 1.7 Hz, 1H, Ar), 7.65 (d, *J* = 8.2 Hz, 2H, Ar), 8.10 (d, *J* = 8.2 Hz, 2H, Ar), 8.28 (d, *J* = 8.5 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.9, 30.0 (3C), 45.2, 45.4, 52.1, 54.2, 123.0, 124.8, 127.0 (2C), 127.3, 129.1, 129.6, 129.8, 130.2 (2C), 138.0, 141.7, 143.8, 147.5, 166.8; HRMS (FAB): *m/z* calcd for C₂₃H₂₆N₃O₂S [M + H]⁺ 408.1746; found: 408.1748.

Compound 31a. Using the general procedure as described for **25a**, compound **29a** (38.4 mg, 0.094 mmol) was allowed to react for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 1:1) gave the title compound **31a** as (27.3 mg, 83 %): mp 185–186 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1719 (C=O), 1619 (C=N), 1566 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.97–2.02 (m, 2H, CH₂), 3.71 (t, *J* = 5.7 Hz, 2H, CH₂), 3.94 (s, 3H, CH₃), 4.04 (t, *J* = 6.0 Hz, 2H, CH₂), 7.27 (d, *J* = 1.7 Hz, 1H, Ar), 7.46 (dd, *J* = 8.0, 1.7 Hz, 1H, Ar), 7.63 (d, *J* = 8.6 Hz, 2H, Ar), 8.10 (d, *J* = 8.6 Hz, 2H, Ar), 8.30 (d, *J* = 8.0 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.0, 43.8, 45.0, 52.2, 122.0, 125.1, 126.2, 126.9 (2C), 129.5, 129.6, 129.7, 130.2 (2C), 142.1, 143.4, 146.2, 153.0, 166.7; HRMS (FAB): *m/z* calcd for C₁₉H₁₈N₃O₂S [M + H]⁺ 352.1120; found: 352.1119.

3.1.39 Synthesis of 9-(4-Cyanophenyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**31b**)

N-(*tert*-Butyl)-9-(4-cyanophenyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**29b**). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 4-cyanophenylboronic acid (26.4 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (8:2) gave the title compound **29b** as colorless solid (53.9 mg, 96 %): mp 188–190 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 2226 (C ≡ N), 1593 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.40 (s, 9H, 3 × CH₃), 1.91–1.96 (m, 2H, CH₂), 3.65 (t, *J* = 5.5 Hz, 2H, CH₂), 3.89 (t, *J* = 6.1 Hz, 2H, CH₂), 7.33 (d, *J* = 1.8 Hz, 1H, Ar), 7.41 (dd, *J* = 8.3, 1.8 Hz, 1H, Ar), 7.68 (d, *J* = 8.1 Hz, 2H, Ar), 7.73 (d, *J* = 8.1 Hz, 2H, Ar), 8.29 (d, *J* = 8.3 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.8, 30.0 (3C), 45.2, 45.4, 54.2, 111.7, 118.6, 123.0, 124.7, 127.6 (2C), 127.8, 129.3, 130.1, 132.6 (2C), 137.6, 140.7, 143.9, 147.4; HRMS (FAB): *m/z* calcd for C₂₂H₂₃N₄S [M + H]⁺ 375.1343; found: 375.1640.

Compound 31b. Using the general procedure as described for **25a**, compound **29b** (32.5 mg, 0.087 mmol) was allowed to react for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (6:4) gave the title compound **31b** as colorless solid (20.8 mg, 75 %): mp 210–211 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 2224 (C ≡ N), 1615 (C=N), 1577 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.97–2.02 (m, 2H, CH₂), 3.71 (d, *J* = 5.4 Hz, 2H, CH₂), 4.04 (t, *J* = 6.1 Hz, 2H, CH₂), 7.24 (d, *J* = 1.7 Hz, 1H, Ar), 7.43 (dd, *J* = 8.3, 1.7 Hz, 1H, Ar), 7.67 (d, *J* = 8.3 Hz, 2H, Ar), 7.73 (d, *J* = 8.3 Hz, 2H, Ar), 8.32 (d, *J* = 8.3 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.0, 43.8, 45.0, 111.9, 118.5, 122.0, 125.0, 126.7, 127.6 (2C), 129.7, 129.9, 132.7 (2C), 141.2, 143.5, 146.0, 152.8; HRMS (FAB): *m/z* calcd for C₁₈H₁₅N₄S [M + H]⁺ 319.1017; found: 319.1015.

3.1.40 Synthesis of 3,4-Dihydro-9-(4-nitrophenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31c)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(4-nitrophenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (29c).** Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (352.3 mg, 1.0 mmol) was allowed to react with 4-nitrophenylboronic acid (200.3 mg, 1.2 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 2:1) gave the title compound **29c** as colorless solid (366.9 mg, 93 %): mp 201–202 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1590 (C=N), 1514 (NO₂); ¹H-NMR (400 MHz, CDCl₃) δ: 1.41 (s, 9H, 3 × CH₃), 1.91–1.97 (m, 2H, CH₂), 3.65 (t, *J* = 5.6 Hz, 2H, CH₂), 3.90 (t, *J* = 6.1 Hz, 2H, CH₂), 7.37 (d, *J* = 1.8 Hz, 1H, Ar), 7.44 (dd, *J* = 8.4, 1.8 Hz, 1H, Ar), 7.74 (d, *J* = 8.5 Hz, 2H, Ar), 8.28–8.32 (m, 3H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.8, 30.0 (3C), 45.2, 45.5, 54.3, 123.2, 124.1 (2C), 124.8, 127.8 (2C), 128.0, 129.3, 130.2, 137.5, 140.4, 145.8, 147.4, 147.5; HRMS (FAB): *m/z* calcd for C₂₁H₂₃N₄O₂S [M + H]⁺ 395.1542; found: 395.1539.

Compound 31c. Using the general procedure as described for **25a**, compound **29c** (77.0 mg, 0.075 mmol) was allowed to react for 4 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **31c** as colorless solid (50.7 mg, 75 %): mp 207–209 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1615 (C=N), 1598 (NO₂), 1573 (C=N), 1508 (NO₂); ¹H-NMR (500 MHz, CDCl₃) δ: 1.98–2.02 (m, 2H, CH₂), 3.72 (t, *J* = 5.7 Hz, 2H, CH₂), 4.05 (t, *J* = 6.0 Hz, 2H, CH₂), 7.27 (s, 1H, Ar), 7.46 (d, *J* = 8.0 Hz, 1H, Ar), 7.72 (d, *J* = 8.6 Hz, 2H, Ar), 8.30 (d, *J* = 8.6 Hz, 2H, Ar), 8.34 (d, *J* = 8.0 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.0, 43.8, 45.0, 122.2, 124.2 (2C), 125.1, 126.9, 127.8 (2C), 129.7, 130.0, 140.8, 145.4, 146.0, 147.6, 152.7; HRMS (FAB): *m/z* calcd for C₁₇H₁₅N₄O₂S [M + H]⁺ 339.0916; found: 339.0912.

3.1.41 Synthesis of 3,4-Dihydro-9-(4-trifluoromethylphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31d)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(4-trifluoromethylphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (29d).** Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 4-(trifluoromethyl)phenylboronic acid (27.4 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29d** as colorless solid (51.9 mg, 83 %): mp 177–179 °C (from *n*-hexane); IR (neat) cm⁻¹: 1594 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.40 (s, 9H,

3 × CH₃), 1.90–1.96 (m, 2H, CH₂), 3.64 (t, *J* = 5.6 Hz, 2H, CH₂), 3.89 (t, *J* = 6.1 Hz, 2H, CH₂), 7.33 (d, *J* = 2.0 Hz, 1H, Ar), 7.41 (dd, *J* = 8.3, 2.0 Hz, 1H, Ar), 7.68 (s, 4H, Ar), 8.29 (d, *J* = 8.3 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.8, 29.9 (3C), 45.1, 45.4, 54.2, 122.9, 124.1 (q, *J* = 271.1 Hz), 124.8, 125.8 (q, *J* = 3.6 Hz, 2C), 127.3 (2C), 127.4, 129.2, 129.9, 130.0 (q, *J* = 32.8 Hz), 137.8, 141.3, 142.9, 147.5; ¹⁹F-NMR (500 MHz, CDCl₃) δ: –63.0; HRMS (FAB): *m/z* calcd for C₂₂H₂₃F₃N₃S [M + H]⁺ 418.1565; found: 418.1563.

Compound 31d. Using the general procedure as described for **25a**, compound **29d** (41.2 mg, 1.0 mmol) was allowed to react for 4 h with TFA (1.0 mL) and MS4 Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **31d** as colorless solid (26.0 mg, 73 %): mp 142–143 °C (from CHCl₃–*n*-hexane); IR (neat) cm^{–1}: 1619 (C=N), 1567 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.95–2.00 (m, 2H, CH₂), 3.70 (t, *J* = 5.4 Hz, 2H, CH₂), 4.03 (t, *J* = 6.0 Hz, 2H, CH₂), 7.22 (s, 1H, Ar), 7.42 (d, *J* = 8.0 Hz, 1H, Ar), 7.64 (d, *J* = 8.0 Hz, 2H, Ar), 7.68 (d, *J* = 8.0 Hz, 2H, Ar), 8.30 (d, *J* = 8.0 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 20.9, 43.8, 44.9, 121.9, 124.0 (q, *J* = 272.2 Hz, 125.0, 125.7 (t, *J* = 3.6 Hz, 2C), 126.2, 127.2 (2C), 129.5, 129.6, 130.1 (q, *J* = 32.4 Hz), 141.7, 142.5, 146.1, 152.8; ¹⁹F-NMR (500 MHz, CDCl₃) δ: –63.1; *Anal.* calcd for C₁₈H₁₄F₃N₃S: C, 59.82; H, 3.90; N, 11.63. Found: C, 59.56; H, 3.81; N, 11.48.

3.1.42 Synthesis of 9-(4-Aminocarbonylphenyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (31e)

9-[(4-Aminocarbonyl)phenyl]-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (29e). Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 4-(aminocarbonyl)phenylboronic acid (29.7 mg, 0.18 mmol) in 1,4-dioxane for 1 h. Purification by preparative TLC over aluminum oxide with CHCl₃–MeOH (95:5) gave the title compound **29e** as colorless solid (31.2 mg, 53 %): mp 261–263 °C (from MeOH–CHCl₃–*n*-hexane); IR (neat) cm^{–1}: 1650 (C=O), 1592 (C=N); ¹H-NMR (400 MHz, CDCl₃–CD₃OD) δ: 1.41 (s, 9H, 3 × CH₃), 1.92–1.98 (m, 2H, CH₂), 3.62 (t, *J* = 5.5 Hz, 2H, CH₂), 3.90 (t, *J* = 6.1 Hz, 2H, CH₂), 7.38 (d, *J* = 1.7 Hz, 1H, Ar), 7.47 (dd, *J* = 8.5, 1.7 Hz, 1H, Ar), 7.66 (d, *J* = 8.3 Hz, 2H, Ar), 7.92 (d, *J* = 8.3 Hz, 2H, Ar), 8.17 (d, *J* = 8.5 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃–CD₃OD) δ: 21.6, 29.7 (3C), 44.7, 45.4, 54.2, 122.9, 124.8, 126.8, 126.9 (2C), 128.0 (2C), 128.8, 129.8, 132.6, 137.8, 141.8, 142.6, 148.7, 169.7; HRMS (FAB): *m/z* calcd for C₂₂H₂₅N₄OS [M + H]⁺ 393.1749; found: 393.1744.

Compound 31e. TFA (17 mL) was added to a mixture of **29e** (27.1 mg, 0.069 mmol) and MS4 Å (4.5 g, powder, activated by heating with Bunsen burner)

in CHCl₃ (3.0 mL) and MeOH (10 drops). After being stirred under reflux for 9 h, the mixture was concentrated. To a stirring mixture of this residue in CHCl₃ was added dropwise Et₃N at 0 °C to adjust pH to 8–9. The whole was extracted with EtOAc. The extract was washed with sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was purified by preparative TLC over aluminum oxide with EtOAc–MeOH (95:5) to give compound **31e** as colorless solid (13.0 mg, 56 %): mp 222–223 °C (from MeOH–CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1666 (C=O), 1616 (C=N), 1556 (C=N); ¹H-NMR (400 MHz, DMSO-*d*₆) δ: 1.83–1.89 (m, 2H, CH₂), 3.59 (t, *J* = 5.1 Hz, 2H, CH₂), 3.92 (t, *J* = 5.7 Hz, 2H, CH₂), 7.40 (s, 1H, NH), 7.60–7.62 (m, 2H, Ar), 7.81 (d, *J* = 8.3 Hz, 2H, Ar), 7.96 (d, *J* = 8.3 Hz, 2H, Ar), 8.04 (s, 1H, NH), 8.24 (d, *J* = 8.3 Hz, 1H, Ar), 8.74 (s, 1H, NH); ¹³C-NMR (100 MHz, DMSO-*d*₆) δ: 20.7, 43.1, 44.4, 121.8, 124.3, 125.4, 126.5 (2C), 128.1 (2C), 129.0, 129.7, 133.8, 140.6, 141.1, 145.1, 149.5, 167.3; HRMS (FAB): *m/z* calcd for C₁₈H₁₇N₄OS [M + H]⁺ 337.1123; found: 337.1118.

3.1.43 Synthesis of 3,4-Dihydro-9-(4-methoxyphenyl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**31f**)

N-(*tert*-Butyl)-3,4-dihydro-9-(4-methoxyphenyl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**29f**). Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 4-methoxyphenylboronic acid (27.4 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29f** as colorless solid (54.7 mg, 96 %): mp 199–200 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1592 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.40 (s, 9H, 3 × CH₃), 1.89–1.95 (m, 2H, CH₂), 3.63 (t, *J* = 5.5 Hz, 2H, CH₂), 3.84 (s, 3H, CH₃), 3.88 (t, *J* = 6.0 Hz, 2H, CH₂), 6.96 (d, *J* = 8.5 Hz, 2H, Ar), 7.29 (d, *J* = 2.0 Hz, 1H, Ar), 7.38 (dd, *J* = 8.3, 2.0 Hz, 1H, Ar), 7.53 (d, *J* = 8.5 Hz, 2H, Ar), 8.22 (d, *J* = 8.3 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.9, 30.0 (3C), 45.1, 45.4, 54.1, 55.3, 114.3 (2C), 122.1, 124.4, 125.9, 128.1 (2C), 128.9, 129.4, 131.9, 138.4, 142.5, 147.8, 159.8; HRMS (FAB): *m/z* calcd for C₂₂H₂₆N₃OS [M + H]⁺ 380.1797; found: 380.1801.

Compound 31f. Using the general procedure as described for **25a**, compound **29f** (28.4 mg, 0.075 mmol) was allowed to react for 2 h with TFA (1.0 mL) and MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (3:1) gave the title compound **31f** as colorless solid (20.0 mg, 82 %): mp 93–94 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1620 (C=N), 1567 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.96–2.02 (m, 2H, CH₂), 3.71 (t, *J* = 5.5 Hz, 2H, CH₂), 3.85 (s, 3H, CH₃), 4.04 (t, *J* = 6.2 Hz, 2H, CH₂), 6.97 (d, *J* = 8.5 Hz, 2H, Ar), 7.20 (d, *J* = 1.7 Hz, 1H, Ar), 7.41 (dd, *J* = 8.3, 1.7 Hz, 1H,

Ar), 7.52 (d, $J = 8.5$ Hz, 2H, Ar), 8.25 (d, $J = 8.3$ Hz, 1H, Ar); ^{13}C -NMR (100 MHz, CDCl_3) δ : 21.0, 43.8, 44.9, 55.4, 114.4 (2C), 121.1, 124.7, 124.8, 128.1 (2C), 129.3, 129.3, 131.5, 143.1, 146.5, 153.5, 159.9; *Anal.* calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{OS}$: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.95; H, 5.50; N, 12.89.

3.1.44 Synthesis of 3,4-Dihydro-9-(4-methylthiophenyl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (31g)

N-(*tert*-Butyl)-3,4-dihydro-9-(4-methylthiophenyl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**29g**). Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 4-(methylthio)phenylboronic acid (30.2 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29g** as colorless solid (50.6 mg, 85 %): mp 201–202 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1592 (C=N); ^1H -NMR (400 MHz, CDCl_3) δ : 1.40 (s, 9H, 3 \times CH_3), 1.89–1.95 (m, 2H, CH_2), 2.51 (s, 3H, CH_3), 3.64 (t, $J = 5.5$ Hz, 2H, CH_2), 3.88 (t, $J = 6.1$ Hz, 2H, CH_2), 7.30–7.32 (m, 3H, Ar), 7.40 (dd, $J = 8.4$, 1.3 Hz, 1H, Ar), 7.51 (d, $J = 8.3$ Hz, 2H, Ar), 8.23 (d, $J = 8.4$ Hz, 1H, Ar); ^{13}C -NMR (100 MHz, CDCl_3) δ : 15.7, 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 122.3, 124.4, 126.4, 126.8 (2C), 127.3 (2C), 129.0, 129.6, 136.0, 138.2, 138.8, 142.2, 147.7; HRMS (FAB): m/z calcd for $\text{C}_{22}\text{H}_{26}\text{N}_3\text{S}_2$ [$\text{M} + \text{H}$] $^+$ 396.1568; found: 396.1566.

Compound 31g. Using the general procedure as described for **25a**, compound **29g** (38.5 mg, 0.097 mmol) was allowed to react for 4 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **31g** as colorless solid (18.4 mg, 56 %): mp 151–153 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1620 (C=N), 1573 (C=N); ^1H -NMR (400 MHz, CDCl_3) δ : 1.96–2.02 (m, 2H, CH_2), 2.52 (s, 3H, CH_3), 3.71 (t, $J = 5.5$ Hz, 2H, CH_2), 4.04 (t, $J = 6.1$ Hz, 2H, CH_2), 7.21 (d, $J = 1.8$ Hz, 1H, Ar), 7.31 (d, $J = 8.3$ Hz, 2H, Ar), 7.42 (dd, $J = 8.5$, 1.8 Hz, 1H, Ar), 7.49 (d, $J = 8.3$ Hz, 2H, Ar), 8.27 (d, $J = 8.5$ Hz, 1H, Ar); ^{13}C -NMR (100 MHz, CDCl_3) δ : 15.6, 21.0, 43.8, 44.9, 121.3, 124.7, 125.3, 126.7 (2C), 127.3 (2C), 129.4 (2C), 135.7, 139.2, 142.8, 146.5, 153.3; HRMS (FAB): m/z calcd for $\text{C}_{18}\text{H}_{18}\text{N}_3\text{S}_2$ [$\text{M} + \text{H}$] $^+$ 340.0942; found: 340.0944.

3.1.45 Synthesis of 3,4-Dihydro-9-(4-trifluoromethoxyphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31h)

N-(*tert*-Butyl)-3,4-dihydro-9-(4-trifluoromethoxyphenyl)-2H,6H-pyrimido [1,2-c][1,3]benzothiazin-6-imine (**29h**). Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 4-(trifluoromethoxy)phenylboronic acid (37.1 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29h** as colorless solid (59.7 mg, 92 %): mp 157 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1595 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.40 (s, 9H, 3 × CH₃), 1.91-1.95 (m, 2H, CH₂), 3.64 (t, *J* = 5.4 Hz, 2H, CH₂), 3.89 (t, *J* = 6.0 Hz, 2H, CH₂), 7.27–7.30 (m, 3H, Ar), 7.38 (dd, *J* = 8.0, 1.7 Hz, 1H, Ar), 7.59 (d, *J* = 8.6 Hz, 2H, Ar), 8.26 (d, *J* = 8.0 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.9, 30.0 (3C), 45.2, 45.5, 54.2, 120.5 (q, *J* = 257.4 Hz), 121.3 (2C), 122.8, 124.7, 127.0, 128.5 (2C), 129.1, 129.8, 138.0, 138.2, 141.5, 147.6, 149.2 (q, *J* = 1.7 Hz); ¹⁹F-NMR (500 MHz, CDCl₃) δ: –58.3; HRMS (FAB): *m/z* calcd for C₂₂H₂₃F₃N₃OS [M + H]⁺ 434.1514; found: 434.1512.

Compound 31h. Using the general procedure as described for **25a**, compound **29h** (44.8 mg, 0.103 mmol) was allowed to react for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1–7:3) gave the title compound **31h** as colorless solid (17.3 mg, 45 %): mp 120 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1621 (C=N), 1571 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.98-2.02 (m, 2H, CH₂), 3.72 (t, *J* = 5.7 Hz, 2H, CH₂), 4.04 (t, *J* = 6.3 Hz, 2H, CH₂), 7.22 (d, *J* = 1.7 Hz, 1H, Ar), 7.29 (d, *J* = 8.6 Hz, 2H, Ar), 7.41 (dd, *J* = 8.0, 1.7 Hz, 1H, Ar), 7.59 (d, *J* = 8.6 Hz, 2H, Ar), 8.29 (d, *J* = 8.6 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 20.9, 43.8, 44.9, 120.4 (q, *J* = 257.5 Hz), 121.3 (2C), 121.7, 124.9, 125.8, 128.4 (2C), 129.4, 129.5, 137.8, 141.9, 146.2, 149.2, 153.0; ¹⁹F-NMR (500 MHz, CDCl₃) δ: –58.4; HRMS (FAB): *m/z* calcd for C₁₈H₁₅F₃N₃OS [M + H]⁺ 378.0888; found: 378.0888.

3.1.46 Synthesis of 3,4-Dihydro-9-(3-methoxycarbonylphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31i)

N-(*tert*-Butyl)-3,4-dihydro-9-(3-methoxycarbonylphenyl)-2H,6Hc[1,3]benzothiazin-6-imine (**29i**). Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3-(methoxycarbonyl)phenylboronic acid (32.4 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over

aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29i** as colorless solid (56.2 mg, 92 %): mp 116–117.5 °C (from *n*-hexane); IR (neat) cm^{-1} : 1723 (C=O), 1592 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.41 (s, 9H, 3 \times CH_3), 1.91–1.96 (m, 2H, CH_2), 3.65 (t, $J = 5.4$ Hz, 2H, CH_2), 3.89 (t, $J = 6.0$ Hz, 2H, CH_2), 3.95 (s, 3H, CH_3), 7.37 (d, $J = 1.7$ Hz, 1H, Ar), 7.45 (dd, $J = 8.6, 1.7$ Hz, 1H, Ar), 7.51 (t, $J = 8.0$ Hz, 1H, Ar), 7.78 (d, $J = 8.0$ Hz, 1H, Ar), 8.04 (d, $J = 8.0$ Hz, 1H, Ar), 8.26–8.28 (m, 2H, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.1, 45.4, 52.2, 54.2, 122.8, 124.7, 127.0, 128.0, 129.0, 129.1 (2C), 129.7, 130.8, 131.3, 138.1, 139.7, 141.7, 147.6, 166.8; HRMS (FAB): m/z calcd for $\text{C}_{23}\text{H}_{26}\text{N}_3\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 408.1746; found: 408.1741.

Compound 31i. Using the general procedure as described for **25a**, compound **29i** (34.2 mg, 0.084 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **31i** as colorless solid (22.8 mg, 77 %): mp 131 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1721 (C=O), 1620 (C=N), 1568 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.97–2.02 (m, 2H, CH_2), 3.72 (t, $J = 5.4$ Hz, 2H, CH_2), 3.96 (s, 3H, CH_3), 4.04 (t, $J = 6.0$ Hz, 2H, CH_2), 7.28 (d, $J = 1.4$ Hz, 1H, Ar), 7.47 (dd, $J = 8.6, 1.4$ Hz, 1H, Ar), 7.52 (t, $J = 7.7$ Hz, 1H, Ar), 7.76 (d, $J = 7.7$ Hz, 1H, Ar), 8.05 (d, $J = 7.7$ Hz, 1H, Ar), 8.25 (s, 1H, Ar), 8.30 (d, $J = 8.6$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 21.0, 43.8, 45.0, 52.3, 121.8, 125.0, 125.9, 128.1, 129.0, 129.2, 129.5, 129.5, 130.9, 131.3, 139.4, 142.3, 146.3, 153.1, 166.7; *Anal.* calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$: C, 64.94; H, 4.88; N, 11.96. Found: C, 64.83; H, 4.79; N, 11.84.

3.1.47 Synthesis of 9-(3-Cyanophenyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31j)

***N*-(tert-Butyl)-9-(3-cyanophenyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (29j).** Using the general procedure as described for **22l**, ***N*-(tert-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (22k)** (52.8 mg, 0.15 mmol) was allowed to react with 3-cyanophenylboronic acid (26.5 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (85:5) gave the title compound **29j** as colorless solid (48.4 mg, 86 %): mp 165–167 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 2230 (C \equiv N), 1593 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.40 (s, 9H, 3 \times CH_3), 1.91–1.96 (m, 2H, CH_2), 3.65 (t, $J = 5.7$ Hz, 2H, CH_2), 3.89 (t, $J = 6.3$ Hz, 2H, CH_2), 7.31 (d, $J = 1.7$ Hz, 1H, Ar), 7.38 (dd, $J = 8.0, 1.7$ Hz, 1H, Ar), 7.55 (t, $J = 7.7$ Hz, 1H, Ar), 7.65 (dt, $J = 7.7, 1.7$ Hz, 1H, Ar), 7.81 (dt, $J = 7.7, 1.7$ Hz, 1H, Ar), 7.86 (t, $J = 1.7$ Hz, 1H, Ar), 8.29 (d, $J = 8.0$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.8, 30.0 (3C), 45.1, 45.4, 54.2, 113.2, 118.5, 122.8, 124.5,

127.6, 129.3, 129.7, 130.1, 130.5, 131.3, 131.4, 137.7, 140.4, 140.8, 147.4; HRMS (FAB): m/z calcd for $C_{22}H_{23}N_4S$ $[M + H]^+$ 375.1643; found: 375.1646.

Compound 31j. Using the general procedure as described for **25a**, compound **29j** (40.3 mg, 0.11 mmol) was allowed to react for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (2:1 to 0:1) gave the title compound **31j** as colorless solid (30.6 mg, 89 %): mp 196–197 °C (from MeOH–CHCl₃–*n*-hexane); IR (neat) cm^{-1} : 2230 (C \equiv N), 1623 (C=N), 1572 (C=N); ¹H-NMR (400 MHz, CDCl₃–CD₃OD) δ : 1.98–2.04 (m, 2H, CH₂), 3.71 (t, $J = 5.5$ Hz, 2H, CH₂), 4.01 (t, $J = 6.1$ Hz, 2H, CH₂), 7.25 (d, $J = 1.8$ Hz, 1H, Ar), 7.44 (dd, $J = 8.5, 1.8$ Hz, 1H, Ar), 7.58 (t, $J = 7.8$ Hz, 1H, Ar), 7.68 (d, $J = 7.8$ Hz, 1H, Ar), 7.81 (d, $J = 7.8$ Hz, 1H, Ar), 7.86 (s, 1H, Ar), 8.27 (d, $J = 8.5$ Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃–CD₃OD) δ : 20.7, 43.9, 44.7, 113.0, 118.3, 121.9, 124.9, 126.2, 129.5, 129.7, 129.7, 130.4, 131.3, 131.5, 140.2, 141.0, 146.6, 153.4; HRMS (FAB): m/z calcd for $C_{18}H_{15}N_4S$ $[M + H]^+$ 319.1017; found: 319.1016.

3.1.48 Synthesis of 3,4-Dihydro-9-(3-nitrophenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31k)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(3-nitrophenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (29k).** Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3-nitrophenylboronic acid (30.0 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 8:2) gave the title compound **29k** as colorless solid (52.3 mg, 88 %): mp 208–209 °C (from CHCl₃–*n*-hexane); IR (neat) cm^{-1} : 1593 (C=N), 1529 (NO₂); ¹H-NMR (500 MHz, CDCl₃) δ : 1.41 (s, 9H, 3 \times CH₃), 1.92–1.96 (m, 2H, CH₂), 3.65 (t, $J = 5.4$ Hz, 2H, CH₂), 3.90 (t, $J = 6.3$ Hz, 2H, CH₂), 7.37 (d, $J = 1.7$ Hz, 1H, Ar), 7.44 (dd, $J = 8.6, 1.7$ Hz, 1H, Ar), 7.62 (t, $J = 8.0$ Hz, 1H, Ar), 7.91 (dd, $J = 8.0, 2.0$ Hz, 1H, Ar), 8.22 (dd, $J = 8.0, 2.0$ Hz, 1H, Ar), 8.31 (d, $J = 8.6$ Hz, 1H, Ar), 8.44 (t, $J = 2.0$ Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ : 21.8, 30.0 (3C), 45.2, 45.4, 54.3, 121.8, 122.7, 122.9, 124.6, 127.7, 129.4, 129.9, 130.2, 132.9, 137.6, 140.2, 141.1, 147.4, 148.7; HRMS (FAB): m/z calcd for $C_{21}H_{23}N_4O_2S$ $[M + H]^+$ 395.1542; found: 395.1544.

Compound 31k. Using the general procedure as described for **25a**, compound **29k** (37.9 mg, 0.096 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:1) gave the title compound **31k** as colorless solid (23.2 mg, 71 %): mp 168–170 °C (from CHCl₃–*n*-hexane); IR (neat) cm^{-1} : 1620 (C=N), 1567 (C=N), 1529 (NO₂); ¹H-NMR (500 MHz, CDCl₃) δ : 1.98–2.03 (m, 2H, CH₂), 3.72 (t, $J = 5.7$ Hz, 2H, CH₂), 4.05 (t, $J = 6.0$ Hz, 2H, CH₂), 7.28 (d, $J = 1.7$ Hz, 1H, Ar), 7.47 (dd, $J = 8.6, 1.7$ Hz,

1H, Ar), 7.63 (t, $J = 7.7$ Hz, 1H, Ar), 7.90 (dd, $J = 7.7, 1.7$ Hz, 1H, Ar), 8.23 (dd, $J = 7.7, 1.7$ Hz, 1H, Ar), 8.34 (d, $J = 8.6$ Hz, 1H, Ar), 8.42 (t, $J = 1.7$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 21.0, 43.8, 45.0, 121.8, 121.9, 122.9, 124.9, 126.7, 129.8, 129.9, 130.0, 132.8, 140.7, 140.8, 146.0, 148.7, 152.8; *Anal.* calcd for $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_2\text{S}$: C, 60.34; H, 4.17; N, 16.56. Found: C, 60.04; H, 4.13; N, 16.28.

3.1.49 Synthesis of (\pm)-3,4-Dihydro-9-[3-(1-hydroxyethyl)phenyl]-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (**31l**)

N-(*tert*-Butyl)-3,4-dihydro-9-(3-vinylphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (**29l**). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (70.6 mg, 0.20 mmol) was allowed to react with 3-vinylphenylboronic acid (35.5 mg, 0.24 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29l** as a colorless oil (64.4 mg, 86 %): IR (neat) cm^{-1} : 1591 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.40 (s, 9H, 3 \times CH_3), 1.90–1.95 (m, 2H, CH_2), 3.64 (t, $J = 5.4$ Hz, 2H, CH_2), 3.89 (t, $J = 6.3$ Hz, 2H, CH_2), 5.30 (d, $J = 10.9$ Hz, 1H, CH), 5.82 (d, $J = 17.8$ Hz, 1H, CH), 6.77 (dd, $J = 17.8, 10.9$ Hz, 1H, CH), 7.34 (d, $J = 1.7$ Hz, 1H, Ar), 7.37–7.47 (m, 4H, Ar), 7.59 (s, 1H, Ar), 8.25 (d, $J = 8.6$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 114.5, 122.7, 124.8, 125.0, 125.8, 126.5, 126.6, 128.9, 129.0, 129.5, 136.5, 138.2, 138.2, 139.7, 142.8, 147.7; HRMS (FAB): m/z calcd for $\text{C}_{23}\text{H}_{26}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 376.1847; found: 376.1850.

Compound 31l. Using the general procedure as described for **25a**, compound **29l** (58.5 mg, 0.16 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 1:1) gave the title compound **31l** as colorless solid (25.9 mg, 49 %): mp 193–195 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1616 (C=N), 1558 (C=N); $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ : 1.36 (d, $J = 6.6$ Hz, 3H, CH_3), 1.84–1.89 (m, 2H, CH_2), 3.59 (t, $J = 5.1$ Hz, 2H, CH_2), 3.92 (t, $J = 6.0$ Hz, 2H, CH_2), 4.76–4.81 (m, 1H, CH), 5.20 (d, $J = 4.4$ Hz, 1H, OH), 7.36–7.43 (m, 2H, Ar), 7.53–7.57 (m, 3H, Ar), 7.67 (s, 1H, Ar), 8.24 (d, $J = 8.3$ Hz, 1H, Ar), 8.71 (s, 1H, NH); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 – CD_3OD) δ : 20.6, 25.0, 44.0, 44.5, 69.5, 121.7, 123.8, 125.0, 125.1, 125.3, 125.6, 128.8, 129.0, 129.0, 138.8, 143.6, 146.8, 147.2, 154.1; HRMS (FAB): m/z calcd for $\text{C}_{19}\text{H}_{20}\text{N}_3\text{OS}$ [$\text{M} + \text{H}$] $^+$ 338.1327; found: 338.1327.

3.1.50 Synthesis of 9-[3-(Acetylamino)phenyl]-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31m)

9-[3-(Acetylamino)phenyl]-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (29m). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3-(acetylamino)phenylboronic acid (32.2 mg, 0.18 mmol) in 1,4-dioxane for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:1) gave the title compound **29m** as colorless solid (44.6 mg, 73 %): mp 221–222 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1670 (C=O), 1590 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.40 (s, 9H, 3 × CH₃), 1.91–1.95 (m, 2H, CH₂), 2.18 (s, 3H, CH₃), 3.64 (t, *J* = 5.4 Hz, 2H, CH₂), 3.89 (t, *J* = 6.0 Hz, 2H, CH₂), 7.29–7.38 (m, 4H, Ar), 7.50 (d, *J* = 7.4 Hz, 1H, Ar), 7.70 (s, 1H, NH), 7.73 (s, 1H, Ar), 8.21 (d, *J* = 8.0 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.9, 24.5, 30.0 (3C), 45.1, 45.4, 54.2, 118.4, 119.5, 122.8, 122.9, 124.8, 126.7, 128.8, 129.5, 129.5, 138.2, 138.5, 140.2, 142.4, 147.9, 168.5; HRMS (FAB): *m/z* calcd for C₂₃H₂₇N₄OS [M + H]⁺ 407.1906; found: 407.1905.

Compound 31m. Using the general procedure as described for **25a**, compound **29m** (35.4 mg, 0.096 mmol) was allowed to react for 3 h. Purification by preparative TLC over aluminum oxide with EtOAc–MeOH (98:2) gave the title compound **31m** as colorless solid (23.7 mg, 78 %): mp 208–210 °C (from MeOH–CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1691 (C=O), 1611 (C=N), 1561 (C=N); ¹H-NMR (DMSO-*d*₆) δ: 1.85–1.90 (m, 2H, CH₂), 2.06 (s, 3H, CH₃), 3.60 (t, *J* = 5.4 Hz, 2H, CH₂), 3.93 (t, *J* = 6.0 Hz, 2H, CH₂), 7.37–7.41 (m, 2H, Ar), 7.46–7.49 (m, 2H, Ar), 7.61 (d, *J* = 6.3 Hz, 1H, Ar), 7.90 (s, 1H, Ar), 8.26 (d, *J* = 8.0 Hz, 1H, Ar), 8.75 (s, 1H, NH), 10.04 (s, 1H, NH); ¹³C-NMR (125 MHz, CDCl₃–CD₃OD) δ: 20.7, 23.7, 44.0, 44.5, 118.3, 119.6, 121.8, 122.4, 125.1 (2C), 129.0, 129.0, 129.2, 138.8, 139.4, 143.3, 147.2, 154.1, 169.7; HRMS (FAB): *m/z* calcd for C₁₉H₁₇N₄OS [M – H]⁻ 349.1123; found: 349.1129.

3.1.51 Synthesis of 3,4-Dihydro-9-[3-(methanesulfonylamino)phenyl]-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31n)

***N*-(*tert*-Butyl)-3,4-dihydro-9-[3-(methanesulfonylamino)phenyl]-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (29n).** Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3-(methanesulfonylamino)phenylboronic acid (38.7 mg, 0.18 mmol) in 1,4-dioxane

for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:2 to 0:1) gave the title compound **29n** as colorless solid (20.1 mg, 30 %): mp 200–202 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1591 (C=N), 1153 (NSO₂); ¹H-NMR (500 MHz, CDCl₃–CD₃OD) δ: 1.41 (s, 9H, 3 × CH₃), 1.92–1.97 (m, 2H, CH₂), 3.02 (s, 3H, CH₃), 3.62 (t, *J* = 5.2 Hz, 2H, CH₂), 3.90 (t, *J* = 6.0 Hz, 2H, CH₂), 7.27 (d, *J* = 7.4 Hz, 1H, Ar), 7.34–7.43 (m, 5H, Ar), 8.15 (d, *J* = 8.6 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.8, 30.0 (3C), 39.5, 44.9, 45.5, 54.3, 119.1, 119.8, 122.9, 123.7, 124.8, 127.0, 129.0, 129.8, 130.1, 137.7, 137.9, 140.9, 142.0, 148.4; HRMS (FAB): *m/z* calcd for C₂₂H₂₇N₄O₂S₂ [M + H]⁺ 443.1575; found: 443.1574.

Compound 31n. Using the general procedure as described for **25a**, compound **29n** (26.1 mg, 0.059 mmol) was allowed to react for 4.5 h. Purification by preparative TLC over aluminum oxide with EtOAc–MeOH (95:5) gave the title compound **31n** as colorless solid (13.4 mg, 59 %): mp 194–196 °C (from MeOH–CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1625 (C=N), 1557 (C=N), 1325 (NSO₂), 1147 (NSO₂); ¹H-NMR (500 MHz, CDCl₃–CD₃OD) δ: 1.98–2.03 (m, 2H, CH₂), 3.02 (s, 3H, CH₃), 3.70 (t, *J* = 5.4 Hz, 2H, CH₂), 4.00 (t, *J* = 6.3 Hz, 2H, CH₂), 7.23–7.46 (m, 6H, Ar), 8.21 (d, *J* = 8.6 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃–CD₃OD) δ: 20.8, 39.1, 44.0, 44.7, 118.8, 120.0, 121.9, 123.4, 125.2, 125.6, 129.3, 129.5, 130.1, 138.0, 140.5, 142.7, 147.0, 153.9; HRMS (FAB): *m/z* calcd for C₁₈H₁₉N₄O₂S₂ [M + H]⁺ 387.0949; found: 387.0957.

3.1.52 Synthesis of 3,4-Dihydro-9-(3-hydroxyphenyl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (31o)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(3-hydroxyphenyl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (29o).** Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3-hydroxyphenylboronic acid (24.8 mg, 0.18 mmol) in 1,4-dioxane for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:1 to 0:1) gave the title compound **29o** as colorless solid (16.1 mg, 29 %): mp 265–267 °C (from MeOH–CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1591 (C=N); ¹H-NMR (500 MHz, CDCl₃–CD₃OD) δ: 1.41 (s, 9H, 3 × CH₃), 1.92–1.97 (m, 2H, CH₂), 3.60 (t, *J* = 5.2 Hz, 2H, CH₂), 3.90 (t, *J* = 6.0 Hz, 2H, CH₂), 6.85 (d, *J* = 8.0 Hz, 1H, Ar), 7.03 (s, 1H, Ar), 7.08 (d, *J* = 8.0 Hz, 1H, Ar), 7.27 (t, *J* = 8.0 Hz, 1H, Ar), 7.34 (s, 1H, Ar), 7.43 (d, *J* = 8.0 Hz, 1H, Ar), 8.09 (d, *J* = 8.0 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃–CD₃OD) δ: 21.5, 29.7 (3C), 44.5, 45.4, 54.2, 113.8, 115.1, 118.2, 122.8, 124.9, 126.0, 128.5, 129.4, 129.8, 138.1, 140.4, 143.2, 149.4, 157.2; HRMS (FAB): *m/z* calcd for C₂₁H₂₄N₃OS [M + H]⁺ 366.1640; found: 366.1639.

Compound 31o. TFA (9 mL) was added to a mixture of **29o** (16.1 mg, 0.044 mmol) and MS4Å (2.0 g, powder, activated by heating with Bunsen burner) in CHCl₃ (1.0 mL) and MeOH (10 drops). After being stirred under reflux for 5 h, the mixture was concentrated. To a mixture of the residue in CHCl₃ was added dropwise Et₃N at 0 °C to adjust pH to 8–9. The whole was extracted with EtOAc. The extract was washed with sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was purified by preparative TLC over aluminum oxide with EtOAc–MeOH (95:5) to give the title compound **31o** as colorless solid (7.9 mg, 58 %): mp 199–200 °C (from MeOH–CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1621 (C=N), 1557 (C=N); ¹H-NMR (500 MHz, DMSO-*d*₆) δ: 1.85–1.90 (m, 2H, CH₂), 3.60 (t, *J* = 5.4 Hz, 2H, CH₂), 3.92 (t, *J* = 5.4 Hz, 2H, CH₂), 6.81 (dd, *J* = 7.7, 2.0 Hz, 1H, Ar), 7.06 (t, *J* = 2.0 Hz, 1H, Ar), 7.13 (d, *J* = 8.3 Hz, 1H, Ar), 7.27 (t, *J* = 7.7 Hz, 1H, Ar), 7.48–7.50 (m, 2H, Ar), 8.22 (d, *J* = 8.3 Hz, 1H, Ar), 8.74 (br s, 1H, NH), 9.57 (s, 1H, OH); ¹³C-NMR (100 MHz, DMSO-*d*₆) δ: 20.7, 43.1, 44.3, 113.5, 115.3, 117.5, 121.4, 124.2, 124.9, 129.0, 129.5, 130.0, 139.5, 142.3, 145.2, 149.7, 157.8; HRMS (FAB): *m/z* calcd for C₁₇H₁₆N₃OS [M + H]⁺ 310.1014; found: 310.1010.

3.1.53 Synthesis of 3,4-Dihydro-9-(4-methoxyphenyl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**31p**)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(3-methoxyphenyl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**29p**).** Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 4-methoxyphenylboronic acid (27.4 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29p** as a colorless oil (55.6 mg, 98 %): IR (neat) cm⁻¹: 1591 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.40 (s, 9H, 3 × CH₃), 1.90–1.96 (m, 2H, CH₂), 3.64 (t, *J* = 5.5 Hz, 2H, CH₂), 3.86 (s, 3H, CH₃), 3.89 (t, *J* = 6.2 Hz, 2H, CH₂), 6.91 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar), 7.10 (t, *J* = 2.5 Hz, 1H, Ar), 7.15–7.18 (m, 1H, Ar), 7.32–7.37 (m, 2H, Ar), 7.41 (dd, *J* = 8.5, 1.7 Hz, 1H, Ar), 8.24 (d, *J* = 8.5 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 55.3, 112.7, 113.5, 119.5, 122.8, 124.9, 126.7, 128.9, 129.5, 129.9, 138.2, 140.9, 142.8, 147.7, 160.0; HRMS (FAB): *m/z* calcd for C₂₂H₂₆N₃OS [M + H]⁺ 380.1797; found: 380.1793.

Compound 31p. Using the general procedure as described for **25a**, compound **29p** (32.1 mg, 0.085 mmol) was allowed to react for 2 h with TFA (1.0 mL) and MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (3:1) gave the title compound **31p** as colorless solid (23.4 mg, 85 %): mp 114–115 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1620 (C=N), 1569 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.96–2.02 (m, 2H, CH₂), 3.71 (t,

$J = 5.5$ Hz, 2H, CH₂), 3.86 (s, 3H, CH₃), 4.04 (t, $J = 6.2$ Hz, 2H, CH₂), 6.93 (dd, $J = 7.9, 2.7$ Hz, 1H, Ar), 7.09 (t, $J = 2.7$ Hz, 1H, Ar), 7.14–7.17 (m, 1H, Ar), 7.21 (br s, NH), 7.24 (d, $J = 1.7$ Hz, 1H, Ar), 7.36 (t, $J = 7.9$ Hz, 1H, Ar), 7.44 (dd, $J = 8.5, 1.7$ Hz, 1H, Ar), 8.27 (d, $J = 8.5$ Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ : 21.0, 43.8, 45.0, 55.4, 112.8, 113.6, 119.5, 121.8, 125.2, 125.6, 129.3, 129.3, 129.9, 140.6, 143.4, 146.4, 153.4, 160.0; *Anal.* calcd for C₁₈H₁₇N₃OS: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.56; H, 5.14; N, 12.83.

3.1.54 Synthesis of 3,4-Dihydro-9-(3-isopropoxyphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31q)

N-(*tert*-Butyl)-3,4-dihydro-9-(3-isopropoxyphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (**29q**). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3-isopropoxyphenylboronic acid (32.4 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29q** as a colorless oil (48.8 mg, 80 %): IR (neat) cm⁻¹: 1592 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ : 1.36 (d, $J = 5.7$ Hz, 6H, 2 × CH₃), 1.40 (s, 9H, 3 × CH₃), 1.90–1.95 (m, 2H, CH₂), 3.64 (t, $J = 5.7$ Hz, 2H, CH₂), 3.89 (t, $J = 6.0$ Hz, 2H, CH₂), 4.58–4.65 (m, 1H, CH), 6.89 (dd, $J = 8.0, 2.0$ Hz, 1H, Ar), 7.10 (t, $J = 2.0$ Hz, 1H, Ar), 7.14 (dd, $J = 7.4, 2.0$ Hz, 1H, Ar), 7.31–7.34 (m, 2H, Ar), 7.41 (dd, $J = 8.0, 1.7$ Hz, 1H, Ar), 8.24 (d, $J = 8.0$ Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ : 21.9, 22.0 (2C), 30.0 (3C), 45.1, 45.4, 54.1, 69.9, 114.9, 115.1, 119.3, 122.8, 124.8, 126.6, 128.8, 129.4, 129.9, 138.3, 140.9, 142.8, 147.7, 158.3; HRMS (FAB): m/z calcd for C₂₄H₃₀N₃OS [M + H]⁺ 408.2110; found: 408.2108.

Compound 31q. Using the general procedure as described for **25a**, compound **29q** (44.0 mg, 0.108 mmol) was allowed to react for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **31q** as a colorless oil (35.5 mg, 94 %): IR (neat) cm⁻¹: 1620 (C=N), 1567 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ : 1.36 (d, $J = 6.1$ Hz, 6H, 2 × CH₃), 1.95–2.01 (m, 2H, CH₂), 3.70 (t, $J = 5.5$ Hz, 2H, CH₂), 4.03 (t, $J = 6.2$ Hz, 2H, CH₂), 4.57–4.66 (m, 1H, CH), 6.90 (dd, $J = 8.3, 2.4$ Hz, 1H, Ar), 7.09 (d, $J = 1.8$ Hz, 1H, Ar), 7.11–7.13 (m, 1H, Ar), 7.23 (d, $J = 1.8$ Hz, 1H, Ar), 7.33 (t, $J = 8.0$ Hz, 1H, Ar), 7.43 (dd, $J = 8.5, 1.8$ Hz, 1H, Ar), 8.26 (d, $J = 8.5$ Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ : 21.0, 22.0 (2C), 43.8, 45.0, 70.0, 115.0, 115.2, 119.2, 121.8, 125.1, 125.5, 129.2, 129.3, 129.9, 140.6, 143.4, 146.4, 153.4, 158.3; HRMS (FAB): m/z calcd for C₂₀H₂₂N₃OS [M + H]⁺ 352.1484; found: 352.1484.

3.1.55 Synthesis of 9-[(1,1'-Biphenyl)-3-yl]-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31r)

9-[(1,1'-Biphenyl)-3-yl]-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (29r). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3-biphenylboronic acid (35.7 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29r** as a colorless oil (65.1 mg, > 99 %): IR (neat) cm^{-1} : 1591 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.41 (s, 9H, 3 \times CH_3), 1.91–1.95 (m, 2H, CH_2), 3.64 (t, $J = 5.4$ Hz, 2H, CH_2), 3.89 (t, $J = 6.3$ Hz, 2H, CH_2), 7.35–7.39 (m, 2H, Ar), 7.44–7.51 (m, 4H, Ar), 7.55–7.60 (m, 2H, Ar), 7.63 (d, $J = 7.4$ Hz, 2H, Ar), 7.78 (s, 1H, Ar), 8.27 (d, $J = 8.0$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 122.8, 124.9, 125.9 (2C), 126.7, 126.9, 127.2 (2C), 127.5, 128.8 (2C), 129.0, 129.3, 129.6, 138.2, 139.9, 140.9, 142.0, 142.8, 147.7; HRMS (FAB): m/z calcd for $\text{C}_{27}\text{H}_{28}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 426.2004; found: 426.2000.

Compound 31r. Using the general procedure as described for **25a**, compound **29r** (56.1 mg, 0.13 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **31r** as colorless solid (37.0 mg, 76 %): mp 179–181 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1620 (C=N), 1568 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.97–2.02 (m, 2H, CH_2), 3.72 (t, $J = 5.4$ Hz, 2H, CH_2), 4.04 (t, $J = 6.0$ Hz, 2H, CH_2), 7.30 (d, $J = 1.7$ Hz, 1H, Ar), 7.38 (t, $J = 7.4$ Hz, 1H, Ar), 7.45–7.56 (m, 5H, Ar), 7.59–7.64 (m, 3H, Ar), 7.77 (s, 1H, Ar), 8.30 (d, $J = 8.6$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 21.0, 43.9, 45.0, 121.9, 125.2, 125.6, 125.9 (2C), 127.1, 127.2 (2C), 127.6, 128.8 (2C), 129.3, 129.4 (2C), 139.7, 140.8, 142.1, 143.4, 146.4, 153.3; HRMS (FAB): m/z calcd for $\text{C}_{23}\text{H}_{20}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 370.1378; found: 370.1378.

3.1.56 Synthesis of 3,4-Dihydro-9-(2-methoxyphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31s)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(2-methoxyphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (29s).** Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 2-methoxyphenylboronic acid (27.4 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title

compound **29s** as a colorless oil (46.0 mg, 81 %): IR (neat) cm^{-1} : 1591 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.39 (s, 9H, 3 \times CH_3), 1.89–1.95 (m, 2H, CH_2), 3.63 (t, $J = 5.4$ Hz, 2H, CH_2), 3.80 (s, 3H, CH_3), 3.88 (t, $J = 5.9$ Hz, 2H, CH_2), 6.97 (d, $J = 8.3$ Hz, 1H, Ar), 7.02 (t, $J = 7.4$ Hz, 1H, Ar), 7.29–7.38 (m, 4H, Ar), 8.21 (d, $J = 8.3$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 22.0, 30.0 (3C), 45.1, 45.4, 54.1, 55.6, 111.4, 120.9, 125.2, 126.2, 127.5, 128.0, 128.6, 129.1, 129.3, 130.6, 138.6, 140.6, 147.9, 156.5; HRMS (FAB): m/z calcd for $\text{C}_{22}\text{H}_{26}\text{N}_3\text{OS}$ [$\text{M} + \text{H}$] $^+$ 380.1797; found: 380.1793.

Compound 31s. Using the general procedure as described for **25a**, compound **29s** (34.7 mg, 0.091 mmol) was allowed to react for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **31s** as colorless solid (21.6 mg, 73 %): mp 130.5 $^\circ\text{C}$ (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1620 (C=N), 1567 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.95–2.01 (m, 2H, CH_2), 3.70 (t, $J = 5.6$ Hz, 2H, CH_2), 3.80 (s, 3H, CH_3), 4.03 (t, $J = 6.2$ Hz, 2H, CH_2), 6.97 (d, $J = 8.3$ Hz, 1H, Ar), 7.02 (td, $J = 7.5, 0.8$ Hz, 1H, Ar), 7.22 (d, $J = 1.5$ Hz, 1H, Ar), 7.28–7.40 (m, 3H, Ar), 8.24 (d, $J = 8.3$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.1, 43.8, 44.9, 55.6, 111.3, 120.9, 124.3, 125.1, 127.7, 128.3, 128.4, 128.7, 129.5, 130.5, 141.1, 146.6, 153.7, 156.4; *Anal.* calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{OS}$: C, 66.85; H, 5.30; N, 12.99. Found: C, 66.56; H, 5.08; N, 12.90.

3.1.57 Synthesis of 9-[(1,1'-Biphenyl)-2-yl]-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31t)

9-[(1,1'-Biphenyl)-2-yl]-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (29t). Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 2-biphenylboronic acid (35.7 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29t** as a colorless oil (64.1 mg, >99 %): IR (neat) cm^{-1} : 1591 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.36 (s, 9H, 3 \times CH_3), 1.86–1.91 (m, 2H, CH_2), 3.59 (t, $J = 5.6$ Hz, 2H, CH_2), 3.85 (t, $J = 6.2$ Hz, 2H, CH_2), 6.91–6.93 (m, 2H, Ar), 7.11–7.14 (m, 2H, Ar), 7.19–7.22 (m, 3H, Ar), 7.40–7.42 (m, 4H, Ar), 7.99 (d, $J = 8.8$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.9, 29.9 (3C), 45.1, 45.4, 54.1, 125.5, 125.9, 126.7, 127.5, 127.9, 127.9, 128.1, 128.1 (2C), 128.6, 129.7 (2C), 130.2, 130.7, 138.4, 138.9, 140.6, 140.9, 143.6, 147.8; HRMS (FAB): m/z calcd for $\text{C}_{27}\text{H}_{28}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 426.2004; found: 426.2002.

Compound 31t. Using the general procedure as described for **25a**, compound **29t** (51.1 mg, 0.12 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **31t** as a colorless oil (35.7 mg, 81 %): IR (neat) cm^{-1} : 1620

(C=N), 1570 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.92–1.98 (m, 2H, CH_2), 3.66 (t, $J = 5.5$ Hz, 2H, CH_2), 3.99 (t, $J = 6.1$ Hz, 2H, CH_2), 6.83 (d, $J = 1.7$ Hz, 1H, Ar), 6.95 (dd, $J = 8.3, 1.7$ Hz, 1H, Ar), 7.11–7.13 (m, 2H, Ar), 7.20–7.23 (m, 3H, Ar), 7.38–7.43 (m, 4H, Ar), 8.03 (d, $J = 8.3$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.0, 43.8, 44.9, 124.5, 124.8, 126.8, 127.6, 128.1 (3C), 128.1, 128.2, 128.3, 128.4, 129.7 (2C), 130.2, 138.5, 140.6, 140.8, 144.2, 146.5, 153.5; HRMS (FAB): m/z calcd for $\text{C}_{23}\text{H}_{20}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 370.1378; found: 370.1378.

3.1.58 Synthesis of 3,4-Dihydro-9-(3,4-dimethoxyphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31u)

N-(*tert*-Butyl)-3,4-dihydro-9-(3,4-dimethoxyphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (**29u**). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3,4-dimethoxyphenylboronic acid (32.8 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29u** as colorless solid (60.3 mg, 98 %): mp 147–148 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1593 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.40 (s, 9H, 3 \times CH_3), 1.90–1.96 (m, 2H, CH_2), 3.64 (t, $J = 5.5$ Hz, 2H, CH_2), 3.89 (t, $J = 6.1$ Hz, 2H, CH_2), 3.92 (s, 3H, CH_3), 3.96 (s, 3H, CH_3), 6.93 (d, $J = 8.3$ Hz, 1H, Ar), 7.09 (d, $J = 2.0$ Hz, 1H, Ar), 7.15 (dd, $J = 8.3, 2.0$ Hz, 1H, Ar), 7.29 (d, $J = 1.7$ Hz, 1H, Ar), 7.39 (dd, $J = 8.3, 1.7$ Hz, 1H, Ar), 8.23 (d, $J = 8.3$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.1, 45.4, 54.1, 56.0, 56.0, 110.1, 111.4, 119.5, 122.2, 124.5, 126.1, 128.9, 129.4, 132.3, 138.3, 142.7, 147.7, 149.3 (2C); HRMS (FAB): m/z calcd for $\text{C}_{23}\text{H}_{28}\text{N}_3\text{O}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 410.1902; found: 410.1907.

Compound 31u. Using the general procedure as described for **25a**, compound **29u** (46.0 mg, 0.11 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **31u** as colorless solid (24.6 mg, 63 %): mp 142 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1620 (C=N), 1567 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.96–2.02 (m, 2H, CH_2), 3.71 (t, $J = 5.6$ Hz, 2H, CH_2), 3.92 (s, 3H, CH_3), 3.96 (s, 3H, CH_3), 4.04 (t, $J = 6.2$ Hz, 2H, CH_2), 6.93 (d, $J = 8.3$ Hz, 1H, Ar), 7.07 (d, $J = 2.0$ Hz, 1H, Ar), 7.14 (dd, $J = 8.3, 2.0$ Hz, 1H, Ar), 7.20 (d, $J = 1.8$ Hz, 1H, Ar), 7.41 (dd, $J = 8.3, 1.8$ Hz, 1H, Ar), 8.25 (d, $J = 8.3$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.0, 43.8, 44.9, 56.0, 56.0, 110.1, 111.5, 119.5, 121.3, 124.7, 125.0, 129.3, 129.4, 132.0, 143.2, 146.4, 149.3, 149.4, 153.4; Anal. calcd for $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$: C, 64.57; H, 5.42; N, 11.89. Found: C, 64.41; H, 5.37; N, 11.93.

3.1.59 Synthesis of 3,4-Dihydro-9-(3,4,5-trimethoxyphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31v)

N-(*tert*-Butyl)-3,4-dihydro-9-(3,4,5-trimethoxyphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (**29v**). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3,4,5-trimethoxyphenylboronic acid (38.2 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29v** as a colorless oil (65.0 mg, 99 %): IR (neat) cm^{-1} : 1585 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.41 (s, 9H, 3 \times CH₃), 1.91–1.96 (m, 2H, CH₂), 3.64 (t, $J = 5.5$ Hz, 2H, CH₂), 3.88–3.91 (m, 5H, CH₃, CH₂), 3.93 (s, 6H, 2 \times CH₃), 6.77 (s, 2H, Ar), 7.28 (d, $J = 1.8$ Hz, 1H, Ar), 7.38 (dd, $J = 8.4$, 1.8 Hz, 1H, Ar), 8.24 (d, $J = 8.4$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 56.3 (2C), 60.9, 104.4 (2C), 122.6, 124.7, 126.5, 128.9, 129.5, 135.3, 138.1, 138.3, 143.0, 147.7, 153.6 (2C); HRMS (FAB): m/z calcd for C₂₄H₃₀N₃O₃S [M + H]⁺ 440.2008; found: 440.2008.

Compound 31v. Using the general procedure as described for **25a**, compound **29v** (49.4 mg, 0.11 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **31v** as colorless solid (14.2 mg, 34 %): mp 156–157 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1620 (C=N), 1569 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.97–2.02 (m, 2H, CH₂), 3.71 (t, $J = 5.5$ Hz, 2H, CH₂), 3.89 (s, 3H, CH₃), 3.93 (s, 6H, 2 \times CH₃), 4.04 (t, $J = 6.1$ Hz, 2H, CH₂), 6.75 (s, 2H, Ar), 7.20 (d, $J = 1.7$ Hz, 1H, Ar), 7.40 (dd, $J = 8.5$, 1.7 Hz, 1H, Ar), 8.27 (d, $J = 8.5$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.0, 43.9, 45.0, 56.3 (2C), 61.0, 104.4 (2C), 121.7, 125.0, 125.4, 129.3 (2C), 135.0, 138.5, 143.6, 146.4, 153.3, 153.6 (2C); HRMS (FAB): m/z calcd for C₂₀H₂₂N₃O₃S [M + H]⁺ 384.1382; found: 384.1381.

3.1.60 Synthesis of 9-(3-Chloro-4-methoxyphenyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (31w)

N-(*tert*-Butyl)-9-(3-chloro-4-methoxyphenyl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (**29w**). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3-chloro-4-methoxyphenylboronic acid (33.6 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the

title compound **29w** as a colorless oil (58.7 mg, 95 %): IR (neat) cm^{-1} : 1592 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.40 (s, 9H, $3 \times \text{CH}_3$), 1.90–1.95 (m, 2H, CH_2), 3.64 (t, $J = 5.4$ Hz, 2H, CH_2), 3.89 (t, $J = 6.0$ Hz, 2H, CH_2), 3.94 (s, 3H, CH_3), 6.98 (d, $J = 8.6$ Hz, 1H, Ar), 7.26 (d, $J = 2.0$ Hz, 1H, Ar), 7.36 (dd, $J = 8.6, 2.0$ Hz, 1H, Ar), 7.45 (dd, $J = 8.6, 2.3$ Hz, 1H, Ar), 7.61 (d, $J = 2.3$ Hz, 1H, Ar), 8.23 (d, $J = 8.6$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 56.2, 112.2, 122.2, 123.0, 124.3, 126.2, 126.4, 128.7, 129.0, 129.7, 132.7, 138.1, 141.2, 147.6, 155.0; HRMS (FAB): m/z calcd for $\text{C}_{22}\text{H}_{25}\text{ClN}_3\text{OS}$ [$\text{M} + \text{H}$] $^+$ 414.1407; found: 414.1402.

Compound 31w. Using the general procedure as described for **25a**, compound **29w** (41.6 mg, 0.10 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **31w** as colorless solid (18.8 mg, 53 %): mp 186–188 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1620 (C=N), 1563 (C=N); $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 1.97–2.01 (m, 2H, CH_2), 3.71 (t, $J = 5.4$ Hz, 2H, CH_2), 3.94 (s, 3H, CH_3), 4.03 (t, $J = 6.0$ Hz, 2H, CH_2), 6.98 (d, $J = 8.6$ Hz, 1H, Ar), 7.17 (d, $J = 1.4$ Hz, 1H, Ar), 7.38 (dd, $J = 8.0, 2.3$ Hz, 1H, Ar), 7.44 (dd, $J = 8.0, 1.4$ Hz, 1H, Ar), 7.59 (d, $J = 2.3$ Hz, 1H, Ar), 8.25 (d, $J = 8.0$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 21.0, 43.8, 44.9, 56.2, 112.2, 121.2, 123.0, 124.5, 125.3, 126.2, 128.7, 129.4, 129.5, 132.4, 141.7, 146.3, 153.2, 155.1; HRMS (FAB): m/z calcd for $\text{C}_{18}\text{H}_{17}\text{ClN}_3\text{OS}$ [$\text{M} + \text{H}$] $^+$ 358.0781; found: 358.0777.

3.1.61 Synthesis of 9-(3-Chloro-6-methoxyphenyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (31x)

N-(*tert*-Butyl)-9-(3-chloro-6-methoxyphenyl)-3,4-dihydro-2H,6H-pyrimido [1,2-*c*][1,3]benzothiazin-6-imine (**29x**). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3-chloro-6-methoxyphenylboronic acid (33.6 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **29x** as a colorless oil (54.9 mg, 88 %): IR (neat) cm^{-1} : 1591 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.39 (s, 9H, $3 \times \text{CH}_3$), 1.89–1.95 (m, 2H, CH_2), 3.64 (t, $J = 5.5$ Hz, 2H, CH_2), 3.78 (s, 3H, CH_3), 3.88 (t, $J = 6.1$ Hz, 2H, CH_2), 6.88 (d, $J = 9.5$ Hz, 1H, Ar), 7.26–7.34 (m, 4H, Ar), 8.21 (d, $J = 8.3$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.9, 30.0 (3C), 45.1, 45.4, 54.1, 55.9, 112.6, 125.1, 125.8, 126.7, 127.2, 128.1, 128.8, 128.8, 130.2, 130.6, 138.4, 139.2, 147.8, 155.1; HRMS (FAB): m/z calcd for $\text{C}_{22}\text{H}_{25}\text{ClN}_3\text{OS}$ [$\text{M} + \text{H}$] $^+$ 414.1407; found: 414.1410.

Compound 31x. Using the general procedure as described for **25a**, compound **29x** (33.2 mg, 0.080 mmol) was allowed to react for 3 h. Purification by flash

chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **31x** as colorless solid (16.3 mg, 57 %): mp 175–178 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1620 (C=N), 1568 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.96–2.02 (m, 2H, CH₂), 3.71 (t, *J* = 5.6 Hz, 2H, CH₂), 3.79 (s, 3H, CH₃), 4.04 (t, *J* = 6.2 Hz, 2H, CH₂), 6.89 (d, *J* = 8.5 Hz, 1H, Ar), 7.19 (d, *J* = 1.7 Hz, 1H, Ar), 7.26–7.30 (m, 2H, Ar), 7.36 (dd, *J* = 8.3, 1.7 Hz, 1H, Ar), 8.27 (d, *J* = 8.3 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 20.9, 43.8, 44.8, 55.9, 112.5, 124.2, 125.3, 125.8, 127.5, 128.6, 128.9, 130.1 (2C), 130.1, 139.8, 146.6, 153.3, 155.0; HRMS (FAB): *m/z* calcd for C₁₈H₁₇ClN₃OS [M + H]⁺ 358.0781; found: 358.0783.

3.1.62 Synthesis of 3,4-Dihydro-9-(naphthalen-2-yl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**32a**)

N-(*tert*-Butyl)-3,4-dihydro-9-(naphthalen-2-yl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**30a**). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 2-naphthaleneboronic acid (30.9 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **30a** as colorless solid (56.3 mg, 94 %): mp 144–145 °C (from *n*-hexane); IR (neat) cm⁻¹: 1592 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.42 (s, 9H, 3 × CH₃), 1.91–1.96 (m, 2H, CH₂), 3.65 (t, *J* = 5.2 Hz, 2H, CH₂), 3.90 (t, *J* = 5.7 Hz, 2H, CH₂), 7.45–7.51 (m, 3H, Ar), 7.55 (d, *J* = 8.0 Hz, 1H, Ar), 7.71 (d, *J* = 8.0 Hz, 1H, Ar), 7.84–7.91 (m, 3H, Ar), 8.04 (s, 1H, Ar), 8.29 (d, *J* = 8.6 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.9, 30.0 (3C), 45.1, 45.5, 54.2, 122.9, 125.0 (2C), 126.0, 126.3, 126.5, 126.6, 127.6, 128.3, 128.6, 129.0, 129.6, 132.9, 133.5, 136.7, 138.3, 142.8, 147.7; HRMS (FAB): *m/z* calcd for C₂₅H₂₆N₃S [M + H]⁺ 400.1847; found: 400.1848.

Compound 32a. Using the general procedure as described for **25a**, compound **30a** (45.3 mg, 0.11 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **32a** as colorless solid (28.2 mg, 73 %): mp 143–145 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1620 (C=N), 1568 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.96–2.02 (m, 2H, CH₂), 3.72 (t, *J* = 5.6 Hz, 2H, CH₂), 4.04 (t, *J* = 6.2 Hz, 2H, CH₂), 7.36 (d, *J* = 1.8 Hz, 1H, Ar), 7.49–7.52 (m, 2H, Ar), 7.57 (dd, *J* = 8.5, 1.8 Hz, 1H, Ar), 7.68 (dd, *J* = 8.5, 1.8 Hz, 1H, Ar), 7.84–7.91 (m, 3H, Ar), 8.02 (d, *J* = 1.5 Hz, 1H, Ar), 8.33 (d, *J* = 8.5 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.0, 43.8, 44.9, 122.0, 124.9, 125.3 (2C), 126.1, 126.4, 126.5, 127.6, 128.3, 128.7, 129.4 (2C), 133.0, 133.5, 136.3, 143.4, 146.5, 153.3; HRMS (FAB): *m/z* calcd for C₂₁H₁₈N₃S [M + H]⁺ 344.1221; found: 344.1222.

3.1.63 Synthesis of 3,4-Dihydro-9-(naphthalen-1-yl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (32b)

N-(*tert*-Butyl)-3,4-dihydro-9-(naphthalen-1-yl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (**30b**). Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 1-naphthaleneboronic acid (30.9 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **30b** as a colorless oil (58.4 mg, 97 %): IR (neat) cm^{-1} : 1590 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.40 (s, 9H, 3 \times CH_3), 1.92–1.98 (m, 2H, CH_2), 3.67 (t, $J = 5.6$ Hz, 2H, CH_2), 3.92 (t, $J = 6.1$ Hz, 2H, CH_2), 7.25–7.25 (m, 1H, Ar), 7.34 (dd, $J = 8.3, 1.7$ Hz, 1H, Ar), 7.39–7.52 (m, 4H, Ar), 7.86 (d, $J = 8.3$ Hz, 2H, Ar), 7.89 (d, $J = 7.6$ Hz, 1H, Ar), 8.31 (d, $J = 8.3$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 22.0, 30.0 (3C), 45.1, 45.4, 54.2, 125.3, 125.6, 125.6, 125.9, 126.3, 126.7, 126.8, 128.0, 128.2, 128.3, 128.3, 129.1, 131.2, 133.7, 138.2, 138.6, 142.8, 147.8; HRMS (FAB): m/z calcd for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 400.1847; found: 400.1845.

Compound 32b. Using the general procedure as described for **25a**, compound **30b** (46.4 mg, 0.12 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **32b** as colorless solid (34.4 mg, 86 %): mp 146–148 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1620 (C=N), 1568 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.98–2.04 (m, 2H, CH_2), 3.73 (t, $J = 5.6$ Hz, 2H, CH_2), 4.06 (t, $J = 6.2$ Hz, 2H, CH_2), 7.17 (d, $J = 1.7$ Hz, 1H, Ar), 7.35–7.52 (m, 5H, Ar), 7.81–7.91 (m, 3H, Ar), 8.33 (d, $J = 8.3$ Hz, 1H, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.1, 43.8, 45.0, 124.7, 125.2, 125.4, 125.6, 126.0, 126.4, 126.8, 128.3, 128.4 (2C), 128.7, 128.9, 131.1, 133.7, 138.2, 143.4, 146.5, 153.3; HRMS (FAB): m/z calcd for $\text{C}_{21}\text{H}_{18}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 344.1221; found: 344.1221.

3.1.64 Synthesis of 3,4-Dihydro-9-(3,4-methylenedioxyphenyl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (32c)

N-(*tert*-Butyl)-3,4-dihydro-9-(3,4-methylenedioxyphenyl)-2H,6H-pyrimido [1,2-c][1,3]benzothiazin-6-imine (**30c**). Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3,4-(methylenedioxy)phenylboronic acid (29.9 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **30c** as colorless solid (54.6 mg, 93 %): mp 173 °C (from CHCl_3 –*n*-hexane); IR (neat) cm^{-1} : 1591 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.40 (s,

9H, 3 × CH₃), 1.89–1.95 (m, 2H, CH₂), 3.63 (t, *J* = 5.5 Hz, 2H, CH₂), 3.88 (t, *J* = 6.2 Hz, 2H, CH₂), 5.99 (s, 2H, CH₂), 6.87 (d, *J* = 8.8 Hz, 1H, Ar), 7.05–7.07 (m, 2H, Ar), 7.24 (d, *J* = 2.0 Hz, 1H, Ar), 7.34 (dd, *J* = 8.3, 2.0 Hz, 1H, Ar), 8.21 (d, *J* = 8.3 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 101.3, 107.4, 108.6, 120.7, 122.3, 124.5, 126.2, 128.9, 129.5, 133.7, 138.3, 142.6, 147.7, 147.7, 148.3; HRMS (FAB): *m/z* calcd for C₂₂H₂₄N₃O₂S [M + H]⁺ 394.1589; found: 394.1592.

Compound 32c. Using the general procedure as described for **25a**, compound **30c** (40.1 mg, 0.102 mmol) was allowed to react for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **32c** as colorless solid (17.0 mg, 49 %): mp 169–170 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1619 (C=N), 1568 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.95–2.01 (m, 2H, CH₂), 3.70 (t, *J* = 5.5 Hz, 2H, CH₂), 4.03 (t, *J* = 6.1 Hz, 2H, CH₂), 6.00 (s, 2H, CH₂), 6.87 (d, *J* = 7.8 Hz, 1H, Ar), 7.04–7.06 (m, 2H, Ar), 7.15 (d, *J* = 1.7 Hz, 1H, Ar), 7.20 (br s, 1H, NH), 7.36 (dd, *J* = 8.3, 1.7 Hz, 1H, Ar), 8.24 (d, *J* = 8.3 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.0, 43.8, 45.0, 101.3, 107.4, 108.7, 120.8, 121.3, 124.8, 125.1, 129.3, 129.3, 133.4, 143.1, 146.4, 147.9, 148.3, 153.4; HRMS (FAB): *m/z* calcd for C₁₈H₁₆N₃O₂S [M + H]⁺ 338.0963; found: 338.0960.

3.1.65 Synthesis of 3,4-Dihydro-9-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (32d)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (30d).** Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid (32.3 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **30d** as a colorless oil (63.9 mg, 96 %): IR (neat) cm⁻¹: 1586 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.40 (s, 9H, 3 × CH₃), 1.89–1.94 (m, 2H, CH₂), 3.63 (t, *J* = 5.4 Hz, 2H, CH₂), 3.88 (t, *J* = 6.0 Hz, 2H, CH₂), 4.28 (s, 4H, 2 × CH₂), 6.92 (d, *J* = 8.6 Hz, 1H, Ar), 7.07–7.09 (m, 1H, Ar), 7.11 (d, *J* = 2.3 Hz, 1H, Ar), 7.26 (s, 1H, Ar), 7.36 (t, *J* = 4.0 Hz, 1H, Ar), 8.21 (d, *J* = 8.6 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.9, 30.0 (3C), 45.1, 45.4, 54.1, 64.4, 64.5, 115.8, 117.6, 120.0, 122.2, 124.4, 126.1, 128.9, 129.4, 132.9, 138.4, 142.3, 143.8 (2C), 147.7; HRMS (FAB): *m/z* calcd for C₂₃H₂₆N₃O₂S [M + H]⁺ 408.1746; found: 408.1746.

Compound 32d. Using the general procedure as described for **25a**, compound **30d** (45.1 mg, 0.11 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the

title compound **32d** as colorless solid (26.7 mg, 69 %): mp 174–176 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1619 (C=N), 1567 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.95–2.00 (m, 2H, CH₂), 3.70 (t, *J* = 5.7 Hz, 2H, CH₂), 4.03 (t, *J* = 6.3 Hz, 2H, CH₂), 4.28 (s, 4H, 2 × CH₂), 6.92 (d, *J* = 8.6 Hz, 1H, Ar), 7.06 (dd, *J* = 8.6, 2.3 Hz, 1H, Ar), 7.09 (d, *J* = 2.3 Hz, 1H, Ar), 7.17 (d, *J* = 2.0 Hz, 1H, Ar), 7.19 (br s, 1H, NH), 7.38 (dd, *J* = 8.6, 2.0 Hz, 1H, Ar), 8.23 (d, *J* = 8.6 Hz, 1H, Ar; ¹³C-NMR (125 MHz, CDCl₃) δ: 21.0, 43.8, 44.9, 64.3, 64.4, 115.8, 117.7, 120.0, 121.2, 124.6, 125.0, 129.2, 129.3, 132.5, 142.8, 143.8, 143.9, 146.4, 153.4; HRMS (FAB): *m/z* calcd for C₁₉H₁₈N₃O₂S [M + H]⁺ 352.1120; found: 352.1121.

3.1.66 Synthesis of 3,4-Dihydro-9-(quinolin-6-yl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**32e**)

N-(*tert*-Butyl)-3,4-dihydro-9-(quinolin-6-yl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**30e**). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 6-quinolineboronic acid (31.1 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 1:1) gave the title compound **30e** as colorless solid (36.2 mg, 60 %): mp 179–180 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1590 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.42 (s, 9H, 3 × CH₃), 1.91–1.97 (m, 2H, CH₂), 3.66 (t, *J* = 5.4 Hz, 2H, CH₂), 3.91 (t, *J* = 6.1 Hz, 2H, CH₂), 7.42–7.46 (m, 2H, Ar), 7.55 (dd, *J* = 8.3, 1.8 Hz, 1H, Ar), 7.95 (dd, *J* = 8.8, 2.0 Hz, 1H, Ar), 8.00 (d, *J* = 1.5 Hz, 1H, Ar), 8.16–8.21 (m, 2H, Ar), 8.32 (d, *J* = 8.3 Hz, 1H, Ar), 8.93 (dd, *J* = 4.1, 1.5 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 121.6, 123.1, 125.0, 125.7, 126.9, 128.4, 128.7, 129.1, 129.8, 130.1, 136.2, 137.5, 138.0, 142.0, 147.6, 148.0, 150.7; HRMS (FAB): *m/z* calcd for C₂₄H₂₅N₄S [M + H]⁺ 401.1800; found: 401.1802.

Compound 32e. Using the general procedure as described for **25a**, compound **30e** (27.0 mg, 0.067 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 1:1) gave the title compound **32e** as colorless solid (19.3 mg, 84 %): mp 165–167 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1620 (C=N), 1572 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.98–2.04 (m, 2H, CH₂), 3.73 (t, *J* = 5.5 Hz, 2H, CH₂), 4.06 (t, *J* = 6.1 Hz, 2H, CH₂), 7.38 (d, *J* = 1.7 Hz, 1H, Ar), 7.45 (dd, *J* = 8.0, 4.3 Hz, 1H, Ar), 7.58 (dd, *J* = 8.3, 1.7 Hz, 1H, Ar), 7.94 (dd, *J* = 8.8, 2.2 Hz, 1H, Ar), 8.01 (d, *J* = 2.2 Hz, 1H, Ar), 8.18 (d, *J* = 8.8 Hz, 1H, Ar), 8.22 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar), 8.35 (d, *J* = 8.3 Hz, 1H, Ar), 8.94 (dd, *J* = 4.3, 1.5 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.0, 43.8, 45.0, 121.7, 122.1, 125.3, 125.8, 125.9, 128.3, 128.6, 129.5, 129.6, 130.2, 136.3, 137.2, 142.5, 146.3, 148.0, 150.8,

153.2; HRMS (FAB): m/z calcd for $C_{20}H_{17}N_4S$ $[M + H]^+$ 345.1174; found: 345.1175.

3.1.67 Synthesis of 3,4-Dihydro-9-[3-(trifluoromethylcarbonyl)indol-6-yl]-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (32f)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(indol-6-yl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (30f).** Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with indol-6-ylboronic acid (29.0 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (2:1) gave the title compound **30f** as colorless solid (56.0 mg, 96 %): mp 256 °C (from MeOH–CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1589 (C=N); ¹H-NMR (500 MHz, DMSO-*d*₆) δ: 1.39 (s, 9H, 3 × CH₃), 1.82–1.87 (m, 2H, CH₂), 3.55 (t, *J* = 5.4 Hz, 2H, CH₂), 3.82 (t, *J* = 6.0 Hz, 2H, CH₂), 6.46 (s, 1H, Ar), 7.37 (d, *J* = 8.3 Hz, 1H, Ar), 7.42 (t, *J* = 2.6 Hz, 1H, Ar), 7.58–7.63 (m, 3H, Ar), 7.72 (s, 1H, Ar), 8.21 (d, *J* = 8.3 Hz, 1H, Ar), 11.21 (br s, 1H, NH); ¹³C-NMR (125 MHz, CDCl₃–CD₃OD) δ: 21.6, 29.7 (3C), 44.6, 45.4, 54.2, 109.6, 118.8, 120.7 (2C), 122.8, 125.1, 125.3, 125.5, 127.8, 128.5, 129.3, 132.7, 136.3, 138.4, 144.5, 149.3; HRMS (FAB): m/z calcd for $C_{23}H_{25}N_4S$ $[M + H]^+$ 389.1800; found: 389.1800.

Compound 32f. TFA (17 mL) was added to a mixture of **30f** (31.9 mg, 0.082 mmol) and MS4 Å (4.5 g, powder, activated by heating with Bunsen burner) in CHCl₃ (3.0 mL) and MeOH (5 drops). After being stirred under reflux for 8.5 h, the mixture was concentrated. To a mixture of this residue in CHCl₃ was added dropwise Et₃N at 0 °C to adjust pH to 8–9. The whole was extracted with EtOAc. The extract was washed with sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was purified by preparative TLC over aluminum oxide with CHCl₃–MeOH (98:2) to give the title compound **32f** as pale yellow solid (17.8 mg, 51 %): mp 270 °C (decomp.) (from MeOH–CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1662 (C=O), 1568 (C=N); ¹H-NMR (500 MHz, DMSO-*d*₆) δ: 1.86–1.91 (m, 2H, CH₂), 3.61 (t, *J* = 5.4 Hz, 2H, CH₂), 3.94 (t, *J* = 6.0 Hz, 2H, CH₂), 7.61–7.62 (m, 2H, Ar), 7.71 (dd, *J* = 8.6, 1.7 Hz, 1H, Ar), 7.88 (s, 1H, Ar), 8.24–8.28 (m, 2H, Ar), 8.55 (d, *J* = 1.7 Hz, 1H, Ar), 8.75 (s, 1H, NH), 12.82 (br s, 1H, NH); ¹³C-NMR (100 MHz, DMSO-*d*₆) δ: 20.7, 43.1, 44.4, 108.8, 111.1, 116.8 (q, *J* = 291.3 Hz), 121.5, 121.7, 122.6, 124.4, 124.8, 125.7, 129.1, 129.6, 134.6, 137.2, 138.5 (q, *J* = 4.7 Hz), 142.4, 145.1, 149.7, 173.9 (q, *J* = 33.9 Hz); HRMS (FAB): m/z calcd for $C_{21}H_{16}F_3N_4OS$ $[M + H]^+$ 429.0997; found: 429.1001.

3.1.68 Synthesis of 3,4-Dihydro-9-[3-(trifluoromethylcarbonyl)indol-5-yl]-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (32g)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(indol-5-yl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (30g).** Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with indol-5-ylboronic acid (29.0 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (2:1) gave the title compound **30g** as colorless solid (59.2 mg, > 99 %): mp 232–233 °C (from MeOH–CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1583 (C=N); ¹H-NMR (400 MHz, CDCl₃–CD₃OD) δ: 1.41 (s, 9H, 3 × CH₃), 1.91–1.97 (m, 2H, CH₂), 3.63 (t, *J* = 5.4 Hz, 2H, CH₂), 3.90 (t, *J* = 6.1 Hz, 2H, CH₂), 6.58 (d, *J* = 3.0 Hz, 1H, Ar), 7.23 (d, *J* = 3.0 Hz, 1H, Ar), 7.41–7.42 (m, 3H, Ar), 7.50 (dd, *J* = 8.5, 0.9 Hz, 1H, Ar), 7.86 (s, 1H, Ar), 8.18 (d, *J* = 8.5 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃–CD₃OD) δ: 21.8, 29.9 (3C), 44.9, 45.5, 54.2, 102.7, 111.4, 119.2, 121.2, 122.7, 125.1, 125.1, 125.3, 128.3, 128.6, 129.3, 131.1, 135.7, 138.6, 144.6, 148.8; HRMS (FAB): *m/z* calcd for C₂₃H₂₅N₄S [M + H]⁺ 389.1800; found: 389.1800.

Compound 32g. TFA (17 mL) was added to a mixture of **30g** (28.5 mg, 0.073 mmol) and MS4Å (4.5 g, powder, activated by heating with Bunsen burner) in CHCl₃ (3.0 mL). After being stirred under reflux for 10 h, the mixture was concentrated. To a mixture of this residue in CHCl₃ was added dropwise Et₃N at 0 °C to adjust pH to 8–9. The whole was extracted with EtOAc. The extract was washed with sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was purified by preparative TLC over aluminum oxide with CHCl₃–MeOH (98:2) to give the compound **32g** as pale yellow solid (28.9 mg, 92 %): mp 250 °C (decomp.) (from MeOH–CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1659 (C=O), 1613 (C=N), 1561 (C=N); ¹H-NMR (500 MHz, DMSO-*d*₆) δ: 1.86–1.91 (m, 2H, CH₂), 3.61 (t, *J* = 5.4 Hz, 2H, CH₂), 3.94 (t, *J* = 5.7 Hz, 2H, CH₂), 7.56–7.59 (m, 2H, Ar), 7.67–7.72 (m, 2H, Ar), 8.28 (d, *J* = 8.6 Hz, 1H, Ar), 8.45 (s, 1H, Ar), 8.56 (d, *J* = 1.7 Hz, 1H, Ar), 8.75 (br s, 1H, NH), 12.82 (br s, 1H, NH); ¹³C-NMR (100 MHz, DMSO-*d*₆) δ: 20.7, 43.1, 44.4, 109.1, 113.6, 116.8 (q, *J* = 290.5 Hz), 119.2, 121.6, 123.7, 124.6, 124.6, 126.4, 129.1, 129.6, 133.9, 136.6, 138.4 (q, *J* = 4.7 Hz), 143.0, 145.2, 149.7, 173.9 (q, *J* = 33.7 Hz); HRMS (FAB): *m/z* calcd for C₂₁H₁₆F₃N₄OS [M + H]⁺ 429.0997; found: 429.0991.

3.1.69 Synthesis of 3,4-Dihydro-9-(pyridin-3-yl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (32h)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(pyridin-3-yl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (30h).** Using the general procedure as described for **22i**,

N-(*tert*-butyl)-9-bromo-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3-pyridineboronic acid (22.1 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **30h** as colorless solid (45.9 mg, 87 %): mp 143–144 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1595 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.40 (s, 9H, 3 × CH₃), 1.91–1.96 (m, 2H, CH₂), 3.65 (t, *J* = 5.6 Hz, 2H, CH₂), 3.89 (t, *J* = 6.2 Hz, 2H, CH₂), 7.33 (d, *J* = 1.7 Hz, 1H, Ar), 7.36 (dd, *J* = 7.8, 4.9 Hz, 1H, Ar), 7.41 (dd, *J* = 8.5, 1.7 Hz, 1H, Ar), 7.87 (ddd, *J* = 7.8, 2.2, 1.5 Hz, 1H, Ar), 8.30 (d, *J* = 8.5 Hz, 1H, Ar), 8.62 (dd, *J* = 4.9, 1.5 Hz, 1H, Ar), 8.85 (d, *J* = 2.2 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.8, 30.0 (3C), 45.1, 45.4, 54.2, 122.8, 123.5, 124.7, 127.3, 129.3, 130.0, 134.2, 135.0, 137.8, 139.6, 147.5, 148.1, 149.2; HRMS (FAB): *m/z* calcd for C₂₀H₂₃N₄S [M + H]⁺ 351.1643; found: 351.1645.

Compound 32h. Using the general procedure as described for **25a**, compound **30h** (36.3 mg, 0.10 mmol) was allowed to react for 2 h with TFA (1.0 mL) and MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:1) gave the title compound **32h** as colorless solid (24.8 mg, 81 %): mp 191–193 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1616 (C=N), 1568 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.97–2.03 (m, 2H, CH₂), 3.72 (t, *J* = 5.5 Hz, 2H, CH₂), 4.05 (t, *J* = 6.1 Hz, 2H, CH₂), 7.24 (d, *J* = 1.7 Hz, 1H, Ar), 7.38 (dd, *J* = 7.9, 4.8 Hz, 1H, Ar), 7.43 (dd, *J* = 8.3, 1.7 Hz, 1H, Ar), 7.86 (dt, *J* = 7.9, 1.8 Hz, 1H, Ar), 8.33 (d, *J* = 8.3 Hz, 1H, Ar), 8.63 (dd, *J* = 4.8, 1.8 Hz, 1H, Ar), 8.83 (d, *J* = 1.8 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.0, 43.8, 44.9, 121.8, 123.6, 124.9, 126.2, 129.7, 129.8, 134.2, 134.7, 140.1, 146.2, 148.1, 149.3, 152.9; HRMS (FAB): *m/z* calcd for C₁₆H₁₅N₄S [M + H]⁺ 295.1017; found: 295.1013.

3.1.70 Synthesis of 3,4-Dihydro-9-(pyridin-4-yl)-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**32i**)

N-(*tert*-Butyl)-3,4-dihydro-9-(pyridin-4-yl)-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**30i**). Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 4-pyridineboronic acid (22.1 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **30i** as colorless solid (27.6 mg, 52 %): mp 196–197 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1593 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.41 (s, 9H, 3 × CH₃), 1.91–1.96 (m, 2H, CH₂), 3.65 (t, *J* = 5.4 Hz, 2H, CH₂), 3.89 (t, *J* = 6.0 Hz, 2H, CH₂), 7.38 (s, 1H, Ar), 7.45 (d, *J* = 8.6 Hz, 1H, Ar), 7.49 (d, *J* = 5.0 Hz, 2H, Ar), 8.30 (d, *J* = 8.6 Hz, 1H, Ar), 8.67 (d, *J* = 5.0 Hz, 2H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.8, 30.0 (3C), 45.1, 45.4, 54.2, 121.4 (2C), 122.8, 124.4, 128.1, 129.3, 130.1, 137.6, 139.8, 146.6, 147.4,

150.4 (2C); HRMS (FAB): m/z calcd for $C_{20}H_{23}N_4S$ $[M + H]^+$ 351.1643; found: 351.1644.

Compound 32i. Using the general procedure as described for **25a**, compound **30i** (23.4 mg, 0.067 mmol) was allowed to react for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:1 to 0:1) gave the title compound **32i** as colorless solid (15.1 mg, 77 %): mp 154–155 °C (from $CHCl_3$ –*n*-hexane); IR (neat) cm^{-1} : 1620 (C=N), 1575 (C=N); 1H -NMR (500 MHz, $CDCl_3$) δ : 1.97–2.02 (m, 2H, CH_2), 3.72 (t, $J = 5.4$ Hz, 2H, CH_2), 4.04 (t, $J = 6.3$ Hz, 2H, CH_2), 7.29 (s, 1H, Ar), 7.46–7.48 (m, 3H, Ar), 8.33 (d, $J = 8.6$ Hz, 1H, Ar), 8.68 (d, $J = 4.6$ Hz, 2H, Ar); ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 21.0, 43.8, 45.0, 121.4 (2C), 121.9, 124.8, 127.1, 129.7, 129.9, 140.3, 146.1, 146.3, 150.4 (2C), 152.8; *Anal.* calcd for $C_{16}H_{14}N_4S$: C, 65.28; H, 4.79; N, 19.03. Found: C, 65.35; H, 4.63; N, 19.24.

3.1.71 Synthesis of 9-(Furan-2-yl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (32j)

N-(*tert*-Butyl)-9-(furan-2-yl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (**30j**). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 2-furanboronic acid (20.1 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **30j** as colorless solid (42.4 mg, 83 %): mp 128–130 °C (from *n*-hexane); IR (neat) cm^{-1} : 1596 (C=N); 1H -NMR (400 MHz, $CDCl_3$) δ : 1.40 (s, 9H, 3 \times CH_3), 1.89–1.94 (m, 2H, CH_2), 3.63 (t, $J = 5.5$ Hz, 2H, CH_2), 3.87 (t, $J = 6.1$ Hz, 2H, CH_2), 6.47–6.49 (m, 1H, Ar), 6.71 (d, $J = 3.4$ Hz, 1H, Ar), 7.42–7.48 (m, 3H, Ar), 8.20 (d, $J = 8.3$ Hz, 1H, Ar); ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 106.7, 111.9, 119.2, 121.4, 126.3, 128.8, 129.6, 132.3, 138.2, 142.8, 147.6, 152.5.; HRMS (FAB): m/z calcd for $C_{19}H_{22}N_3OS$ $[M + H]^+$ 340.1484; found: 340.1484.

Compound 32j. Using the general procedure as described for **25a**, compound **30j** (30.3 mg, 0.089 mmol) was allowed to react for 4 h with TFA (1.0 mL) and MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **32j** as colorless solid (18.3 mg, 73 %): mp 133 °C (from $CHCl_3$ –*n*-hexane); IR (neat) cm^{-1} : 1620 (C=N), 1567 (C=N); 1H -NMR (400 MHz, $CDCl_3$) δ : 1.95–2.01 (m, 2H, CH_2), 3.70 (t, $J = 5.6$ Hz, 2H, CH_2), 4.02 (t, $J = 6.1$ Hz, 2H, CH_2), 6.49 (dd, $J = 3.4, 1.7$ Hz, 1H, Ar), 6.73 (d, $J = 3.4$ Hz, 1H, Ar), 7.21 (br s, 1H, NH), 7.33 (d, $J = 1.7$ Hz, 1H, Ar), 7.47–7.49 (m, 2H, Ar), 8.22 (d, $J = 8.5$ Hz, 1H, Ar); ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 21.0, 43.8, 45.0, 107.1, 112.0, 118.2, 121.6, 125.2, 129.3, 129.5, 132.7, 143.0, 146.3, 152.2, 153.3; *Anal.* calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.40; H, 4.46; N, 14.72.

3.1.72 Synthesis of 9-(Benzofuran-2-yl)-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (32k)

9-(Benzofuran-2-yl)-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3] benzothiazin-6-imine (30k) Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 2-benzofuranboronic acid (29.2 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **30k** as colorless solid (54.3 mg, 93 %): mp 211 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1595 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.41 (s, 9H, 3 × CH₃), 1.90–1.94 (m, 2H, CH₂), 3.64 (t, *J* = 5.4 Hz, 2H, CH₂), 3.88 (t, *J* = 6.0 Hz, 2H, CH₂), 7.06 (s, 1H, Ar), 7.23 (t, *J* = 7.4 Hz, 1H, Ar), 7.30 (t, *J* = 7.4 Hz, 1H, Ar), 7.50 (d, *J* = 7.4 Hz, 1H, Ar), 7.58 (d, *J* = 7.4 Hz, 1H, Ar), 7.62–7.64 (m, 2H, Ar), 8.25 (d, *J* = 8.0 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.9, 30.0 (3C), 45.2, 45.4, 54.2, 103.0, 111.2, 120.4, 121.2, 122.3, 123.1, 124.9, 127.3, 128.9 (2C), 129.8, 132.0, 138.0, 147.5, 154.2, 155.0; HRMS (FAB): *m/z* calcd for C₂₃H₂₄N₃OS [M + H]⁺ 390.1640; found: 390.1645.

Compound 32k. Using the general procedure as described for **25a**, compound **30k** (41.5 mg, 0.11 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **32k** as pale yellow solid (30.5 mg, 85 %): mp 189–191 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1620 (C=N), 1565 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.95–2.00 (m, 2H, CH₂), 3.70 (t, *J* = 5.4 Hz, 2H, CH₂), 4.02 (t, *J* = 6.3 Hz, 2H, CH₂), 7.07 (s, 1H, Ar), 7.22–7.25 (m, 1H, Ar), 7.31 (t, *J* = 7.2 Hz, 1H, Ar), 7.50–7.51 (m, 2H, Ar), 7.58 (d, *J* = 7.2 Hz, 1H, Ar), 7.65 (dd, *J* = 8.6, 1.1 Hz, 1H, Ar), 8.28 (d, *J* = 8.6 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.0, 43.8, 45.0, 103.4, 111.3, 119.4, 121.2, 122.6, 123.2, 125.1, 126.2, 128.8, 129.3, 129.6, 132.4, 146.2, 153.1, 153.9, 155.1; HRMS (FAB): *m/z* calcd for C₁₉H₁₆N₃OS [M + H]⁺ 334.1014; found: 334.1017.

3.1.73 Synthesis of 3,4-Dihydro-9-(thiophen-3-yl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (32l)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(thiophen-3-yl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (30l).** Using the general procedure as described for **22i**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 3-thiopheneboronic acid (23.0 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **30l** as colorless solid (54.0 mg, >99 %): mp 132–133 °C (from *n*-hexane); IR (neat) cm⁻¹: 1592 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.40 (s, 9H, 3 × CH₃), 1.89–1.95 (m, 2H, CH₂),

3.63 (t, $J = 5.6$ Hz, 2H, CH₂), 3.88 (t, $J = 6.2$ Hz, 2H, CH₂), 7.32 (d, $J = 2.0$ Hz, 1H, Ar), 7.36–7.43 (m, 3H, Ar), 7.50 (dd, $J = 2.7, 1.5$ Hz, 1H, Ar), 8.21 (d, $J = 8.5$ Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ : 21.9, 30.0 (3C), 45.1, 45.4, 54.2, 121.5, 121.9, 124.1, 126.0, 126.3, 126.6, 129.0, 129.6, 137.4, 138.2, 140.6, 147.7; HRMS (FAB): m/z calcd for C₁₉H₂₂N₃S₂ [M + H]⁺ 356.1255; found: 356.1253.

Compound 32l. Using the general procedure as described for **25a**, compound **30l** (37.6 mg, 0.11 mmol) was allowed to react for 2 h with TFA (1.0 mL) and MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (4:1) gave the title compound **32l** as colorless solid (25.9 mg, 82 %): mp 120–121 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1619 (C=N), 1569 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ : 1.96–2.01 (m, 2H, CH₂), 3.70 (t, $J = 5.4$ Hz, 2H, CH₂), 4.03 (t, $J = 6.1$ Hz, 2H, CH₂), 7.23 (d, $J = 1.1$ Hz, 1H, Ar), 7.35–7.41 (m, 2H, Ar), 7.44 (dd, $J = 8.3, 1.1$ Hz, 1H, Ar), 7.51–7.52 (m, 1H, Ar), 8.24 (d, $J = 8.3$ Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ : 21.0, 43.8, 44.9, 120.9, 121.8, 124.4, 125.0, 125.9, 126.7, 129.4 (2C), 138.0, 140.3, 146.5, 153.3; Anal. calcd for C₁₅H₁₃N₃S₂: C, 60.17; H, 4.38; N, 14.03. Found: C, 60.12; H, 4.11; N, 14.04.

3.1.74 Synthesis of 9-(Benzothiophen-2-yl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (32m)

9-(Benzothiophen-2-yl)-*N*-(*tert*-butyl)-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (30m). Using the general procedure as described for **22l**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with 2-benzothiopheneboronic acid (32.0 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **30m** as colorless solid (44.8 mg, 74 %): mp 222–223 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1590 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ : 1.41 (s, 9H, 3 × CH₃), 1.90–1.94 (m, 2H, CH₂), 3.63 (t, $J = 5.4$ Hz, 2H, CH₂), 3.88 (t, $J = 6.3$ Hz, 2H, CH₂), 7.30–7.36 (m, 2H, Ar), 7.42 (d, $J = 1.7$ Hz, 1H, Ar), 7.52 (dd, $J = 8.6, 1.7$ Hz, 1H, Ar), 7.58 (s, 1H, Ar), 7.76 (dd, $J = 7.2, 1.4$ Hz, 1H, Ar), 7.82 (d, $J = 8.0$ Hz, 1H, Ar), 8.23 (d, $J = 8.6$ Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ : 21.8, 30.0 (3C), 45.1, 45.4, 54.2, 120.7, 121.9, 122.3, 123.8, 123.9, 124.7, 124.8, 127.2, 129.0, 129.9, 136.0, 137.9, 139.7, 140.4, 142.3, 147.5; HRMS (FAB): m/z calcd for C₂₃H₂₄N₃S₂ [M + H]⁺ 406.1412; found: 406.1407.

Compound 32m. Using the general procedure as described for **25a**, compound **30m** (35.8 mg, 0.09 mmol) was allowed to react for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1 to 7:3) gave the title compound **32m** as pale yellow solid (26.9 mg, 86 %): mp 198–200 °C (from

MeOH–CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1615 (C=N), 1567 (C=N); ¹H-NMR (500 MHz, CDCl₃–CD₃OD) δ: 1.95–2.00 (m, 2H, CH₂), 3.69 (t, *J* = 5.4 Hz, 2H, CH₂), 4.01 (t, *J* = 6.0 Hz, 2H, CH₂), 7.25 (br s, 1H, NH), 7.32–7.37 (m, 3H, Ar), 7.54 (dd, *J* = 8.6, 1.7 Hz, 1H, Ar), 7.58 (s, 1H, Ar), 7.77 (t, *J* = 4.0 Hz, 1H, Ar), 7.82 (d, *J* = 7.4 Hz, 1H, Ar), 8.23 (d, *J* = 8.6 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃–CD₃OD) δ: 20.9, 43.9, 44.9, 120.9, 121.0, 122.3, 123.9, 124.2, 124.7, 124.9, 125.9, 129.4, 129.6, 136.6, 139.7, 140.3, 141.8, 146.4, 153.2; HRMS (FAB): *m/z* calcd for C₁₉H₁₆N₃S₂ [M + H]⁺ 350.0786; found: 350.0785.

3.1.75 Synthesis of 3,4-Dihydro-9-(1H-pyrazol-1-yl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (32n)

***N*-(*tert*-Butyl)-3,4-dihydro-9-(1H-pyrazol-1-yl)-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (30n).** To a solution of *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol), pyrazole (12.3 mg, 0.18 mmol), CuCl (1.5 mg, 0.015 mmol) and K₂CO₃ (21.8 mg, 0.16 mol) in *N*-methylpyrrolidone (0.3 mL) was added acetylacetone (3.8 μL, 0.038 mmol) under an Ar atmosphere. After being stirred at 130 °C for 19 h, EtOAc was added. The organic layers were washed with H₂O, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) to give the title compound **30n** as colorless solid (39.8 mg, 71 %): mp 132–133 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1597 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.39 (s, 9H, 3 × CH₃), 1.90–1.96 (m, 2H, CH₂), 3.63 (t, *J* = 5.6 Hz, 2H, CH₂), 3.88 (t, *J* = 6.2 Hz, 2H, CH₂), 6.48 (dd, *J* = 2.7, 1.8 Hz, 1H, Ar), 7.47 (dd, *J* = 8.8, 2.2 Hz, 1H, Ar), 7.56 (d, *J* = 2.2 Hz, 1H, Ar), 7.73 (d, *J* = 1.8 Hz, 1H, Ar), 7.94 (d, *J* = 2.7 Hz, 1H, Ar), 8.28 (d, *J* = 8.8 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.8, 30.0 (3C), 45.0, 45.4, 54.2, 108.2, 114.3, 115.9, 125.4, 126.7, 129.9, 130.8, 137.7, 141.0, 141.7, 147.3; HRMS (FAB): *m/z* calcd for C₁₈H₂₂N₅S [M + H]⁺ 340.1596; found: 340.1598.

Compound 32n. Using the general procedure as described for **25a**, compound **30n** (21.6 mg, 0.064 mmol) was allowed to react for 1 h. Purification by preparative TLC over aluminum oxide with CHCl₃ gave the title compound **32n** as colorless solid (16.2 mg, 89 %): mp 158–159 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1615 (C=N), 1561 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.96–2.02 (m, 2H, CH₂), 3.70 (t, *J* = 5.6 Hz, 2H, CH₂), 4.03 (t, *J* = 6.2 Hz, 2H, CH₂), 6.49 (dd, *J* = 2.6, 1.8 Hz, 1H, Ar), 7.27 (s, 1H, NH), 7.48–7.51 (m, 2H, Ar), 7.74 (d, *J* = 1.5 Hz, 1H, Ar), 7.95 (d, *J* = 2.7 Hz, 1H, Ar), 8.31 (d, *J* = 9.5 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.0, 43.8, 44.9, 108.4, 113.3, 116.1, 124.3, 126.7, 130.3, 130.6, 141.3, 141.8, 145.9, 152.8; HRMS (FAB): *m/z* calcd for C₁₄H₁₄N₅S [M + H]⁺ 284.0970; found: 284.0966.

3.1.76 Synthesis of 3,4-Dihydro-9-(1H-imidazol-1-yl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (32o)

N-(*tert*-Butyl)-3,4-dihydro-9-(1H-imidazol-1-yl)-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (**30o**). Using the general procedure as described for **30n**, *N*-(*tert*-butyl)-9-bromo-3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine **22k** (52.8 mg, 0.15 mmol) was allowed to react with imidazole (12.3 mg, 0.18 mmol) for 3 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:1 to 0:1) gave the title compound **30o** as colorless solid (25.8 mg, 51 %): mp 170–171 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1599 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.40 (s, 9H, 3 × CH₃), 1.91–1.96 (m, 2H, CH₂), 3.64 (t, *J* = 5.6 Hz, 2H, CH₂), 3.89 (t, *J* = 6.2 Hz, 2H, CH₂), 7.15 (d, *J* = 2.3 Hz, 1H, Ar), 7.22 (dd, *J* = 8.8, 2.3 Hz, 1H, Ar), 7.22 (s, 1H, Ar), 7.30 (s, 1H, Ar), 7.90 (s, 1H, Ar), 8.32 (d, *J* = 8.8 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.8, 30.0 (3C), 45.0, 45.5, 54.3, 116.2, 117.7, 118.4, 126.5, 130.5, 130.8, 131.3, 135.3, 136.9, 138.4, 146.9; HRMS (FAB): *m/z* calcd for C₁₈H₂₂N₅S [M + H]⁺ 340.1596; found: 340.1598.

Compound 32o. Using the general procedure as described for **25a**, compound **30o** (20.6 mg, 0.061 mmol) was allowed to react for 1 h. Purification by preparative TLC over aluminum oxide with EtOAc–MeOH (9:1) gave the title compound **32o** as colorless solid (9.7 mg, 56 %): mp 183–185 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1622 (C=N), 1561 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.97–2.03 (m, 2H, CH₂), 3.71 (t, *J* = 5.7 Hz, 2H, CH₂), 4.04 (t, *J* = 6.1 Hz, 2H, CH₂), 7.07 (d, *J* = 2.2 Hz, 1H, Ar), 7.22 (s, 1H, Ar), 7.25 (dd, *J* = 8.8, 2.2 Hz, 1H, Ar), 7.29 (s, 1H, Ar), 7.89 (s, 1H, Ar), 8.36 (d, *J* = 8.8 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 20.9, 43.8, 44.9, 115.2, 117.7, 118.6, 125.5, 130.9, 131.0, 131.1, 135.3, 138.8, 145.6, 152.2; HRMS (FAB): *m/z* calcd for C₁₄H₁₄N₅S [M + H]⁺ 284.0970; found: 284.0966.

3.1.77 Synthesis of 2,3-Dihydro-5H-imidazo[1,2-c][1,3]benzothiazin-5-imine (36a)

Using the general procedure as described for **25a**, *N*-(*tert*-butyl)-2,3-dihydroimidazo[1,2-c][1,3]benzothiazin-5-imine **35a** (18.4 mg, 0.07 mmol) was allowed to react for 12 h with TFA (1.0 mL) and MS4Å (150 mg). Purification by flash chromatography over silica gel with *n*-hexane–EtOAc (1:1) gave the title compound **36a** as colorless solid (11.1 mg, 78 %): mp 176–178 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1621 (C=N), 1585 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 4.11 (4H, s, 2 × CH₂), 5.82 (1H, br s, NH), 7.12 (1H, d, *J* = 8.0 Hz, Ar), 7.24–7.28 (1H, m, Ar), 7.38–7.42 (1H, m, Ar), 8.20 (1H, dd, *J* = 7.7, 1.4 Hz, Ar); ¹³C-

NMR (125 MHz, CDCl₃) δ : 47.3, 52.9, 120.8, 123.8, 126.5, 129.1, 132.0, 132.4, 150.0, 154.0; HRMS (FAB): m/z calcd for C₁₀H₁₀N₃S [M + H]⁺ 204.0595; found: 204.0600.

3.1.78 Synthesis of 6*H*,8*H*-Quinazolino[3,2-*c*][1,3]benzothiazin-6-imine (36*b*)

***N*-(*tert*-Butyl)-6*H*,8*H*-quinazolino[3,2-*c*][1,3]benzothiazin-6-imine (35*b*)**. To a solution of 2-fluorobenzaldehyde (1.41 g, 11.39 mmol) in *t*-BuOH (38 mL) was added 2-aminobenzylamine **33b** (1.53 g, 12.53 mmol). The mixture was stirred at 80 °C for 30 min, and then K₂CO₃ (4.73 g, 34.18 mmol) and I₂ (3.61 g, 14.24 mmol) were added. After being stirred at same temperature for 4 h, the mixture was quenched with sat. Na₂SO₃. The organic layer was separated and concentrated. The resulting solid was dissolved with H₂O and CHCl₃, and then pH was adjusted to 12–14 with 5 N NaOH. The whole was extracted with CHCl₃. The extract was washed with brine, dried over Na₂SO₄. To a mixture of resulting residue in DMAc (7.4 mL) were added KO*t*-Bu (496 mg, 4.42 mmol) and *tert*-butylisothiocyanate (0.56 mL, 4.42 mmol) under an N₂ atmosphere. After being stirred at 80 °C for 2.5 h, sat. NH₄Cl was added. The whole was extracted with EtOAc. The extract was washed with brine, and dried over Na₂SO₄. After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (1:0 to 9:1) to give the title compound **35b** as yellow solid (114.1 mg, 3.1 % over 2 steps): mp 92.2 °C; IR (neat) cm⁻¹: 1588 (C=N); ¹H-NMR (300 MHz, CDCl₃) δ : 1.42 (9H, s, 3 × CH₃), 5.10 (2H, s, CH₂), 7.08–7.23 (3H, m, Ar), 7.27–7.40 (4H, m, Ar), 8.43 (1H, dd, *J* = 8.0, 1.4 Hz, Ar); ¹³C-NMR (75 MHz, CDCl₃) δ : 29.9 (3C), 46.2, 54.7, 124.0, 124.8, 124.9, 125.4, 125.8, 126.4, 127.7, 128.3, 129.0, 129.4, 130.7, 138.3, 141.1, 148.3; *Anal.* calcd for C₁₉H₁₉N₃S: C, 70.99; H, 5.96; N, 13.07. Found: C, 71.05; H, 5.99; N, 12.91.

Compound 36*b*. TFA (0.5 mL) was added to **35b** (100 mg, 0.311 mmol). After being stirred under reflux for 30 min, the mixture was added dropwise to Et₃N at 0 °C to adjust pH to 8–9. The whole was extracted with EtOAc. The extract was washed with sat. NaHCO₃ aq., brine, and dried over Na₂SO₄. After concentration, the residue was purified by preparative TLC over aluminum oxide with *n*-hexane–EtOAc (9:1) to give the title compound **36b** as colorless solid (13 mg, 16 %): mp 133–135 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1594 (C=N), 1541 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ : 5.27 (2H, s, CH₂), 7.08–7.13 (2H, m, Ar), 7.16 (1H, t, *J* = 7.2 Hz, Ar), 7.26–7.34 (3H, m, Ar), 7.39 (1H, td, *J* = 6.9, 1.1 Hz, Ar), 7.59 (1H, br s, NH), 8.50 (1H, d, *J* = 8.0 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ : 45.1, 123.0, 123.8, 125.4, 125.6, 126.3, 126.5, 126.6, 128.5, 129.2, 129.5, 131.1, 140.1, 146.3, 153.3; HRMS (FAB): m/z calcd for C₁₅H₁₂N₃S [M + H]⁺ 266.0752; found: 266.0750.

3.1.79 Synthesis of (\pm)-3,4-Dihydro-3-methyl-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (36c)

2-(2-Fluorophenyl)-5-methyl-1,4,5,6-tetrahydropyrimidine (34c). 2-Fluorobenzaldehyde (0.62 g, 5.0 mmol) was subjected to the general procedure for **18j** using 2-methylpropylenediamine **33c** (0.48 g, 5.5 mmol) to give the title compound **34c** as colorless crystals (0.72 g, 75 %): mp 98–99 °C (from CHCl₃-*n*-hexane); IR (neat) cm⁻¹: 1628 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ : 1.01 (3H, d, $J = 6.9$ Hz, CH₃), 1.92–1.99 (1H, m, CH), 3.06 (2H, dd, $J = 13.2, 9.7$ Hz, 2 \times CH), 3.52 (2H, dd, $J = 13.2, 3.4$ Hz, 2 \times CH), 5.27 (1H, br s, NH), 7.04 (1H, dd, $J = 11.7, 8.3$ Hz, Ar), 7.15 (1H, t, $J = 7.4$ Hz, Ar), 7.30–7.35 (1H, m, Ar), 7.81 (1H, td, $J = 7.4, 1.7$ Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ : 16.8, 25.2, 49.4 (2C), 115.9 (d, $J = 24.0$ Hz), 124.2, 124.3 (d, $J = 3.6$ Hz), 130.6 (d, $J = 3.6$ Hz), 130.8 (d, $J = 8.4$ Hz), 151.3, 160.1 (d, $J = 247.1$ Hz); ¹⁹F-NMR (500 MHz, CDCl₃) δ : -117.1; HRMS (FAB): m/z calcd for C₁₁H₁₄FN₂ [M + H]⁺ 193.1141; found: 193.1136.

(\pm)-N-(*tert*-Butyl)-3,4-dihydro-3-methyl-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (35c). Using the general procedure as described for **22e**, compound **34c** (384.5 mg, 2.0 mmol) was allowed to react at 80 °C for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 95:5) gave the title compound **35c** as colorless solid (288.4 mg, 50 %): mp 60–62 °C (from *n*-hexane); IR (neat) cm⁻¹: 1598 (C=N), 1570 (C=N); ¹³C-NMR (500 MHz, CDCl₃) δ : 1.05 (3H, d, $J = 6.3$ Hz, CH₃), 1.39 (9H, s, 3 \times CH₃), 1.91–1.99 (1H, m, CH), 3.09–3.17 (2H, m, CH₂), 3.72 (1H, dt, $J = 15.5, 3.7$ Hz, CH), 4.19 (1H, dt, $J = 13.7, 3.7$ Hz, CH), 7.11 (1H, d, $J = 8.0$ Hz, Ar), 7.19 (1H, t, $J = 8.0$ Hz, Ar), 7.30 (1H, t, $J = 8.0$ Hz, Ar), 8.19 (1H, d, $J = 8.0$ Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ : 16.7, 26.9, 30.0 (3C), 51.6, 52.4, 54.2, 124.4, 126.0, 127.7, 128.5, 129.1, 130.1, 138.4, 147.6; HRMS (FAB): m/z calcd for C₁₆H₂₂N₃S [M + H]⁺ 288.1534; found: 288.1535.

Compound 36c. Using the general procedure as described for **25a**, compound **35c** (57.5 mg, 0.20 mmol) was allowed to react for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) gave the title compound **36c** as colorless solid (36.7 mg, 79 %): mp 82–84 °C (from CHCl₃-*n*-hexane); IR (neat) cm⁻¹: 1621 (C=N), 1574 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ : 1.09 (3H, d, $J = 6.3$ Hz, CH₃), 1.96–2.08 (1H, m, CH), 3.19 (1H, dd, $J = 15.8, 10.6$ Hz, CH), 3.27 (1H, dd, $J = 13.0, 10.6$ Hz, CH), 3.80 (1H, ddd, $J = 15.8, 4.5, 3.2$ Hz, CH), 4.37 (1H, ddd, $J = 13.0, 4.5, 3.2$ Hz, CH), 7.04 (1H, d, $J = 7.4$ Hz, Ar), 7.18–7.25 (2H, m, Ar, NH), 7.33 (1H, td, $J = 7.4, 1.4$ Hz, Ar), 8.23 (1H, dd, $J = 8.3, 1.4$ Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ : 16.4, 26.1, 49.9, 52.2, 123.5, 126.3, 126.6, 128.8, 128.9, 130.6, 146.2, 153.4; *Anal.* calcd for C₁₂H₁₃N₃S: C, 62.31; H, 5.66; N, 18.17. Found: C, 62.04; H, 5.75; N, 17.88.

3.1.80 Synthesis of 3,4-Dihydro-3,3-dimethyl-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine (36d)

2-(2-Fluorophenyl)-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine (34d). 2-Fluorobenzaldehyde (0.62 g, 5.0 mmol) was subjected to the general procedure for **18j** using 2,2-dimethylpropylenediamine **33d** (0.56 g, 5.5 mmol) to give the title compound **34d** as colorless crystals (0.82 g, 79 %): mp 150–153 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1629 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.02 (6H, s, 2 × CH₃), 3.13 (4H, s, 2 × CH₂), 5.14 (1H, br s, NH), 7.05 (1H, ddd, *J* = 11.7, 7.8, 1.0 Hz, Ar), 7.15 (1H, td, *J* = 7.8, 1.0 Hz, Ar), 7.30–7.35 (1H, m, Ar), 7.81 (1H, td, *J* = 7.8, 2.0 Hz, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 25.0 (2C), 26.2, 54.3 (2C), 115.8 (d, *J* = 23.2 Hz), 124.2, 124.3 (d, *J* = 3.3 Hz), 130.6 (d, *J* = 4.1 Hz), 130.8 (d, *J* = 9.1 Hz), 150.5 (d, *J* = 1.7 Hz), 160.2 (d, *J* = 247.5 Hz); ¹⁹F-NMR (500 MHz, CDCl₃) δ: –117.3; HRMS (FAB): *m/z* calcd for C₁₂H₁₆FN₂ [M + H]⁺ 207.1298; found: 207.1299.

***N*-(*tert*-Butyl)-3,4-dihydro-3,3-dimethyl-2H,6H-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (35d).** Using the general procedure as described for **22e**, compound **34d** (412.5 mg, 2.0 mmol) was allowed to react at 80 °C for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **35d** as colorless solid (236.6 mg, 39 %): mp 70–72 °C (from *n*-hexane); IR (neat) cm⁻¹: 1602 (C=N), 1570 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.01 (6H, s, 2 × CH₃), 1.39 (9H, s, 3 × CH₃), 3.33 (2H, s, CH₂), 3.58 (2H, s, CH₂), 7.12 (1H, d, *J* = 8.0 Hz, Ar), 7.20 (1H, t, *J* = 8.0 Hz, Ar), 7.31 (1H, td, *J* = 8.0, 1.1 Hz, Ar), 8.21 (1H, dd, *J* = 8.0, 1.1 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 24.8 (2C), 28.5, 29.9 (3C), 54.2, 55.7, 57.4, 124.5, 126.0, 127.5, 128.5, 129.1, 130.1, 138.7, 146.7; HRMS (FAB): *m/z* calcd for C₁₇H₂₄N₃S [M + H]⁺ 302.1691; found: 302.1695.

Compound 36d. Using the general procedure as described for **25a**, compound **35d** (60.3 mg, 0.20 mmol) was allowed to react for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) gave the title compound **36d** as colorless solid (42.0 mg, 86 %): mp 113–114 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1627 (C=N), 1575 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.05 (6H, s, 2 × CH₃), 3.41 (2H, s, CH₂), 3.74 (2H, s, CH₂), 7.05 (1H, dd, *J* = 7.6, 1.1 Hz, Ar), 7.21–7.25 (2H, m, Ar, NH), 7.34 (1H, td, *J* = 7.6, 1.4 Hz, Ar), 8.26 (1H, dd, *J* = 8.3, 1.4 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 24.6 (2C), 27.9, 54.0, 57.2, 123.5, 126.3, 126.3, 128.8, 128.9, 130.6, 145.3, 153.8; HRMS (FAB): *m/z* calcd for C₁₃H₁₆N₃S [M + H]⁺ 246.1065; found: 246.1069.

3.1.81 Synthesis of 2,3,4,5-Tetrahydro-7H-1,3-diazepino [1,2-*c*][1,3]benzothiazin-7-imine (36e)

***N*-(*tert*-Butoxycarbonyl)-2-(2-fluorophenyl)-4,5,6,7-tetrahydro-1,3-diazepine (37).** To a solution of 2-fluorobenzaldehyde (2.48 g, 20.0 mmol) in *t*-BuOH (188 mL) was added 1,4-diaminobutane **33e** (2.21 mL, 22.0 mmol). The mixture was stirred at 70 °C for 30 min, and then K₂CO₃ (8.29 g, 60.0 mmol) and I₂ (6.35 g, 25 mmol) were added. After being stirred at same temperature for 3 h, the mixture was quenched with sat. Na₂SO₃. The organic layer was separated and concentrated. The resulting solid was dissolved with H₂O, and then pH was adjusted to 12–14 with 2 N NaOH. The whole was extracted with CHCl₃, and dried over Na₂SO₄. After concentration, Et₃N (8.67 mL, 60.0 mmol) and Boc₂O (13.8 mL, 60.0 mmol) were added to the solution of residue in CH₂Cl₂ (100 mL). After being stirred for 30 min at rt, sat. NaHCO₃ was added. After being stirred at rt for 1 h, the whole was extracted with CHCl₃. The extract was washed with brine, and dried over MgSO₄. After concentration, the residue was purified by column chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give the title compound **37** as colorless solid (2.18 g, 37 %): mp 63–65 °C (from *n*-hexane); IR (neat) cm⁻¹: 1710 (C=O), 1631 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.14 (9H, s, 3 × CH₃), 1.66–1.70 (2H, m, CH₂), 1.78–1.83 (2H, m, CH₂), 3.61 (2H, br s, CH₂), 3.76 (2H, t, *J* = 5.2 Hz, CH₂), 7.03 (1H, dd, *J* = 11.2, 8.3 Hz, Ar), 7.15 (1H, td, *J* = 7.7, 1.1 Hz, Ar), 7.33–7.38 (1H, m, Ar), 7.60 (1H, t, *J* = 7.7 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 23.2, 26.4, 27.7 (3C), 44.9, 50.7, 81.1, 115.7 (d, *J* = 21.6 Hz), 124.0 (d, *J* = 2.4 Hz), 126.5, 130.9 (d, *J* = 2.4 Hz), 131.1 (d, *J* = 8.4 Hz), 152.8, 154.8, 160.5 (d, *J* = 250.7 Hz); ¹⁹F-NMR (500 MHz, CDCl₃) δ: -118.9; HRMS (FAB) *m/z* calcd for C₁₆H₂₂FN₂O₂ [M + H]⁺ 293.1665; found: 293.1669.

2-(2-Fluorophenyl)-4,5,6,7-tetrahydro-1H-1,3-diazepine (34e). To a solution of **37** (877.1 mg, 3.0 mmol) in CH₂Cl₂ (6.0 mL) was added TFA (6.0 mL). The mixture was stirred under reflux for 2 h, mixture was washed with 2 N NaOH. The organic phase was dried over MgSO₄. After concentration, the residue was recrystallized from CHCl₃–*n*-hexane to give the title compound **34e** as colorless crystals (461.2 mg, 80 %): mp 92 °C; IR (neat) cm⁻¹: 1627 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.80–1.83 (4H, m, 2 × CH₂), 3.48 (4H, br s, 2 × CH₂), 4.86 (1H, br s, NH), 7.02–7.06 (1H, m, Ar), 7.12 (1H, td, *J* = 7.7, 1.1 Hz, Ar), 7.30–7.34 (1H, m, Ar), 7.63 (1H, td, *J* = 7.7, 1.7 Hz, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 28.4 (2C), 47.9 (2C), 115.7 (d, *J* = 22.8 Hz), 124.2 (d, *J* = 3.6 Hz), 127.0 (d, *J* = 12.0 Hz), 130.9 (d, *J* = 8.4 Hz), 131.2 (d, *J* = 3.6 Hz), 157.2, 160.4 (d, *J* = 247.1 Hz); ¹⁹F-NMR (500 MHz, CDCl₃) δ: -117.7; HRMS (FAB) *m/z* calcd for C₁₁H₁₄FN₂ [M + H]⁺ 193.1141; found: 193.1140.

***N*-(*tert*-Butyl)-7H-2,3,4,5-tetrahydro-1,3-diazepino[1,2-*c*][1,3]benzothiazin-7-imine (35e).** Using the general procedure as described for **25e**, compound **34e** (192.2 mg, 1.0 mmol) was allowed to react at rt overnight. Purification by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) gave the title compound

35e as a yellow oil (50.3 mg, 18 %): IR (neat) cm^{-1} : 1588 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.37 (9H, s, $3 \times \text{CH}_3$), 1.87–1.93 (4H, m, $2 \times \text{CH}_2$), 3.82 (2H, t, $J = 5.4$ Hz, CH_2), 3.88 (2H, t, $J = 5.4$ Hz, CH_2), 7.16–7.23 (2H, m, Ar), 7.26–7.31 (1H, m, Ar), 7.84 (1H, d, $J = 7.1$ Hz, Ar); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 23.3, 24.5, 30.2 (3C), 48.3, 49.2, 53.8, 124.9, 126.3, 127.0, 129.4, 129.7, 133.5, 140.0, 152.2; HRMS (FAB) m/z calcd for $\text{C}_{16}\text{H}_{22}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 288.1534; found: 288.1540.

Compound 36e. Using the general procedure as described for **25a**, compound **35e** (50.3 mg, 0.18 mmol) was allowed to react for 2 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (4:1 to 2:1) gave the title compound **36e** as a colorless oil (11.3 mg, 27 %): IR (neat) cm^{-1} : 1638 (C=N), 1578 (C=N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.94–2.01 (4H, m, $2 \times \text{CH}_2$), 3.92 (2H, t, $J = 5.5$ Hz, CH_2), 3.96 (2H, t, $J = 5.6$ Hz, CH_2), 7.00 (1H, br s, NH), 7.12–7.14 (1H, m, Ar), 7.23–7.28 (1H, m, Ar), 7.31–7.35 (1H, m, Ar), 7.90 (1H, dd, $J = 7.8, 1.5$ Hz, Ar); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3) δ : 23.3, 24.3, 47.5, 49.0, 124.2, 126.6, 127.5, 129.3, 129.9, 132.0, 151.0, 155.5; HRMS (FAB) m/z calcd for $\text{C}_{12}\text{H}_{14}\text{N}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 232.0908; found: 232.0906.

3.1.82 Synthesis of 9-Bromo-2H-spiro(benzo[e]pyrimido [1,2-*c*][1,3]thiazine-3,1'-cyclohexan)-6(4H)-imine (49)

Cyclohexane-1,1-dicarbonitrile (42). To a solution of malononitrile (660.6 mg, 10.0 mmol) in DMF (25.0 mL) was added DBU (2.99 mL, 20.0 mmol). After being stirred at 50 °C for 2 h, a solution of 1,5-dibromopentane **38** (1.35 mL, 10.0 mmol) in DMF (10.0 mL) was added to the reaction mixture. After being stirred at the same temperature for additional 5 h, EtOAc was added. The mixture was washed with 5 % aq. NaHCO_3 , and dried over MgSO_4 . After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1). The resulting solid was recrystallized from CHCl_3 –*n*-hexane to give the title compound **42** as colorless crystals (801.8 mg, 60 %): mp 62 °C, IR (neat) cm^{-1} : 2254 (C \equiv N); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 1.51–1.57 (m, 2H, CH_2), 1.73–1.78 (m, 4H, $2 \times \text{CH}_2$), 2.13 (t, $J = 5.9$ Hz, 4H, $2 \times \text{CH}_2$); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 21.6 (2C), 23.9, 32.4, 34.6 (2C), 115.9 (2C); MS (FAB) m/z (%): 135 (MH^+ , 100).

3-(4-Bromo-2-fluorophenyl)-2,4-diazaspiro[5.5]undec-2-ene (45). To a solution of **42** (134.2 mg, 1.0 mmol) in THF (2.5 mL) was added BH_3 –THF in THF (5.0 mL, 5.0 mmol, 1.0 M) at 0 °C under an Ar atmosphere. The mixture was warmed to rt. After being stirred at 65 °C for 5 h, the reaction mixture was cooled to 0 °C, and was added 1 N HCl. After being stirred at rt for 1 h, the mixture was basified with 2 N NaOH. The whole was extracted with CHCl_3 and dried over MgSO_4 . After concentration, the residue was dissolved in *t*-BuOH (10.0 mL), and 4-bromo-2-fluorobenzaldehyde (203.0 mg, 1.0 mmol) was added.

After being stirred at 70 °C for 30 min, K₂CO₃ (414.6 mg, 3.0 mmol) and I₂ (317.3 mg, 1.25 mmol) were added. After being stirred at same temperature for 3 h, the reaction mixture was quenched with sat. Na₂SO₃ until the iodine color almost disappeared. The reaction mixture was basified with 2 N NaOH. The whole was extracted with CHCl₃, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over aluminum oxide with EtOAc–MeOH (1:0 to 95:5) gave the title compound **45** as colorless solid (200.1 mg, 62 %): mp 204–205 °C (from CHCl₃–*n*-hexane), IR (neat) cm⁻¹: 1626 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.35–1.37 (m, 4H, 2 × CH₂), 1.47–1.49 (m, 6H, 3 × CH₂), 3.20 (s, 4H, 2 × CH₂), 5.07 (s, 1H, NH), 7.23 (dd, *J* = 11.2, 2.0 Hz, 1H, Ar), 7.28 (dd, *J* = 8.3, 2.0 Hz, 1H, Ar), 7.69 (t, *J* = 8.3 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.7 (2C), 26.5, 28.8 (2C), 33.5, 52.2 (2C), 119.4 (d, *J* = 27.6 Hz), 123.1 (d, *J* = 12.0 Hz), 123.5 (d, *J* = 10.8 Hz), 127.7 (d, *J* = 3.6 Hz), 131.8 (d, *J* = 3.6 Hz), 149.9, 159.8 (d, *J* = 251.9 Hz); ¹⁹F-NMR (500 MHz, CDCl₃) δ: –114.6; HRMS (FAB): *m/z* calcd for C₁₅H₁₉BrFN₂ [M + H]⁺ 325.0716; found: 325.0724.

9-Bromo-*N*-(*tert*-butyl)-2*H*-spiro(benzo[*e*]pyrimido[1,2-*c*][1,3]thiazine-3,1'-cyclohexan)-6(4*H*)-imine (48). To a mixture of compound **45** (164.5 mg, 0.51 mmol) and NaH (40.8 mg, 1.02 mmol; 60 % oil suspension) in DMF (3.3 mL) was added *t*-BuNCS (129.4 μL, 1.02 mmol) under an Ar atmosphere. After being stirred at rt overnight, the reaction mixture was warmed at 60 °C. After being stirred at this temperature for 1 h, EtOAc was added. The resulting solution was washed with sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **48** as colorless solid (180.1 mg, 84 %): mp 118–119 °C (from *n*-hexane); IR (neat) cm⁻¹: 1578 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.32–1.37 (m, 4H, 2 × CH₂), 1.38 (s, 9H, 3 × CH₃), 1.43–1.52 (m, 6H, 3 × CH₂), 3.38 (s, 2H, CH₂), 3.71 (s, 2H, CH₂), 7.26–7.31 (m, 2H, Ar), 8.04 (d, *J* = 8.6 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 21.8 (2C), 26.5, 29.9 (3C), 31.2, 33.4 (2C), 52.5, 54.2, 55.9, 124.3, 126.5, 126.8, 129.1, 130.0, 130.9, 137.6, 146.2; HRMS (FAB): *m/z* calcd for C₂₀H₂₇BrN₃S [M + H]⁺ 420.1109; found: 420.1117.

Compound 49. Using the general procedure as described for **25a**, **48** (124.7 mg, 0.3 mmol) was allowed to react under reflux for 2.5 h with TFA (3.0 mL) and MS4Å (0.45 g). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **49** as pale yellow solid (89.8 mg, 82 %): mp 130 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1626 (C=N), 1572 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.37–1.55 (m, 10H, 5 × CH₂), 3.46 (s, 2H, CH₂), 3.82 (s, 2H, CH₂), 7.21 (d, *J* = 2.0 Hz, 1H, Ar), 7.24 (s, 1H, NH), 7.33 (dd, *J* = 8.8, 2.0 Hz, 1H, Ar), 8.10 (d, *J* = 8.8 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 21.6 (2C), 26.3, 30.6, 33.3 (2C), 51.4, 55.4, 125.0, 125.3, 125.9, 129.5, 130.5, 130.7, 144.8, 152.7; HRMS (FAB): *m/z* calcd for C₁₆H₁₉BrN₃S [M + H]⁺ 364.0483; found: 364.0485.

3.1.83 Synthesis of 9-Bromo-2',3',5',6'-tetrahydro-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-pyran)-6(4H)-imine (51)

Dihydro-2H-pyran-4,4(3H)-dicarbonitrile (43). To a solution of malononitrile (660.6 mg, 10.0 mmol) in DMF (25.0 mL) was added DBU (2.99 mL, 20.0 mmol). After stirring at 50 °C for 2 h, the reaction mixture was added a solution of bis(2-chloroethyl)ether **39** (1.18 mL, 10.0 mmol) in DMF (10.0 mL). After being stirred at same temperature for 5 h, EtOAc was added. The mixture was washed with 5 % aq. NaHCO₃, and dried over MgSO₄. The filtrate was concentrated. The residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1). The resulting solid was recrystallized from CHCl₃–*n*-hexane to give the title compound **43** as colorless crystals (112.2 mg, 8 %): mp 96 °C, IR (neat) cm⁻¹: 2253 (C ≡ N); ¹H-NMR (400 MHz, CDCl₃) δ: 2.24 (t, *J* = 5.2 Hz, 4H, 2 × CH₂), 3.87 (t, *J* = 5.2 Hz, 4H, 2 × CH₂); ¹³C-NMR (100 MHz, CDCl₃) δ: 30.2, 33.8 (2C), 63.0 (2C), 114.9 (2C); MS (FAB) *m/z* (%): 137 (MH⁺, 100).

3-(4-Bromo-2-fluorophenyl)-9-oxa-2,4-diazaspiro[5.5]undec-2-ene (46). Using the general procedure as described for **45**, **43** (84.1 mg, 0.62 mmol) was allowed to react. Purification by flash chromatography over aluminum oxide with EtOAc–MeOH (1:0 to 95:5) gave the title compound **46** as colorless solid (21.4 mg, 11 %): mp 200–201 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1626 (C=N); ¹H-NMR (500 MHz, CDCl₃) δ: 1.52 (t, *J* = 5.4 Hz, 4H, 2 × CH₂), 3.31 (s, 4H, 2 × CH₂), 3.72 (t, *J* = 5.4 Hz, 4H, 2 × CH₂), 4.03 (br s, 1H, NH), 7.25 (dd, *J* = 11.7, 2.0 Hz, 1H, Ar), 7.31 (dd, *J* = 8.6, 2.0 Hz, 1H, Ar), 7.70 (t, *J* = 8.6 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃) δ: 27.0, 33.3 (2C), 51.4 (2C), 63.7 (2C), 119.5 (d, *J* = 27.6 Hz), 122.5 (d, *J* = 13.2 Hz), 124.0 (d, *J* = 9.6 Hz), 127.9 (d, *J* = 3.6 Hz), 131.7 (d, *J* = 3.6 Hz), 150.4, 159.7 (d, *J* = 251.9 Hz); HRMS (FAB): *m/z* calcd for C₁₄H₁₇BrFN₂O [M + H]⁺ 327.0508; found: 327.0512.

9-Bromo-*N*-(*tert*-butyl)-2',3',5',6'-tetrahydro-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-pyran)-6(4H)-imine (50). Using the general procedure as described for **48**, **46** (21.4 mg, 0.065 mmol) was allowed to react at rt overnight. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) gave the title compound **50** as colorless solid (21.5 mg, 78 %): mp 148–149 °C (from *n*-hexane); IR (neat) cm⁻¹: 1578 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.38 (s, 9H, 3 × CH₃), 1.48–1.53 (m, 4H, 2 × CH₂), 3.48 (s, 2H, CH₂), 3.71–3.74 (m, 4H, 2 × CH₂), 3.84 (s, 2H, CH₂), 7.29–7.33 (m, 1H, Ar), 7.37 (d, *J* = 4.1 Hz, 1H, Ar), 8.05 (d, *J* = 8.5 Hz, 1H, Ar); ¹³C-NMR (125 MHz, CDCl₃–CD₃OD) δ: 29.4, 29.9 (3C), 33.1 (2C), 51.4, 54.3, 55.5, 63.8 (2C), 124.6, 126.1, 126.9, 129.3, 130.0, 130.9, 137.6, 146.4; HRMS (FAB): *m/z* calcd for C₁₉H₂₅BrN₃OS [M + H]⁺ 422.0902; found: 422.0898.

Compound 51. Using the general procedure as described for **25a**, **50** (21.4 mg, 0.065 mmol) was allowed to react under reflux for 2.5 h with TFA (1.0 mL) and

MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **51** as colorless solid (12.3 mg, 66 %): mp 212–214 °C (from CHCl₃–*n*-hexane); IR (neat) cm⁻¹: 1626 (C=N), 1573 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.54 (t, *J* = 5.4 Hz, 4H, 2 × CH₂), 3.56 (s, 2H, CH₂), 3.74 (t, *J* = 5.4 Hz, 4H, 2 × CH₂), 3.93 (s, 2H, CH₂), 7.22 (d, *J* = 2.0 Hz, 1H, Ar), 7.31 (br s, 1H, NH), 7.34 (dd, *J* = 8.8, 2.0 Hz, 1H, Ar), 8.10 (d, *J* = 8.8 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃–CD₃OD) δ: 28.6, 32.9 (2C), 50.7, 54.6, 63.4 (2C), 124.7, 125.3, 125.9, 129.6, 130.3, 130.5, 145.4, 152.9; HRMS (FAB): *m/z* calcd for C₁₅H₁₇BrN₃OS [M + H]⁺ 366.0276; found: 366.0280.

3.1.84 Synthesis of 9-Bromo-1'-(4-methoxybenzyl)-2H-spiro(benzof[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine (53a)

Bis(2-chloroethyl)-*N*-(4-methoxybenzyl)amine (41). To a suspension of bis(2-chloroethyl)amine hydrochloride **40** (8.92 g, 50.0 mmol) in CH₂Cl₂ (300 mL) were added Et₃N (2.89 mL, 100.0 mmol) and 4-methoxybenzoyl chloride (6.77 mL, 50.0 mmol). After being stirred at rt for 2 h, the reaction mixture was washed with 1 N HCl, sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was dissolved in anhydrous Et₂O (250 mL), and LiAlH₄ (2.1 g, 55.0 mmol) was slowly added to the mixture at 0 °C under an Ar atmosphere. After being stirred at rt overnight, the reaction mixture was quenched by the addition of water, 2 N NaOH, and water. The mixture was dried over MgSO₄. After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (19:1) to give the title compound **41** as colorless oil (9.88 g, 75 %): ¹H-NMR (400 MHz, CDCl₃) δ: 2.90 (t, *J* = 7.1 Hz, 4H, 2 × CH₂), 3.48 (t, *J* = 7.1 Hz, 4H, 2 × CH₂), 3.67 (s, 2H, CH₂), 3.80 (s, 3H, CH₃), 6.86 (d, *J* = 8.5 Hz, 2H, Ar), 7.24 (d, *J* = 8.5 Hz, 2H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 42.0 (2C), 55.2, 56.2 (2C), 58.6, 113.8 (2C), 129.7 (2C), 130.7, 158.9; MS (FAB) *m/z* (%): 262 (MH⁺, 100).

1-(4-Methoxybenzyl)piperidine-4,4-dicarbonitrile (44). To a solution of malononitrile (2.49 g, 37.7 mmol) in DMF (94.3 mL) was added K₂CO₃ (5.73 mg, 41.5 mmol). After being stirred at 65 °C for 2 h, a solution of **41** (9.88 mg, 37.7 mmol) in DMF (37.7 mL) was added. After being stirred at same temperature for 5 h, EtOAc was added. The mixture was washed with 5 % aq. NaHCO₃, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) to give the title compound **44** as yellow oil (8.13 g, 85 %): IR (neat) cm⁻¹: 2248 (C ≡ N); ¹H-NMR (400 MHz, CDCl₃) δ: 2.22 (t, *J* = 5.4 Hz, 4H, 2 × CH₂), 2.61 (br s, 4H, 2 × CH₂), 3.48 (s, 2H, CH₂), 3.80 (s, 3H, CH₂), 6.86 (d, *J* = 8.5 Hz, 2H, Ar), 7.19 (d, *J* = 8.8 Hz, 2H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 31.1, 34.1 (2C), 48.5

(2C), 55.2, 61.9, 113.8 (2C), 115.4 (2C), 129.2, 130.1 (2C), 159.0; HRMS (FAB): m/z calcd for $C_{15}H_{18}N_3O$ $[M + H]^+$ 256.1450; found: 256.1454.

3-(4-Bromo-2-fluorophenyl)-9-(4-methoxybenzyl)-2,4,9-triazaspiro[5.5]undec-2-ene (47). Using the general procedure as described for **45**, **44** (4.05 g, 15.9 mmol) was allowed to react. Purification by flash chromatography over aluminum oxide with EtOAc–MeOH (1:0 to 95:5) to give the title compound **47** as colorless solid (752.6 mg, 11 %): mp 179–181 °C (from $CHCl_3$ –*n*-hexane), IR (neat) cm^{-1} : 1630 (C=N); 1H -NMR (500 MHz, $CDCl_3$) δ : 1.45 (t, $J = 5.4$ Hz, 4H, $2 \times CH_2$), 2.35 (t, $J = 5.4$ Hz, 4H, $2 \times CH_2$), 3.16 (s, 4H, $2 \times CH_2$), 3.40 (s, 2H, CH_2), 3.73 (s, 3H, CH_3), 4.63 (s, 1H, NH), 6.78 (d, $J = 8.6$ Hz, 2H, Ar), 7.14–7.23 (m, 4H, Ar), 7.62 (t, $J = 8.3$ Hz, 1H, Ar); ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 27.3, 32.8 (2C), 49.1 (2C), 51.4 (2C), 55.2, 62.7, 113.5 (2C), 119.4 (d, $J = 27.3$ Hz), 122.7 (d, $J = 12.4$ Hz), 123.7 (d, $J = 9.9$ Hz), 127.8 (d, $J = 3.3$ Hz), 130.2, 130.3 (2C), 131.7 (d, $J = 4.1$ Hz), 150.3 (d, $J = 1.7$ Hz), 158.6, 159.7 (d, $J = 251.6$ Hz); ^{19}F -NMR (500 MHz, $CDCl_3$) δ : –114.6; HRMS (FAB): m/z calcd for $C_{22}H_{26}BrFN_3O$ $[M + H]^+$ 446.1243; found: 446.1237.

9-Bromo-*N*-(*tert*-butyl)-1'-(4-methoxybenzyl)-2*H*-spiro(benzo[*e*]pyrimido[1,2-*c*][1,3]thiazine-3,4'-piperidin)-6(4*H*)-imine (52a). Using the general procedure as described for **48**, **47** (2.0 g, 4.48 mmol) was allowed to react at rt overnight. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1) to give the title compound **52a** as colorless solid (2.28 g, 94 %): mp 89–91 °C (from $CHCl_3$ –*n*-hexane); IR (neat) cm^{-1} : 1577 (C=N); 1H -NMR (500 MHz, $CDCl_3$) δ : 1.37 (s, 9H, $3 \times CH_3$), 1.49–1.52 (m, 4H, $2 \times CH_2$), 2.40–2.46 (m, 4H, $2 \times CH_2$), 3.41 (s, 2H, CH_2), 3.47 (s, 2H, CH_2), 3.75 (s, 2H, CH_2), 3.80 (s, 3H, CH_3), 6.85 (d, $J = 8.6$ Hz, 2H, Ar), 7.22 (d, $J = 8.6$ Hz, 2H, Ar), 7.28–7.31 (m, 2H, Ar), 8.03 (d, $J = 8.6$ Hz, 1H, Ar); ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 29.7, 29.9 (3C), 32.6 (2C), 49.2 (2C), 51.6, 54.3, 55.2, 55.5, 62.7, 113.6 (2C), 124.5, 126.3, 126.8, 129.2, 130.0, 130.1, 130.4 (2C), 130.9, 137.5, 146.3, 158.7; HRMS (FAB): m/z calcd for $C_{27}H_{34}BrN_4OS$ $[M + H]^+$ 541.1637; found: 541.1633.

Compound 53a. Using the general procedure as described for **25a**, compound **52a** (448.1 mg, 0.83 mmol) was allowed to react for 2 h with TFA (10.0 mL) and $MS4\text{\AA}$ (1.50 g). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **53a** as colorless solid (288.8 mg, 72 %): mp 160–162 °C (from $CHCl_3$ –*n*-hexane); IR (neat) cm^{-1} : 1626 (C=N), 1573 (C=N); 1H -NMR (400 MHz, $CDCl_3$) δ : 1.54 (t, $J = 5.5$ Hz, 4H, $2 \times CH_2$), 2.39–2.51 (m, 4H, $2 \times CH_2$), 3.46 (s, 2H, CH_2), 3.48 (s, 2H, CH_2), 3.79 (s, 3H, CH_3), 3.86 (s, 2H, CH_2), 6.84 (d, $J = 8.8$ Hz, 2H, Ar), 7.20–7.22 (m, 3H, Ar), 7.28 (s, 1H, NH), 7.32 (dd, $J = 8.8, 2.0$ Hz, 1H, Ar), 8.08 (d, $J = 8.8$ Hz, 1H, Ar); ^{13}C -NMR (100 MHz, $CDCl_3$) δ : 29.2, 32.6 (2C), 49.1 (2C), 50.8, 55.1, 55.2, 62.6, 113.6 (2C), 125.1, 125.1, 125.9, 129.5, 130.3 (2C), 130.3, 130.4, 130.7, 145.0, 152.6, 158.7; HRMS (FAB): m/z calcd for $C_{23}H_{26}BrN_4OS$ $[M + H]^+$ 485.1011; found: 485.1010.

3.1.85 Synthesis of 9-Bromo-1'-(methoxycarbonyl)-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine (53b)

9-Bromo-N-(tert-butyl)-1'-(methoxycarbonyl)-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine (52b). To the solution of 9-bromo-N-(tert-butyl)-1'-(4-methoxybenzyl)-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine **52a** (40.6 mg, 0.075 mmol) in CH₂Cl₂ (0.38 mL) was added methyl chloroformate (86.4 μ L, 1.13 mmol) at 0 °C under an Ar atmosphere. After being stirred at same temperature for 30 min, the reaction mixture was concentrated. The residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (1:1) to give the title compound **52b** as a colorless solid (29.2 mg, 81 %): mp 157–158 °C (from *n*-hexane); IR (neat) cm⁻¹: 1699 (C=O), 1577 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ : 1.37 (s, 9H, 3 \times CH₃), 1.46 (t, *J* = 5.6 Hz, 4H, 2 \times CH₂), 3.44 (br s, 4H, 2 \times CH₂), 3.56 (br s, 2H, CH₂), 3.70 (s, 3H, CH₃), 3.81 (s, 2H, CH₂), 7.29–7.33 (m, 2H, Ar), 8.05 (d, *J* = 8.5 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ : 29.9 (3C), 30.1, 32.2 (2C), 39.9 (2C), 50.8, 52.5, 54.3, 55.2, 124.7, 126.1, 126.8, 129.3, 130.0, 130.9, 137.7, 146.3, 155.9; HRMS (FAB): *m/z* calcd for C₂₁H₂₈BrN₄O₂S [M + H]⁺ 479.1116; found: 479.1115.

Compound 53b. Using the general procedure as described for **25a**, compound **52b** (6.4 mg, 0.013 mmol) was allowed to react for 2 h with TFA (1.0 mL) and MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:3) gave the title compound **53b** as colorless solid (4.0 mg, 73 %): mp 139–141 °C (from MeCN–H₂O); IR (neat) cm⁻¹: 1692 (C=O), 1626 (C=N), 1573 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ : 1.49 (t, *J* = 5.7 Hz, 4H, 2 \times CH₂), 3.45–3.57 (m, 6H, 3 \times CH₂), 3.70 (s, 3H, CH₃), 3.91 (s, 2H, CH₂), 7.22 (d, *J* = 2.0 Hz, 1H, Ar), 7.31 (br s, 1H, NH), 7.34 (dd, *J* = 8.8, 2.0 Hz, 1H, Ar), 8.10 (d, *J* = 8.8 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ : 29.5, 32.2 (2C), 39.7 (2C), 50.0, 52.6, 54.6, 125.0, 125.3, 126.0, 129.6, 130.5, 130.6, 145.1, 152.6, 155.9; HRMS (FAB): *m/z* calcd for C₁₇H₂₀BrN₄O₂S [M + H]⁺ 423.0490; found: 423.0492.

3.1.86 Synthesis of 1'-Acetyl-9-bromo-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine (53c)

1'-Acetyl-9-bromo-N-(tert-butyl)-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine (52c). Using the general procedure as described for **52b**, 9-bromo-N-(tert-butyl)-1'-(4-methoxybenzyl)-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine **52a** (40.6 mg, 0.075 mmol)

was allowed to react for 10 min with AcCl (53.3 μ L, 0.75 mmol). Purification by flash chromatography over aluminum oxide with n-hexane–EtOAc (1:1) gave the title compound **52c** as colorless solid (33.3 mg, 96 %): mp 181–182 °C (from CHCl₃–n-hexane); IR (neat) cm⁻¹: 1632 (C=O), 1578 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ : 1.37 (s, 9H, 3 \times CH₃), 1.46–1.52 (m, 4H, 2 \times CH₂), 2.10 (s, 3H, CH₃), 3.45–3.56 (m, 5H, 5 \times CH), 3.72–3.78 (m, 2H, 2 \times CH), 3.90 (d, J = 13.4 Hz, 1H, CH), 7.29–7.33 (m, 2H), 8.05 (d, J = 8.5 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ : 21.4, 29.9 (3C), 30.3, 32.2, 32.8, 37.5, 42.6, 50.8, 54.4, 55.1, 124.7, 126.0, 126.9, 129.3, 130.0, 130.8, 137.7, 146.3, 168.8; HRMS (FAB): m/z calcd for C₂₁H₂₈BrN₄OS [M + H]⁺ 463.1167; found: 463.1164.

Compound 53c. Using the general procedure as described for **25a**, compound **52c** (6.5 mg, 0.014 mmol) was allowed to react for 2 h with TFA (1.0 mL) and MS4 Å (150 mg). Purification by flash chromatography over aluminum oxide with n-hexane–EtOAc (1:2) gave the title compound **53c** as colorless solid (4.5 mg, 79 %): mp 147–148 °C (from CHCl₃–n-hexane); IR (neat) cm⁻¹: 1625 (C=O), 1573 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ : 1.49–1.55 (m, 4H, 2 \times CH₂), 2.09 (s, 3H, CH₃), 3.47–3.61 (m, 5H, 5 \times CH), 3.70–3.77 (m, 1H, CH), 3.84 (d, J = 13.4 Hz, 1H, CH), 4.04 (d, J = 13.2 Hz, 1H, CH), 7.22 (d, J = 1.2 Hz, 1H, Ar), 7.33–7.36 (m, 2H, Ar, NH), 8.10 (d, J = 8.8 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ : 21.4, 29.7, 32.1, 32.7, 37.3, 42.4, 49.8, 54.7, 124.9, 125.3, 126.0, 129.6, 130.4, 130.6, 145.1, 152.6, 168.9; Anal. calcd for C₁₇H₁₉BrN₄OS: C, 50.13; H, 4.70; N, 13.75. Found: C, 50.24; H, 4.78; N, 13.57.

3.1.87 Synthesis of 9-Bromo-1'-(methanesulfonyl)-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine (53d)

9-Bromo-N-(tert-butyl)-1'-(methanesulfonyl)-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine (52d). To the solution of 9-bromo-N-(tert-butyl)-1'-(4-methoxybenzyl)-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine **52a** (54.2 mg, 0.10 mmol) in CH₂Cl₂ (0.5 mL) were added Et₃N (28.9 μ L, 0.20 mmol) and 1-chloroethyl chloroformate (21.8 μ L, 0.20 mmol) at 0 °C under an Ar atmosphere. After being stirred at same temperature for 30 min, the reaction mixture was concentrated. The residue was dissolved in MeOH (2.0 mL). After being stirred under reflux for 10 min, the reaction mixture was concentrated. The residue was dissolved in CHCl₃, and was washed with sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was dissolved in CH₂Cl₂ (1.0 mL) and Et₃N (28.9 μ L, 0.20 mmol), and MsCl (15.5 μ L, 0.20 mmol) was added at rt under an Ar atmosphere. After being stirred at rt for 10 min, the reaction mixture was washed with sat. NaHCO₃, brine, and dried over MgSO₄. After concentration, the residue was purified by flash chromatography over aluminum oxide with n-hexane–EtOAc (6:4) to give the title

compound **52d** as a colorless solid (40.9 mg, 82 %): mp 177 °C (from CHCl₃–n-hexane); IR (neat) cm⁻¹: 1577 (C=N), 1331 (NSO₂), 1155 (NSO₂); ¹H-NMR (400 MHz, CDCl₃) δ: 1.38 (s, 9H, 3 × CH₃), 1.62 (t, J = 5.5 Hz, 4H, 2 × CH₂), 2.80 (s, 3H, CH₃), 3.21–3.27 (m, 2H, CH₂), 3.31–3.37 (m, 2H, CH₂), 3.46 (s, 2H, CH₂), 3.84 (s, 2H, CH₂), 7.29–7.33 (m, 2H, Ar), 8.05 (d, J = 8.5 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 29.8, 29.9 (3C), 32.0 (2C), 34.7, 42.0 (2C), 50.1, 54.4, 55.1, 124.8, 125.9, 126.9, 129.4, 130.0, 130.8, 137.9, 146.3; HRMS (FAB): m/z calcd for C₂₀H₂₈BrN₄O₂S₂ [M + H]⁺ 499.0837; found: 499.0840.

Compound 53d. Using the general procedure as described for **25a**, compound **52d** (9.2 mg, 0.018 mmol) was allowed to react for 2 h with TFA (1.0 mL) and MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with n-hexane–EtOAc (1:1) gave the title compound **53d** as colorless solid (5.3 mg, 65 %): mp 171–172 °C (from CHCl₃–n-hexane); IR (neat) cm⁻¹: 1621 (C=N), 1564 (C=N), 1320 (NSO₂), 1152 (NSO₂); ¹H-NMR (400 MHz, CDCl₃–CD₃OD) δ: 1.64–1.67 (m, 4H, 2 × CH₂), 2.82 (s, 3H, CH₃), 3.19–3.25 (m, 2H, CH₂), 3.35–3.41 (m, 2H, CH₂), 3.52 (s, 2H, CH₂), 3.92 (s, 2H, CH₂), 7.24 (d, J = 2.0 Hz, 1H, Ar), 7.37 (dd, J = 8.5, 2.0 Hz, 1H, Ar), 8.07 (d, J = 8.5 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃–CD₃OD) δ: 29.0, 31.9 (2C), 34.7, 41.7 (2C), 49.2, 54.6, 124.7, 125.4, 126.0, 129.7, 130.3, 130.4, 145.3, 153.1; HRMS (FAB): m/z calcd for C₁₆H₂₀BrN₄O₂S₂ [M + H]⁺ 443.0211; found: 443.0210.

3.1.88 Synthesis of 1'-(Aminocarbonyl)-9-bromo-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine (53e)

1'-(Aminocarbonyl)-9-bromo-N-(tert-butyl)-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine (52e). Using the general procedure as described for **52d**, 9-bromo-N-(tert-butyl)-1'-(4-methoxybenzyl)-2H-spiro(benzo[e]pyrimido[1,2-c][1,3]thiazine-3,4'-piperidin)-6(4H)-imine **52a** (54.2 mg, 0.10 mmol) was allowed to react with 1-chloroethyl chloroformate (21.8 μL, 0.20 mmol) followed with N-trimethylsilylisocyanate (26.5 μL, 0.20 mmol). Purification by flash chromatography over aluminum oxide with EtOAc–MeOH (1:0 to 9:1) gave the title compound **52e** as colorless solid (11.8 mg, 29 %): mp 203–205 °C (from CHCl₃–n-hexane); IR (neat) cm⁻¹: 1649 (C=O), 1577 (C=N); ¹H-NMR (400 MHz, CDCl₃) δ: 1.37 (s, 9H, 3 × CH₃), 1.51 (t, J = 5.6 Hz, 4H, 2 × CH₂), 3.37–3.51 (m, 6H, 3 × CH₂), 3.82 (s, 2H, CH₂), 4.46 (s, 2H, NH₂), 7.30–7.33 (m, 2H, Ar), 8.05 (d, J = 8.5 Hz, 1H, Ar); ¹³C-NMR (100 MHz, CDCl₃) δ: 29.9 (3C), 30.0, 32.1 (2C), 40.3 (2C), 50.9, 54.4, 55.1, 124.7, 126.0, 126.8, 129.3, 130.0, 130.9, 137.6, 146.3, 158.0; HRMS (FAB): m/z calcd for C₂₀H₂₇BrN₅OS [M + H]⁺ 464.1120; found: 464.1122.

Compound 53e. Using the general procedure as described for **25a**, compound **52e** (5.1 mg, 0.011 mmol) was allowed to react for 2 h with TFA (1.0 mL) and

MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with EtOAc–MeOH (1:0 to 9:1) gave the title compound **53e** as colorless solid (4.2 mg, 94 %): mp 222 °C (from MeOH–CHCl₃–n-hexane); IR (neat) cm⁻¹: 1651 (C=O), 1624 (C=N), 1585 (C=N); ¹H-NMR (400 MHz, DMSO-d₆) δ: 1.31 (t, J = 5.6 Hz, 4H, 2 × CH₂), 3.20–3.38 (m, 4H, 2 × CH₂), 3.45 (s, 2H, CH₂), 3.84 (s, 2H, CH₂), 5.88 (s, 2H, NH₂), 7.42 (dd, J = 8.5, 1.5 Hz, 1H), 7.59 (d, J = 1.5 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H, Ar), 8.91 (s, 1H, NH). ¹³C-NMR (125 MHz, DMSO-d₆) δ: 29.0, 31.6 (2C), 39.5 ± 1.0 (2C), 48.9, 54.0, 124.3, 124.7, 126.0, 129.0, 130.2, 131.2, 144.0, 149.2, 158.0; HRMS (FAB): m/z calcd for C₁₆H₁₉BrN₅OS [M + H]⁺ 408.0494; found: 408.0496.

3.1.89 Determination of Anti-HIV Activity

The sensitivity of HIV-1_{III_B} strain was determined by the MAGI assay. The target cells (HeLa-CD4/CCR5-LTR/β-gal; 10⁴ cells/well) were plated in 96-well flat microtiter culture plates. On the following day, the cells were inoculated with the HIV-1 (60 MAGI U/well, giving 60 blue cells after 48 h of incubation) and cultured in the presence of various concentrations of the test compounds in fresh medium. Forty-eight hours after viral exposure, all the blue cells stained with X-Gal (5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside) were counted in each well. The activity of test compounds was determined as the concentration that blocked HIV-1 infection by 50 % (50 % effective concentration [EC₅₀]). EC₅₀ was determined by using the following formula:

$$EC_{50} = 10^{[\log(A/B) \times (50 - C)/(D - C) + \log(B)]},$$

wherein

A: of the two points on the graph which bracket 50 % inhibition, the higher concentration of the test compound,

B: of the two points on the graph which bracket 50 % inhibition, the lower concentration of the test compound,

C: inhibitory activity (%) at the concentration B,

D: inhibitory activity (%) at the concentration A.

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