Supplementary Information

Concise synthesis and anti-HIV activity of pyrimido[1,2-*c*][1,3]benzothiazin-6-imines and related tricyclic heterocycles

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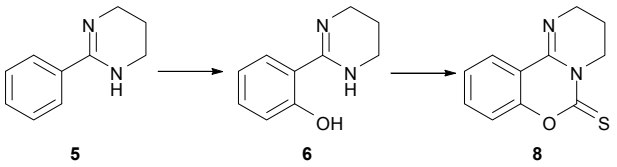
Experimental Section

Synthesis of compound 8

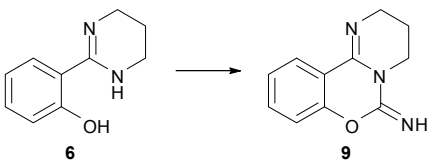


5 6 8

2-(2-Hydroxyphenyl)tetrahydropyrimidine (6). DMF (0.83 cm^3) and water (0.0045 cm^3, 0.25 mmol) were added to a flask containing **5** (40.1 mg, 0.25 mmol) and $Cu(OAc)_2$ (45.4 mg, 0.25 mmol) under O_2 atmosphere. After being stirred at 130 °C for 20 min, mixture was concentrated. The residue was purified by flash chromatography over aluminum oxide with $CHCl_3$–MeOH (95:5) to give the title compound **6** as brown solid (30.3 mg, 69%): IR (neat) ν_{max}/cm^{-1}: 3257-3041 (OH), 1613 (C=N); δ_H (500 MHz, DMSO-d_6) 1.84-1.88 (2H, m, CH_2), 3.40 (4H, t, J = 5.7 Hz, 2 × CH_2), 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). δ_C (125 MHz, CD_3OD) 20.0, 39.3 (2C), 111.2, 114.5, 124.4, 126.3, 135.1, 161.0, 172.4; LRMS (FAB): *m/z* calcd for $C_{10}H_{13}N_2O$ $[M + H]^+$ 177; found: 177.

3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzoxazine-6-thione (8). To a suspension of **6** (33.0 mg, 0.19 mmol) and Et_3N (0.068 cm^3, 0.47 mmol) in CH_2Cl_2 (10.0 cm^3) was added dropwise a solution of thiophosgene (0.016 cm^3, 0.21 mmol) in CH_2Cl_2 (1.0 cm^3) at 0 °C. After being stirred at room temperature for 1h, the mixture was quenched with sat. $NaHCO_3$, and concentrated. The whole was extracted with EtOAc. The extract was washed with sat. $NaHCO_3$, brine, and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to give the title compound **8** as yellow solid (41.9 mg, quant): mp 135–136 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1655 (C=N); δ_H (400 MHz, $CDCl_3$) 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.23; H, 4.72; N, 12.62.

Synthesis of 3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzoxazin-6-imine (9)

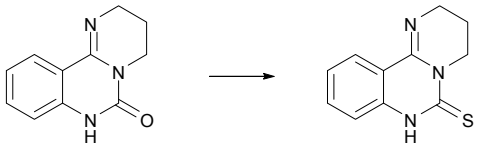


6 9

Compound **6** (5.4 mg, 0.03 mmol) was suspended with CH_2Cl_2 (0.3 cm^3) and added the solution of BrCN (3.3 mg, 0.06 mmol) in CH_2Cl_2 (0.3 cm^3). After being stirred for 1h at room temperature, the additional portion of BrCN (3.3 mg, 0.06 mmol) in CH_2Cl_2 (0.3 cm^3) was added. After being stirred for 1 h at room temperature, 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 **9** as colorless solid (2.1 mg, 34%): mp 104–105 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1639 (C=N), 1611 (C=N); δ_H (500 MHz,

$CDCl_3$) 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.55; H, 5.40; N, 20.70.

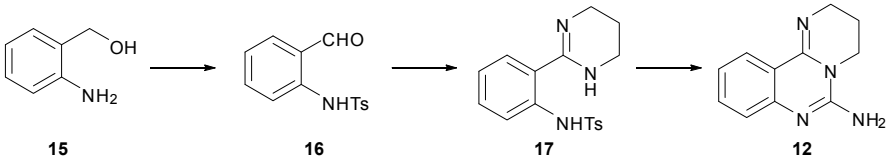
Synthesis of 3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*]quinazolin-6(7*H*)-thione (11)



10 **11**

Xylene (4.0 mL) was added to a flask containing **10** (50.3 mg, 0.25 mmol), Lawesson's reagent (202.2 mg, 0.50 mmol). After being stirred under reflux for 24 h, xylene (2 cm^3) and additional amount of Lawesson's reagent (101.1 mg, 0.25 mmol) was added. After being stirred under reflux for additional 12 h, the mixture was cooled to room temperature. 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 **11** as colorless solid (10.4 mg, 19%): mp 258–259 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1618 (C=N); δ_H (500 MHz, DMSO-d_6) 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). δ_C (100 MHz, DMSO-d_6) 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 $C_{11}H_{12}N_3S$ $[M + H]^+$ 218.0752; found: 218.0757.

Synthesis of compound 12



15 **16** **17** **12**

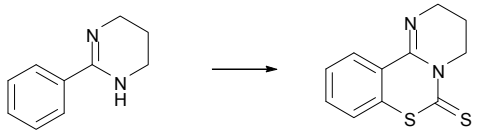
2-[*N*-(*p*-Toluenesulfonyl)amino]benzaldehyde (16). To a solution of **15** (2.0 g, 16.2 mmol) and pyridine (1.6 cm^3, 19.4 mmol) in $CHCl_3$ (60 cm^3) was added a solution of *p*-TsCl (3.4 g, 18.0 mmol) in $CHCl_3$ (17 cm^3), and the mixture was stirred at rt for 3 h. After concentration, EtOAc and sat. NH_4Cl was 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 cm^3). 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 **16** as colorless solid (3.6 g, 80%): mp 134–136 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1672 (C=O), 1492 (NSO_2), 1157 (NSO_2); δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, CH_3), 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). δ_C (100 MHz, $CDCl_3$) 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

$C_{14}H_{13}NO_3S$: 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 (17). To a solution of **16** (2.75 g, 10 mmol) in *t*-BuOH (94 cm^3) was added propylenediamine (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 **17** as pale yellow crystals (3.23 g, 98%): mp 211–213 °C; IR (neat) ν_{max}/cm^{-1}: 1630 (C=N); 1478 (NSO_2), 1124 (NSO_2); δ_H (400 MHz, $CDCl_3$) 1.77-1.82 (2H, m, CH_2), 2.34 (3H, s, CH_3), 3.36 (4H, t, J = 5.7 Hz, 2 × CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{17}H_{20}N_3O_2S$ $[M + H]^+$ 330.1276; found: 330.1273.

3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-c]quinazolin-6-amine (12). To a flask containing **17** (164.7 mg, 0.5 mmol) was added conc. H_2SO_4 (5.0 cm^3). 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 2N NaOH. The whole was extracted with $CHCl_3$, and dried over MgSO4. After concentration, the residue was dissolved in anhydrous EtOH (2 cm^3). Then, BrCN (105.9 mg, 1.0 mmol) was added to the mixture under Ar atmosphere. After being stirred under reflux for 2 h, the reaction was quenched with 2N NaOH. The whole was extracted with $CHCl_3$, 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 **12** as colorless solid (66.0 mg, 66%): mp 259–260 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1620 (C=N), 1603 (C=N); δ_H (400 MHz, DMSO-d_6) 1.81-1.87 (2H, m, CH_2), 3.44 (2H, t, J = 5.4 Hz, CH_2), 3.70 (2H, t, J = 6.1 Hz, CH_2), 6.49 (2H, br s, NH_2), 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). δ_C (100 MHz, DMSO-d_6) 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 $C_{11}H_{13}N_4$ $[M + H]^+$ 201.1140; found: 201.1138.

Synthesis of 3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzthiazine-6-thione (13) via C-H functionalization

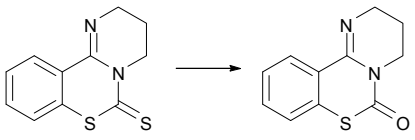


5 13

To a solution of **5** (40.1 mg, 0.25 mmol), $Cu(OAc)_2$ (45.4 mg, 0.25 mmol) in 1,4-dioxane (0.83 cm^3) was added CS_2 (0.045 cm^3, 0.75 mmol) under O_2 atmosphere. After being stirred at 130 °C for 15 min, the mixture was concentrated. The residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (9:1) to give the title compound **13** as pale yellow solid (6.6 mg, 11%). Spectral data

were in good agreement with those previously reported.[2]

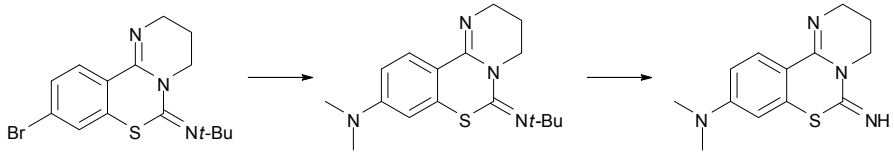
Synthesis of 3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-one (14).



13 14

Compound **13** (58.6 mg, 0.25 mmol) was suspended into a 0.1M NaOH in MeOH-H_2O (9:1, 5 cm^3). After being stirred under reflux for 12 h, the mixture was concentrated. To a stirring solution of the residue and Et_3N (0.029 cm^3, 2.0 mmol) in CH_2Cl_2 (16.6 cm^3) was added dropwise a solution of triphosgene (155.8 mg, 0.52 mmol) in CH_2Cl_2 (1.7 cm^3) at 0 °C. After being stirred at room temperature for 1 h, the mixture was quenched with sat. $NaHCO_3$. The whole was extracted with $CHCl_3$. The extract was washed with sat. $NaHCO_3$, brine, and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (9:1) to give the title compound **14** as colorless solid (35.3 mg, 65%): mp 102–103 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1639 (C=O) 1612 (C=N); δ_H (500 MHz, $CDCl_3$) 1.95-1.99 (2H, m, CH_2), 3.73 (2H, t, J = 5.7 Hz, CH_2), 4.00 (2H, t, J = 6.0 Hz, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{11}H_{11}N_2OS$ $[M + H]^+$ 219.0592; found: 219.0592.

Synthesis of compound 28a



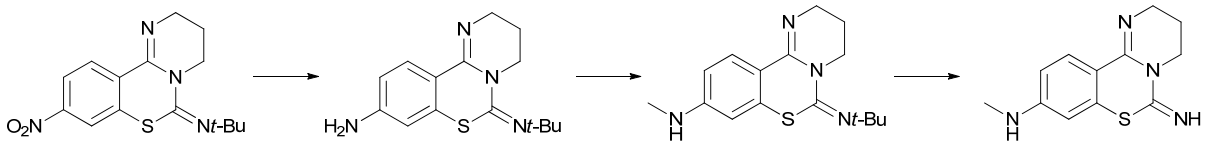
25k 25a 28a

***N*-(*tert*-Butyl)-9-(*N*',*N*'-dimethylamino)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25a)**. To a mixture of **25k** (88.1 mg, 0.25 mmol) and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and KO*t*-Bu (84.2 mg, 0.75 mmol) in toluene (2.0 cm^3) were added P(*tert*-Bu)$_3$ (0.009 cm^3, 0.038 mmol) and 2N Me_2NH in THF (0.38 cm^3, 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 **25a** as colorless solid (80.9 mg, quant): mp 161–162 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1587 (C=N); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, 3 × CH_3), 1.86-1.92 (2H, m, CH_2), 2.97 (6H, s, 2 × CH_3), 3.58 (2H, t, J = 5.5 Hz, CH_2), 3.85 (2H, t, J = 6.1 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{17}H_{25}N_4S$ $[M + H]^+$ 317.1800; found: 317.1803.

9-(*N*,*N*-Dimethylamino)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28a). TFA (2.0 cm^3) was added to a mixture of **25a** (63.3 mg, 0.2 mmol) in small amount of $CHCl_3$ and MS4Å (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 $CHCl_3$ was added dropwise 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 $MgSO_4$. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) to give the title compound **28a** as colorless solid (38.2 mg, 73%): mp 150–151 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1600 (C=N), 1562 (C=N); δ_H (500 MHz, $CDCl_3$) 1.93-1.98 (2H, m, CH_2), 2.98 (6H, s, 2 × CH_3), 3.64 (2H, t, J = 5.7 Hz, CH_2), 4.00 (2H, t, J = 6.3 Hz, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{13}H_{17}N_4S$ $[M + H]^+$ 261.1174; found: 261.1173.

Synthesis of compound 28b

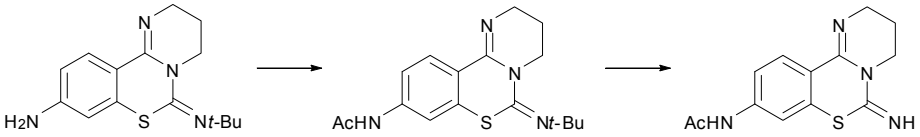


9-Amino-*N*-(*tert*-butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (31). To a suspension of **25e** (477.0 mg, 1.5 mmol) in EtOH (10 cm^3) was added 10% Pd-C (ca. 55% in water, 400 mg) under a H_2 atmosphere. After being stirred at room temperature overnight, the mixture was filtered through a celite pad. After concentration, the resulting solid was recrystallized from $CHCl_3$–*n*-hexane to give the title compound **31** as colorless crystals (381.1 mg, 88%): mp 152–155 °C; IR (neat) ν_{max}/cm^{-1}: 1589 (C=N); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, 3 × CH_3), 1.86-1.92 (2H, m, CH_2), 3.57 (2H, t, J = 5.4 Hz, CH_2), 3.84 (2H, t, J = 6.0 Hz, CH_2), 3.88 (2H, br s, NH_2), 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). δ_C (100 MHz, CD_3OD) 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 $C_{15}H_{21}N_4S$ $[M + H]^+$ 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 (25b).** To a flask containing **31** (108.5 mg, 0.38 mmol), MeONa (30.6 mg, 0.57 mmol), and paraformaldehyde (34.2 mg, 1.1 mmol) was added dehydrate MeOH (2.5 cm^3) under an Ar atmosphere, and the reaction was continued for 5 h under reflux. Then, $NaBH_4$ (28.8 mg, 0.76 mmol) was added to the mixture and the reaction was continues for additional 30 min under reflux. After concentration, the residue was dissolved in AcOEt, and washed with sat. $NaHCO_3$, brine, and dried over $MgSO_4$. After concentration, the residue was purified by flash column chromatography over aluminum oxide with *n*-hexane–EtOAc (1:1) to give the title compound **25b** as yellow solid (104.9 mg, 91%): mp 156–158 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1590 (C=N); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, 3 × CH_3), 1.87-1.92 (2H, m, CH_2), 2.83 (3H, s, CH_3), 3.57 (2H, t, J = 5.4 Hz, CH_2), 3.85 (2H, t, J = 6.0 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{16}H_{23}N_4S$ $[M + H]^+$ 303.1643; found: 303.1638.

3,4-Dihydro-9-(*N*-methylamino)-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28b). Using the general procedure as described for **28a**, compound **25b** (30.7 mg, 0.1 mmol) was allowed to react for 1 h with TFA (1.0 cm^3) and MS4Å (200 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:1 to 0:10) gave the title compound **28b** as pale yellow solid (9.0 mg, 37%): mp 129–131 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1602 (C=N), 1555 (C=N); δ_H (400 MHz, $CDCl_3$) 1.92-1.98 (2H, m, CH_2), 2.84 (3H, d, J = 4.1 Hz, CH_3), 3.64 (2H, t, J = 5.6 Hz, CH_2), 4.00 (2H, t, J = 6.2 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{12}H_{14}N_4S$: C, 58.51; H, 5.73; N, 22.74. Found: C, 58.30; H, 5.62; N, 22.45.

Synthesis of compound 28c

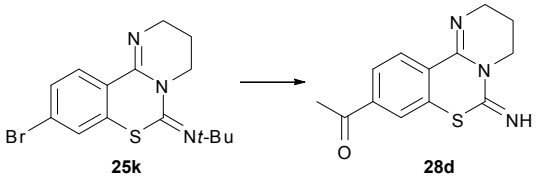


31 **25c** **28c**

9-(*N*-Acethylamino)-*N*-(*tert*-butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25c). To a mixture of **31** (100.9 mg, 0.35 mmol), Et_3N (0.015 cm^3, 1.05 mmol), DMAP (4.3 mg, 0.04 mmol) in CH_2Cl_2 (3.5 cm^3) was added Ac_2O (0.066 cm^3, 0.70 mmol) under an Ar atmosphere. After being stirred under reflux for 1 h, the mixture was added sat. $NaHCO_3$. The whole was extracted with AcOEt. The extract was washed with brine, and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:1 to 0:10) to give the title compound **25c** as colorless solid (120.1 mg, quant): mp 213–214 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1680 (C=O), 1596 (C=N); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, 3 × CH_3), 1.88-1.93 (2H, m, CH_2), 2.15 (3H, s, CH_3), 3.59 (2H, t, J = 5.4 Hz, CH_2), 3.86 (2H, t, J = 6.1 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{17}H_{23}N_4OS$ $[M + H]^+$ 331.1593; found: 331.1590.

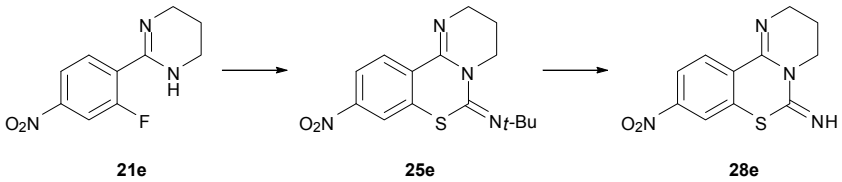
9-(*N*-Acethylamino)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28c). Using the general procedure as described for **28a**, compound **25c** (120.1mg, 0.36 mmol) was allowed to react for 10 h. Purification by recrystallization from MeOH–$CHCl_3$–Et_2O gave the title compound **28c** as pale yellow crystals (64.9 mg, 65%): mp 214 °C (decomp.); IR (neat) ν_{max}/cm^{-1}: 1681 (C=O), 1619 (C=N), 1550 (C=N); δ_H (400 MHz, DMSO-d_6) 1.85-1.91 (2H, m, CH_2), 2.07 (3H, s, CH_3), 3.55 (2H, t, J = 5.5 Hz, CH_2), 3.92 (2H, t, J = 6.0 Hz, CH_2), 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). δ_C (100 MHz, DMSO-d_6) 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 $C_{13}H_{15}N_4OS$ $[M + H]^+$ 275.0967; found: 275.0967.

Synthesis of 9-acetyl-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28d).



To a mixture of **25k** (100 mg, 0.284 mmol), $Pd(OAc)_2$ (6.4 mg, 0.0284 mmol), K_2CO_3 (120 mg, 0.852 mmol) and dppp (23.7 mg, 0.0568 mmol) in H_2O (0.57 cm^3) was added ethylene glycol monovinyl ether (0.13 cm^3, 1.42 mmol). After being stirred at reflux for 12 h, the whole was extracted with $CHCl_3$. The extract was washed with brine, and dried over Na_2SO_4. After concentration, TFA (2.84 cm^3) was added to resulting residue. After being stirred under reflux for 1.5 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 brine, and dried over Na_2SO_4. After concentration, the residue was purified by preparative TLC over aluminium oxide with *n*-hexane–EtOAc (7:3) to give the title compound **28d** as pale yellow solid (9.7 mg, 13.1%): mp 148.4 °C; IR (neat) ν_{max}/cm^{-1}: 1678 (C=O), 1616 (C=N), 1567 (C=N); δ_H (300 MHz, $CDCl_3$) 1.95-2.03 (2H, m, CH_2), 2.60 (3H, s, CH_3), 3.72 (2H, t, J = 5.7 Hz, CH_2), 4.03 (2H, t, J = 6.3 Hz, CH_2), 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). δ_C (75 MHz, $CDCl_3$) 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 $C_{13}H_{13}N_3OS$: C, 60.21; H, 5.05; N, 16.20. Found: C, 60.16; H, 5.02; N, 15.94.

Synthesis of compound 28e

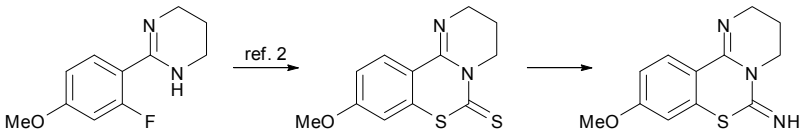


***N*-(*tert*-Butyl)-3,4-dihydro-9-nitro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25e)**. To a mixture of **21e** (2.0 g, 9.0 mmol) and NaH (716.8 mg, 17.9 mmol; 60% oil suspension) in DMF (29.8 cm^3) was added *tert*-butylisothiocyanate (2.28 cm^3, 17.9 mmol) under an Ar atmosphere, and 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. $NaHCO_3$, brine, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (10:0 to 9:1) to give the title compound **25e** as pale yellow solid (1.77 g, 62%): mp 152–153 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1591 (NO_2), 1581 (C=N), 1523 (NO_2); δ_H (500 MHz, $CDCl_3$) 1.39 (9H, s, 3 × CH_3), 1.91-1.96 (2H, m, CH_2), 3.66 (2H, t, J = 5.2 Hz, CH_2), 3.88 (2H, t, J = 5.7 Hz, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{15}H_{19}N_4O_2S$ $[M + H]^+$ 319.1229; found: 319.1229.

3,4-Dihydro-9-nitro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28e). Using the general procedure as described for **28a**, compound **25e** (47.8 mg, 0.15 mmol) was allowed to react for 1 h with TFA (1.5 cm^3) and MS4Å (225 mg). Purification by flash chromatography over aluminum oxide with

n-hexane–EtOAc (19:1 to 1:1) gave the title compound **28e** as pale yellow solid (24.9 mg, 63%): mp 170–172 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1620 (C=N), 1587 (NO_2), 1568 (C=N), 1523 (NO_2); δ_H (400 MHz, $CDCl_3$) 1.97-2.03 (2H, m, CH_2), 3.74 (2H, t, J = 5.6 Hz, CH_2), 4.04 (2H, t, J = 6.2 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36. Found: C, 50.29; H, 4.03; N, 21.08.

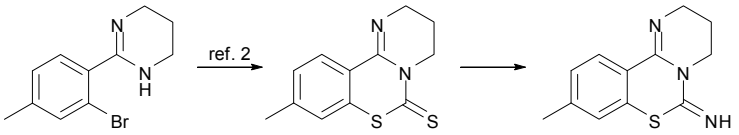
Synthesis of 3,4-dihydro-9-methoxy-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28f)



21f **24f** **28f**

Compound **24f** (66.1 mg, 0.25 mmol) was suspended into a 0.1M solution of NaOH in MeOH-H_2O (9:1) (5 cm^3), and the mixture was stirred for 12 h under reflux. After concentration, the residue was suspended in anhydrous EtOH (1 cm^3). 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 2N NaOH, and the whole was extracted with $CHCl_3$, and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) to give the title compound **28f** as colorless solid (37.6 mg, 61%): mp 106 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1620 (C=N), 1572 (C=N); δ_H (500 MHz, $CDCl_3$) 1.94-1.98 (2H, m, CH_2), 3.66 (2H, t, J = 5.7 Hz, CH_2), 3.81 (3H, s, CH_3), 4.01 (2H, t, J = 6.0 Hz, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{12}H_{13}N_3OS$: C, 58.28; H, 5.30; N, 16.99. Found: C, 58.15; H, 5.23; N, 16.79.

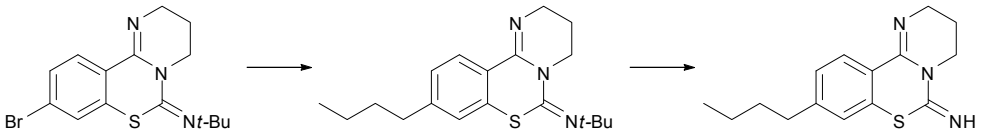
Synthesis of 3,4-dihydro-9-methyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28g)



21g **24g** **28g**

Compound **24g** (62.1 mg, 0.25 mmol) was subjected to general procedure as described for **28f** to give the title compound **28g** as colorless solid (39.2 mg, 68%): mp 121 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1620 (C=N), 1569 (C=N); δ_H (500 MHz, $CDCl_3$) 1.94-1.99 (2H, m, CH_2), 2.32 (3H, s, CH_3), 3.67 (2H, t, J = 5.7 Hz, CH_2), 4.01 (2H, t, J = 6.3 Hz, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{12}H_{14}N_3S$ $[M + H]^+$ 232.0908; found: 232.0912.

Synthesis of compound 28h

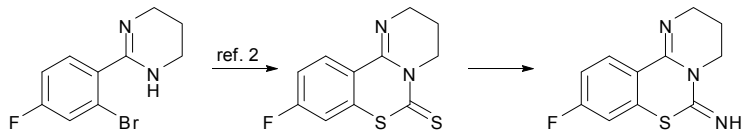


25k **25h** **28h**

9-(*n*-Butyl)-*N*-(*tert*-butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25h). To a mixture of **25k** (352.3 mg, 1.0 mmol), *n*-butylboronic acid (152.9 mg, 1.5 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (51.8 mg, 0.05 mmol) and Ce_2CO_3 (391.0 mg, 1.2 mmol) in 1,4-dioxane (2.5 cm^3) was added P(*tert*-Bu)$_3$ (0.024 cm^3, 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 (10:0 to 19:1) to give the title compound **25h** as a colorless oil (21.0 mg, 6%): IR (neat) ν_{max}/cm^{-1}: 1593 (C=N); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, J = 7.3 Hz, CH_3), 1.29-1.36 (2H, m, CH_2), 1.38 (9H, s, 3×CH_3), 1.54-1.62 (2H, m, CH_2), 1.87-1.93 (2H, m, CH_2), 2.57 (2H, t, J = 7.7 Hz, CH_2), 3.60 (2H, t, J = 5.4 Hz, CH_2), 3.86 (2H, t, J = 6.0 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{19}H_{28}N_3S$ $[M + H]^+$ 330.2004; found: 330.1999.

9-(*n*-Butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28h). Using the general procedure as described for **28a**, compound **25h** (10.3 mg, 0.03 mmol) was allowed to react for 1 h with TFA (1.0 cm^3) and MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) gave the title compound **28h** as colorless solid (5.2 mg, 61%): mp 52–55 °C (from *n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1621 (C=N), 1571 (C=N); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, J = 7.3 Hz, CH_3), 1.29-1.38 (2H, m, CH_2), 1.54-1.61 (2H, m, CH_2), 1.93-1.99 (2H, m, CH_2), 2.58 (2H, t, J = 7.7 Hz, CH_2), 3.67 (2H, t, J = 5.6 Hz, CH_2), 4.01 (2H, t, J = 6.2 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{15}H_{20}N_3S$ $[M + H]^+$ 274.1378; found: 274.1372.

Synthesis of 9-fluoro-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28i)

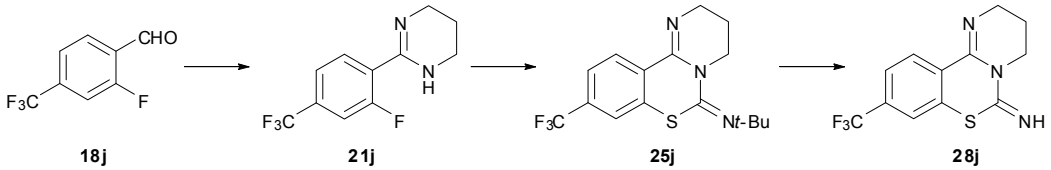


21i **24i** **28i**

Compound **24i** (63.1 mg, 0.25 mmol) was subjected to general procedure as described for **28f** to give the title compound **28i** as colorless solid (30.4 mg, 52%): mp 123–124 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1624 (C=N), 1585 (C=N); δ_H (500 MHz, $CDCl_3$) 1.94-2.00 (2H, m, CH_2), 3.67 (2H, t, J = 5.7 Hz, CH_2), 4.01 (2H, t, J = 6.3 Hz, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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); δ_F (500 MHz, $CDCl_3$) –109.1; *Anal.* calcd for $C_{11}H_{10}FN_3S$:

C, 56.15; H, 4.28; N, 17.86. Found: C, 56.13; H, 4.44; N, 17.78.

Synthesis of compound 28j



18j **21j** **25j** **28j**

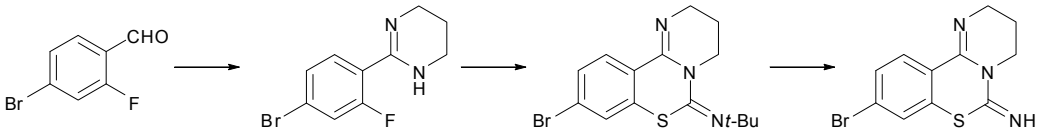
2-(2-Fluoro-4-trifluoromethylphenyl)-1,4,5,6-tetrahydropyrimidine (21j). To a solution of **18j** (1.00 g, 5.21 mmol) in *t*-BuOH (49 cm^3) was added propylenediamine (424.7 mg, 5.73 mmol). The mixture was stirred at 70 °C for 30 min, and then K_2CO_3 (2.16 g, 15.6 mmol) and I_2 (1.65 g, 6.51 mmol) were added. After being stirred at same temperature for 3 h, the mixture was quenched with sat. Na_2SO_3. The organic layer was separated and concentrated. The resulting solid was dissolved with H_2O, and then pH was adjusted to 12–14 with 2N NaOH. The whole was extracted with $CHCl_3$, and the extract was dried over $MgSO_4$. After concentration, the resulting solid was recrystallized from $CHCl_3$–*n*-hexane to give the title compound **21j** as colorless crystals (0.84 g, 65%): mp 108–110 °C; IR (neat) ν_{max}/cm^{-1}: 1620 (C=N); δ_H (500 MHz, $CDCl_3$) 1.86-1.90 (2H, m, CH_2), 3.52 (4H, t, J = 5.2 Hz, 2 × CH_2), 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). δ_C (100 MHz, $CDCl_3$) 20.5, 42.2 (2C), 113.4 (dq, J = 26.9, 3.9 Hz), 120.9-121.0 (m), 123.0 (dq, J = 2.5, 273.0 Hz), 128.0 (d, J = 13.2 Hz), 131.5 (d, J = 4.1 Hz), 132.8 (dq, J = 9.1, 33.7 Hz), 150.4, 159.6 (d, J = 249.1 Hz). δ_F (500 MHz, $CDCl_3$) –63.4, –115.1; *Anal.* calcd for $C_{11}H_{10}F_4N_2$: 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-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25j).** Using the general procedure as described for **25e**, compound **21j** (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 (10:0 to 9:1) gave the title compound **25j** as colorless solid (219.4 mg, 64%): mp 82 °C (from *n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1601 (C=N), 1569 (C=N); δ_H (500 MHz, $CDCl_3$) 1.39 (9H, s, 3 × CH_3), 1.90-1.95 (2H, m, CH_2), 3.64 (2H, t, J = 5.4 Hz, CH_2), 3.88 (2H, t, J = 6.3 Hz, CH_2), 7.38 (1H, s, Ar), 7.41 (1H, d, J = 8.6 Hz, Ar), 8.31 (1H, d, J = 8.6 Hz, Ar). δ_C (100 MHz, $CDCl_3$) 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; δ_F (500 MHz, $CDCl_3$) –63.6. HRMS (FAB): *m/z* calcd for $C_{16}H_{19}F_3N_3S$ $[M + H]^+$ 342.1252; found: 342.1252.

3,4-Dihydro-9-trifluoromethyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28j). Using the general procedure as described for **28a**, compound **25j** (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 **28j** as colorless solid (48.2 mg, 84%): mp 91.5 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1625 (C=N), 1561 (C=N); δ_H (500 MHz, $CDCl_3$) 1.96-2.01 (2H, m, CH_2), 3.71 (2H, t, J = 5.7 Hz, CH_2), 4.03 (2H, t, J = 6.3 Hz, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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; δ_F (500 MHz, $CDCl_3$) –63.8. *Anal.* calcd for $C_{12}H_{10}F_3N_3S$: C, 50.52; H, 3.53; N, 14.73. Found: C, 50.51; H, 3.50; N, 14.69.

Synthesis of compound 28k



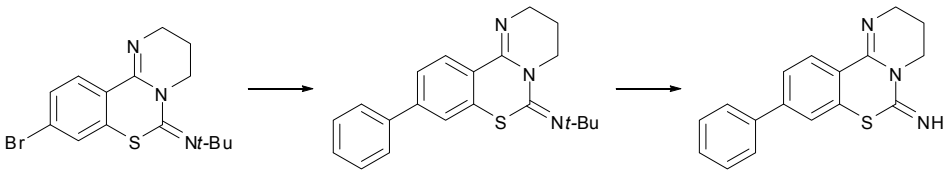
18k **21k** **25k** **28k**

2-(4-Bromo-2-fluorophenyl)-1,4,5,6-tetrahydropyrimidine (21k). Compound **18k** (1.02 g, 5.0 mmol) was subjected to general procedure as described for **21j** to give the title compound **21k** as colorless crystals (0.80 g, 62%): mp 135–137 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1622 (C=N); δ_H (400 MHz, $CDCl_3$) 1.83-1.89 (2H, m, CH_2), 3.49 (4H, t, J = 5.9 Hz, 2 × 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 = 8.3, 8.5 Hz, Ar). δ_C (100 MHz, $CDCl_3$) 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); δ_F (500 MHz, $CDCl_3$) –114.7; *Anal.* calcd for $C_{10}H_{10}BrFN_2$: 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-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25k). Using the general procedure as described for **25e**, compound **21k** (257.1 mg, 1.00 mmol) was allowed to react at room temperature overnight. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (10:0 to 9:1) gave the title compound **25k** as colorless solid (295.6 mg, 84%): mp 107–108 °C (from *n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1596 (C=N); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, 3 × 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{15}H_{18}BrN_3S$: C, 51.14; H, 5.15; N, 11.93. Found: C, 51.30; H, 5.07; N, 11.82.

9-Bromo-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28k). Using the general procedure as described for **28a**, compound **25k** (52.8 mg, 0.15 mmol) was allowed to react for 2 h with TFA (1.5 cm^3) and MS4Å (225 mg). Purification by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) gave the title compound **28k** as colorless solid (40.2 mg, 91%): mp 104–105 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1620 (C=N), 1569 (C=N); δ_H (400 MHz, $CDCl_3$) 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{11}H_{10}BrN_3S$: C, 44.61; H, 3.40; N, 14.19. Found: C, 44.37; H, 3.28; N, 13.93.

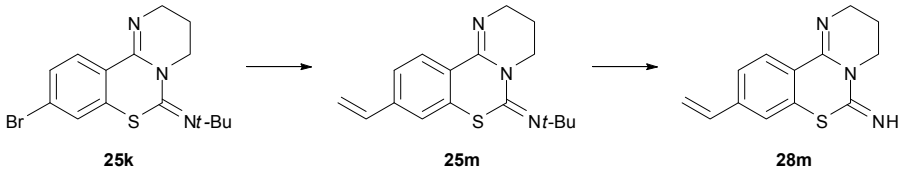
Synthesis of compound 28l



***N*-(*tert*-Butyl)-3,4-dihydro-9-phenyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25l).** To a solution of **25k** (52.8 mg, 0.15 mmol) and phenylboronic acid (21.9 mg, 0.18 mmol) in a mixture of toluene (1.5 cm^3), EtOH (0.9 cm^3) and 1M aq. K_2CO_3 (1.5 cm^3) was added $Pd(Ph_3P)_4$ (6.9 mg, 4 mol%) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (3.7 mg, 3 mol%). After being stirred at reflux for 1 h, the mixture was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (10:0 to 9:1) to give the title compound **25l** as colorless solid (44.8 mg, 85%): mp 122.5–124 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1592 (C=N); δ_H (500 MHz, $CDCl_3$) 1.40 (9H, s, 3 × 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), 7.33-7.37 (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). δ_C (125 MHz, $CDCl_3$) 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 $C_{21}H_{24}N_3S$ $[M + H]^+$ 350.1691; found: 350.1683.

3,4-Dihydro-9-phenyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28l). Using the general procedure as described for **28a**, compound **25l** (25.1 mg, 0.07 mmol) was allowed to react for 1 h with TFA (1.0 cm^3) and MS4Å (105 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (8:2) gave the title compound **28l** as pale yellow solid (19.4 mg, 92%): mp 122–124 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1619 (C=N), 1567 (C=N); δ_H (500 MHz, $CDCl_3$) 1.97-2.02 (2H, m, CH_2), 3.72 (2H, t, J = 5.4 Hz, CH_2), 4.04 (2H, t, J = 6.3 Hz, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{17}H_{16}N_3S$ $[M + H]^+$ 294.1065; found: 294.1069.

Synthesis of compound 28m

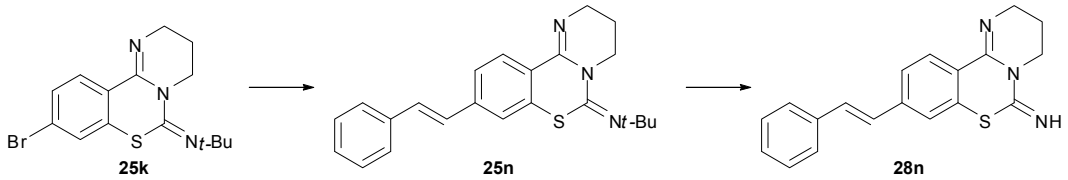


***N*-(*tert*-Butyl)-3,4-dihydro-9-vinyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25m).** Using the general procedure as described for **25l**, compound **25k** (528.4 mg, 1.5 mmol) was allowed to react with vinylboronic acid pinacol ester (0.305 cm^3, 1.8 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (10:0 to 9:1) gave the title compound **25m** as colorless solid (455.7 mg, quant): mp 67–68 °C (from *n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1589 (C=N); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, 3 × 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{17}H_{22}N_3S$ $[M + H]^+$ 300.1534; found: 300.1536.

3,4-Dihydro-9-vinyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28m). Using the general procedure as described for **28a**, compound **25m** (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 **28m** as colorless solid (42.1 mg, 87%): mp 76–77 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1618 (C=N), 1564 (C=N); δ_H (400 MHz, $CDCl_3$) 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{13}H_{14}N_3S$ $[M + H]^+$ 244.0908; found: 244.0911.

Synthesis of compound 28n

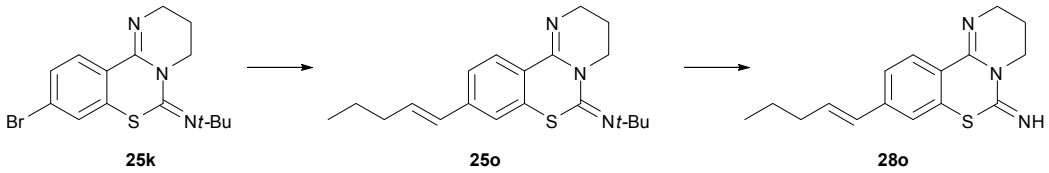


***N*-(*tert*-Butyl)-3,4-dihydro-9-styryl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25n).** Using the general procedure as described for **25l**, compound **25k** (52.8 mg, 0.15 mmol) was allowed to react with styrylboronic acid pinacol ester (41.4 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (10:0 to 9:1) gave the title compound **25n** as colorless solid (50.9 mg, 90%): mp 124.5–125 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1590 (C=N); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, 3 × 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{23}H_{26}N_3S$ $[M + H]^+$ 376.1847; found: 376.1845.

3,4-Dihydro-9-styryl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28n). Using the general procedure as described for **28a**, compound **25n** (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 **28n** as colorless solid (20.2 mg, 75%): mp 111–113 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1618 (C=N), 1567 (C=N); δ_H (400 MHz, $CDCl_3$) 1.94-2.00 (2H, m, CH_2), 3.69 (2H, t, J = 5.6 Hz, CH_2), 4.02 (2H, t, J = 6.2 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{19}H_{17}N_3S$: C, 71.44; H, 5.36; N,

13.15. Found: C, 71.17; H, 5.24; N, 13.07.

Synthesis of compound 28o

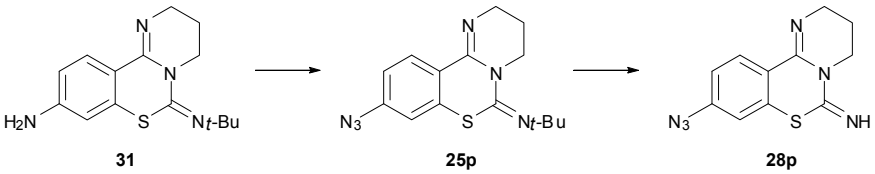


25k **25o** **28o**

***N*-(*tert*-Butyl)-3,4-dihydro-9-pentenyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25o).** Using the general procedure as described for **25l**, compound **25k** (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 (10:0 to 9:1) gave the title compound **25o** as a colorless oil (44.2 mg, 86%): IR (neat) ν_{max}/cm^{-1}: 1590 (C=N); δ_H (400 MHz, $CDCl_3$) 0.95 (t, J = 7.4 Hz, 3H, CH_3), 1.38 (9H, s, 3 × CH_3), 1.46-1.54 (2H, m, CH_2), 1.87-1.93 (2H, m, CH_2), 2.16-2.21 (2H, m, CH_2), 3.61 (2H, t, J = 5.6 Hz, CH_2), 3.86 (2H, t, J = 6.2 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{20}H_{28}N_3S$ $[M + H]^+$ 342.2004; found: 342.2007.

3,4-Dihydro-9-pentenyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28o). Using the general procedure as described for **28a**, compound **25o** (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 **28o** as a colorless oil (31.9 mg, 95%): IR (neat) ν_{max}/cm^{-1}: 1619 (C=N), 1568 (C=N); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, J = 7.4 Hz, CH_3), 1.45-1.54 (2H, m, CH_2), 1.93-1.99 (2H, m, CH_2), 2.17-2.22 (2H, m, CH_2), 3.68 (2H, t, J = 5.5 Hz, CH_2), 4.01 (2H, t, J = 6.2 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{16}H_{20}N_3S$ $[M + H]^+$ 286.1378; found:286.1376.

Synthesis of compound 28p



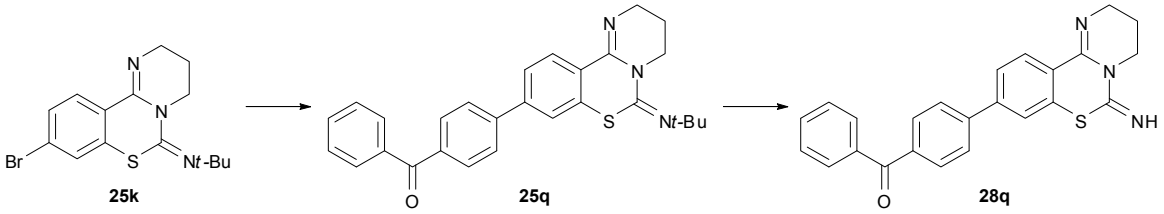
31 **25p** **28p**

9-Azido-*N*-(*tert*-butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25p). To a solution of **31** (100.9 mg, 0.35 mmol) in AcOH (2 cm^3) and H_2O (1 cm^3) was added $NaNO_2$ (33.8 mg, 0.49 mmol) at 0 °C, and the stirring was continued for 1 h. NaN_3 (34.1 mg, 0.53 mmol) was added to the reaction mixture, and the reaction was continued for 30 min at rt. Reaction mixture was neutralized with K_2CO_3, and the whole was extracted with $CHCl_3$, and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) to give the title compound **25p** as pale yellow solid (77.3 mg, 70%): mp 79–80 °C (from *n*-hexane); IR (neat) ν_{max}/cm^{-1}:

2104 (N_3), 1592 (C=N); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, 3 × CH_3), 1.88-1.94 (2H, m, CH_2), 3.60 (2H, t, J = 5.6 Hz, CH_2), 3.86 (2H, t, J = 6.2 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{15}H_{19}N_6S$ $[M + H]^+$ 315.1392; found:315.1398.

9-Azido-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28p). Using the general procedure as described for **28a**, compound **25p** (77.3 mg, 0.25 mmol) was allowed to react for 2 h with TFA (3.5 cm^3) and MS4Å (525 mg). Purification by recrystallization from MeOH–Et_2O gave the title compound **28p** as pale yellow crystals (27.0 mg, 42%): mp 120–121 °C; IR (neat) ν_{max}/cm^{-1}: 2107 (N_3), 1615 (C=N), 1569 (C=N); δ_H (400 MHz, DMSO-d_6) 1.82-1.88 (2H, m, CH_2), 3.56 (2H, t, J = 5.5 Hz, CH_2), 3.89 (2H, t, J = 5.4 Hz, CH_2), 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). δ_C (100 MHz, DMSO-d_6) 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 $C_{11}H_{10}N_6S$: C, 51.15; H, 3.90; N, 32.54. Found: C, 51.07; H, 3.88; N, 32.28.

Synthesis of compound 28q

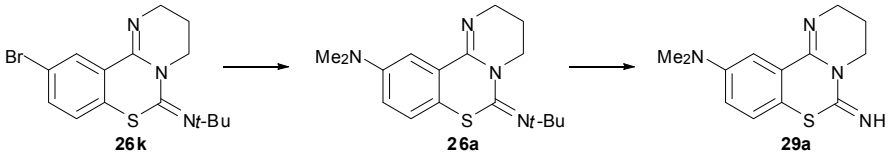


9-(4-Benzoylphenyl)-*N*-(*tert*-butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (25q). Using the general procedure as described for **25l**, compound **25k** (52.8 mg, 0.15 mmol) was allowed to react with 4-benzoylphenylboronic acid (40.7 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (8:2) gave the title compound **25q** as colorless solid (55.6 mg, 82%): mp 187–189 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1656 (C=O), 1593 (C=N); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, 3 × CH_3), 1.91-1.97 (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), 7.46-7.53 (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). δ_C (100 MHz, $CDCl_3$) 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 $C_{28}H_{28}N_3OS$ $[M + H]^+$ 454.1953; found: 454.1954.

9-(4-Benzoylphenyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (28q). Using the general procedure as described for **28a**, compound **28q** (30.4 mg, 0.067 mmol) was allowed to react for 1 h with TFA (1.0 cm^3) and MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **28q** as colorless solid (16.7 mg, 63%): mp 155–156 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1655 (C=O), 1619 (C=N), 1561 (C=N); δ_H (400 MHz, $CDCl_3$) 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{20}H_{18}N_3OS$ $[M + H]^+$ 398.1327; found: 398.1333.

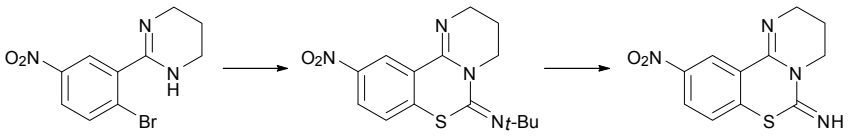
Synthesis of compound 29a



***N*-(*tert*-Butyl)-10-(*N*,*N*-dimethylamino)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imin e (26a).** To a mixture of **26k** (600.2 mg, 1.70 mmol) and Pd(P*t*-Bu)$_2$ (174.2 mg, 0.341 mmol) and KO*t*-Bu (573.3 mg, 5.11 mmol) in toluene (1.7 cm^3) was added 2.0M Me_2NH in THF (2.55 cm^3, 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 **26a** as pale yellow solid (363.3 mg, 67.4%): mp 86.1 °C; IR (neat) ν_{max}/cm^{-1}: 1583 (C=N); δ_H (300 MHz, $CDCl_3$) 1.38 (9H, s, 3 × CH_3), 1.86-1.94 (2H, m, CH_2), 2.97 (6H, s, 2 × 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). δ_C (75 MHz, $CDCl_3$) 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 $C_{17}H_{25}N_4S$ $[M + H]^+$ 317.1800; found: 317.1796.

10-(*N*,*N*-Dimethylamino)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (29a). TFA (0.63 cm^3) was added to a mixture of **26a** (20 mg, 0.063 mmol) and MS4Å (110 mg, powder, activated by heating with Bunsen burner) in small amount of $CHCl_3$. After being stirred under reflux for 40 min, 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 aluminium oxide with *n*-hexane–EtOAc (7:3) to give the title compound **29a** as yellow solid (11.4 mg, 68.3%): mp 134.5 °C; IR (neat) ν_{max}/cm^{-1}: 1617 (C=N), 1552 (C=N); δ_H (300 MHz, $CDCl_3$) 1.92-2.00 (2H, m, CH_2), 2.97 (6H, s, 2 × CH_3), 3.68 (2H, t, J = 5.7 Hz, CH_2), 4.01 (2H, t, J = 6.3 Hz, CH_2), 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). δ_C (75 MHz, $CDCl_3$) 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 $C_{13}H_{16}N_4S$: C, 59.97; H, 6.19; N, 21.52. Found: C, 59.91; H, 6.19; N, 21.41.

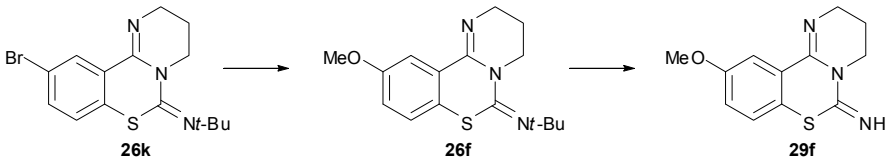
Synthesis of compound 29e



***N*-(*tert*-Butyl)-3,4-dihydro-10-nitro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (26e).** To a mixture of **22e** (50 mg, 0.209 mmol) in DMAc (0.70 cm^3) was added *tert*-butylisothiocyanate (0.053 cm^3, 0.418 mmol) and KO*t*-Bu (46.9 mg, 0.418 mmol) at 0 °C under an N_2 atmosphere. After being stirred at 0 °C for 1 h, sat. NH_4Cl was added. 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 (10:0 to 9:1) to give the title compound **26e** as pale yellow solid (39.1 mg, 58.9%): mp 123.8 °C; IR (neat) ν_{max}/cm^{-1}: 1593 (NO_2), 1520 (NO_2); δ_H (300 MHz, $CDCl_3$) 1.40 (s, 9H, 3 × CH_3), 1.90-1.98 (2H, m, CH_2), 3.67 (2H, t, J = 5.6 Hz, CH_2), 3.89 (2H, t, J = 6.3 Hz, CH_2), 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). δ_C (75 MHz, $CDCl_3$) 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 $C_{15}H_{19}N_4O_2S$ $[M + H]^+$ 319.1229; found: 319.1232.

3,4-Dihydro-10-nitro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (29e). TFA (3.2 cm^3) was added to compound **26e** (100 mg, 0.314 mmol). After being stirred under reflux for 1.5 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 aluminium oxide with *n*-hexane–EtOAc (7:3) to give the title compound **29e** as orange solid (15.9 mg, 19.3%): mp 167.9 °C; IR (neat) ν_{max}/cm^{-1}: 1614 (C=N), 1576 (NO_2), 1557 (C=N), 1519 (NO_2); δ_H (300 MHz, $CDCl_3$) 1.97-2.04 (2H, m, CH_2), 3.74 (2H, t, J = 5.6 Hz, CH_2), 4.05 (2H, t, J = 6.2 Hz, CH_2), 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). δ_C (75 MHz, $CDCl_3$) 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 $C_{11}H_{11}N_4O_2S$ $[M + H]^+$ 263.0603; found: 263.0606. The purity of the compound was 75% by HPLC.

Synthesis of compound 29f

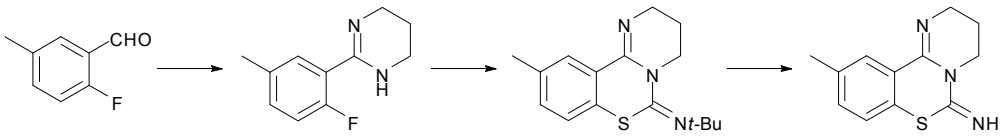


***N*-(*tert*-Butyl)-3,4-dihydro-10-methoxy-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (26f).** To a mixture of **25k** (500.3 mg, 1.42 mmol) and NaOMe (767 mg, 14.2 mmol, 28% solution in MeOH,) in DMF (2.5 cm^3) was added CuBr (20.4 mg, 0.142 mmol). The mixture was stirred at 110 °C for 2.5 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 titlecompound **26f** as colorless solid (171.5 mg, 39.8%): mp 87.1 °C; IR (neat) ν_{max}/cm^{-1}: 1588 (C=N); δ_H (300 MHz, $CDCl_3$) 1.38 (9H, s, 3 × 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). δ_C (75 MHz, $CDCl_3$) 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 $C_{16}H_{21}N_3OS$: C, 63.33; H, 6.98; N, 13.85. Found: C, 63.04; H, 6.97; N, 13.68.

3,4-Dihydro-10-methoxy-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (29f). TFA (0.88 cm^3) was added to compound **26f** (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 aluminium oxide with *n*-hexane–EtOAc (7:3) to give the title compound **29f** as colorless solid (9.6 mg, 44%): mp 89.0 °C; IR (neat) ν_{max}/cm^{-1}: 1614 (C=N), 1562 (C=N); δ_H (300 MHz, $CDCl_3$) 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). δ_C (75 MHz, $CDCl_3$) 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 $C_{12}H_{13}N_3OS$: 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.

Synthesis of compound 29g



19g **22g** **26g** **29g**

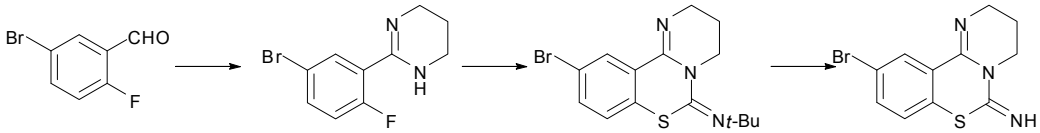
2-(2-Fluoro-5-methylphenyl)-1,4,5,6-tetrahydropyrimidine (22g). Compound **19g** (3.0 g, 21.7 mmol) was subjected to general procedure as described for **21j** to give the title **22g** as colorless crystals (3.1 g, 75%): mp 119–121 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1626 (C=N); δ_H (500 MHz, $CDCl_3$) 1.84-1.89 (2H, m, CH_2), 2.31 (3H, s, CH_3), 3.51 (4H, t, *J* = 5.7 Hz, 2 × CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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); δ_F (500 MHz, $CDCl_3$) –122.4; HRMS (FAB): *m/z* calcd for $C_{11}H_{14}FN_2$ $[M + H]^+$ 193.1141; found:193.1140.

***N*-(*tert*-Butyl)-3,4-dihydro-10-methyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (26g).** To a mixture of compound **22g** (0.50 g, 2.6 mmol) and KO*t*-Bu (0.58 g, 5.2 mmol) in DMAc (8.7 cm^3) was added *tert*-butylisothiocyanate (0.66 cm^3, 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. $NaHCO_3$, brine, and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (1:1) to give the title compound **26g** as colorless solid (0.21 g, 28%): mp 76–77 °C (from *n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1597 (C=N); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, 3 × CH_3), 1.88-1.94 (2H, m, CH_2), 2.33 (3H, s, CH_3), 3.62 (2H, t, *J* = 5.6 Hz, CH_2), 3.87 (2H, t, *J* = 6.2 Hz, CH_2), 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). δ_C (100 MHz,

$CDCl_3$) 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 $C_{16}H_{22}N_3S$ $[M + H]^+$ 288.1534; found: 288.1535.

3,4-Dihydro-10-methyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (29g). Using the general procedure as described for **28a**, compound **26g** (200 mg, 0.7 mmol) was allowed to react for 1 h with TFA (3.0 cm^3) and MS4Å (450 mg). Purification by preparative TLC over aluminum oxide with *n*-hexane–EtOAc (9:1) gave the title compound **29g** as colorless solid (150 mg, 92%): mp 116 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1623 (C=N), 1556 (C=N); δ_H (400 MHz, $CDCl_3$) 1.94-2.00 (2H, m, CH_2), 2.34 (3H, s, CH_3), 3.69 (2H, t, *J* = 5.6 Hz, CH_2), 4.01 (2H, t, *J* = 6.1 Hz, CH_2), 6.94 (1H, d, *J* = 8.0 Hz, Ar), 7.15-7.17 (2H, m, Ar, NH), 8.04 (1H, s, Ar). δ_C (100 MHz, $CDCl_3$) 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 $C_{12}H_{14}N_3S$ $[M + H]^+$ 232.0908; found: 239.0913.

Synthesis of compound 29k



19k **22k** **26k** **29k**

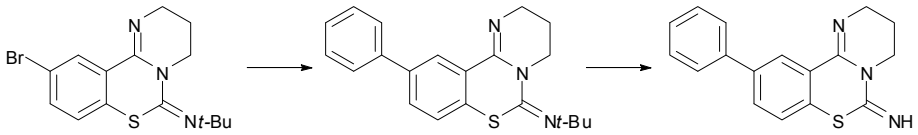
2-(5-Bromo-2-fluorophenyl)-1,4,5,6-tetrahydropyrimidine (22k). Compound **19k** (1.02 g, 5.0 mmol) was subjected to general procedure as described for **21j** to give the title compound **22k** as colorless crystals (1.02 g, 79%): mp 121–122 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1623 (C=N); δ_H (400 MHz, $CDCl_3$) 1.83-1.89 (2H, m, CH_2), 3.50 (4H, t, *J* = 5.7 Hz, 2 × CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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); δ_F (500 MHz, $CDCl_3$) –119.5; *Anal.* calcd for $C_{10}H_{10}BrFN_2$: 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-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (26k). Using the general procedure as described for **25e**, compound **22k** (257.1 mg, 1.00 mmol) was allowed to react at room temperature overnight. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (10:0 to 9:1) gave the title compound **26k** as colorless solid (111.6 mg, 32%): mp 93–94 °C (from *n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1599 (C=N); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, 3 × CH_3), 1.88-1.93 (2H, m, CH_2), 3.62 (2H, t, *J* = 5.6 Hz, CH_2), 3.86 (2H, t, *J* = 6.1 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{15}H_{18}BrN_3S$: C, 51.14; H, 5.15; N, 11.93. Found: C, 51.09; H, 4.98; N, 11.89.

10-Bromo-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (29k). Using the general procedure as described for **28a**, compound **26k** (52.8 mg, 0.15 mmol) was allowed to react for 2 h with TFA (1.5 cm^3) and MS4Å (225 mg). Purification by flash chromatography over silica gel with

n-hexane–EtOAc (2:1) gave the title compound **29k** as colorless crystals (39.7 mg, 89%): mp 106–107 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1621 (C=N), 1571 (C=N); δ_H (500 MHz, $CDCl_3$) 1.94-1.99 (2H, m, CH_2), 3.69 (2H, t, J = 5.4 Hz, CH_2), 4.01 (2H, t, J = 6.3 Hz, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{11}H_{10}BrN_3S$: C, 44.61; H, 3.40; N, 14.19. Found: C, 44.51; H, 3.66; N, 14.06.

Synthesis of compound 29l

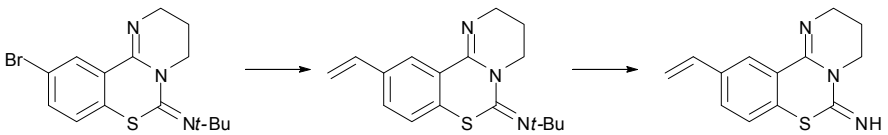


26k **26l** **29l**

***N*-(*tert*-Butyl)-3,4-dihydro-10-phenyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (26l).** Using the general procedure as described for **25l**, compound **26k** (52.8 mg, 0.15 mmol) was allowed to react for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (10:0 to 9:1) gave the title compound **26l** as colorless solid (32.6 mg, 62%): mp 101–103 °C (from *n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1594 (C=N); δ_H (500 MHz, $CDCl_3$) 1.40 (9H, s, 3 × 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{21}H_{24}N_3S$ $[M + H]^+$ 350.1691; found:350.1683.

3,4-Dihydro-10-phenyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (29l). Using the general procedure as described for **28a**, compound **26l** (13.1 mg, 0.037 mmol) was allowed to react for 2 h with TFA (1.0 cm^3) and MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) gave the title compound **29l** as colorless solid (8.4 mg, 77%): mp 82 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1621 (C=N), 1550 (C=N); δ_H (400 MHz, $CDCl_3$) 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{17}H_{15}N_3S$: C, 69.59; H, 5.15; N, 14.32. Found: C, 69.61; H, 5.13; N, 14.22.

Synthesis of compound 29m



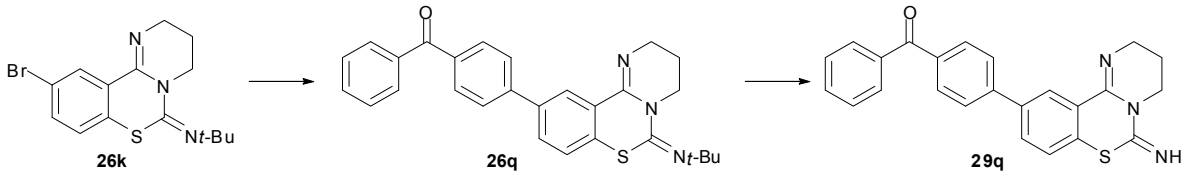
26k **26m** **29m**

***N*-(*tert*-Butyl)-3,4-dihydro-10-vinyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (26m)**. Using the general procedure as described for **25l**, compound **26k** (52.8 mg, 0.15 mmol) was allowed to react

with vinylboronic acid pinacol ester (0.031 cm^3, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (10:0 to 9:1) gave the title compound **26m** as a colorless oil (30.5 mg, 68%): IR (neat) ν_{max}/cm^{-1}: 1595 (C=N); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, 3 × 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{17}H_{22}N_3S$ $[M + H]^+$ 300.1534; found: 300.1532.

3,4-Dihydro-10-vinyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (29m). Using the general procedure as described for **28a**, compound **26m** (7.3 mg, 0.024 mmol) was allowed to react for 1 h with TFA (1.0 cm^3) and MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) gave the title compound **29m** as colorless solid (3.7 mg, 62%): mp 69–70 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1622 (C=N), 1550 (C=N); δ_H (400 MHz, $CDCl_3$) 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{13}H_{14}N_3S$ $[M + H]^+$ 244.0908; found: 244.0902.

Synthesis of compound 29q

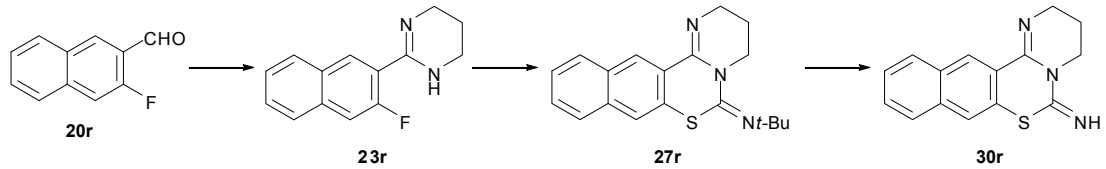


10-(4-Benzoylphenyl)-*N*-(*tert*-butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (26q). Using the general procedure as described for **25l**, compound **26k** (52.8 mg, 0.15 mmol) was allowed to react with 4-benzoylphenylboronic acid (40.7 mg, 0.18 mmol) for 1 h. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (8:2) gave the title compound **26q** as colorless solid (65.1 mg, 96%): mp 192–193 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1654 (C=O), 1592 (C=N); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, 3 × 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{28}H_{28}N_3OS$ $[M + H]^+$ 454.1953; found: 454.1952.

10-(4-Benzoylphenyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (29q). Using the general procedure as described for **28a**, compound **26q** (36.2 mg, 0.08 mmol) was allowed to react for 1 h

with TFA (1.0 cm^3) and MS4Å (150 mg). Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **29q** as colorless solid (23.4 mg, 74%): mp 163–165 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1654 (C=O), 1622 (C=N), 1561 (C=N); δ_H (400 MHz, $CDCl_3$) 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{24}H_{20}N_3OS$ $[M + H]^+$ 398.1327; found: 398.1327.

Synthesis of compound 30r



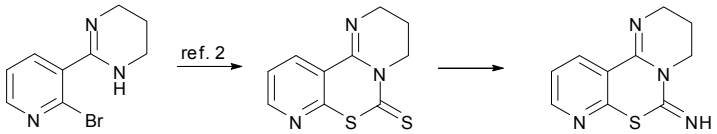
2-(3-Fluoronaphthalen-2-yl)-1,4,5,6-tetrahydropyrimidine (23r). Compound **20r** (0.96 g, 5.52 mmol) was subjected to general procedure as described for **21j** to give the title compound **23r** as pale yellow crystals (0.85 g, 67%): mp 128–130 °C (from $CHCl_3$–EtOAc–Et_2O); IR (neat) ν_{max}/cm^{-1}: 1619 (C=N); δ_H (500 MHz, $CDCl_3$) 1.86-1.91 (2H, m, CH_2), 3.52 (4H, t, J = 5.7 Hz, 2 × CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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). δ_F (500 MHz, $CDCl_3$) –119.8; HRMS (FAB) *m/z* calcd for $C_{14}H_{14}FN_2$ $[M + H]^+$ 229.1141; found: 229.1143.

***N*-(*tert*-Butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*]naphtho[2,3-*e*][1,3]thiazine-6-imine (27r).** Using the general procedure as described for **25e**, compound **23r** (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 **27r** as colorless solid (284.8 mg, 88%): mp 82.5–83.5 °C, IR (neat) ν_{max}/cm^{-1}: 1594 (C=N); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, 3 × CH_3), 1.92-1.98 (2H, m, CH_2), 3.69 (2H, t, J = 5.6 Hz, CH_2), 3.91 (2H, t, J = 6.2 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{19}H_{22}N_3S$ $[M + H]^+$ 324.1534; found: 324.1526.

3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-*c*]naphtho[2,3-*e*][1,3]thiazine-6-imine (30r). Using the general procedure as described for **28a**, compound **27r** (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 **30r** as colorless solid (36.6 mg, 68%): mp 180–181 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1627 (C=N), 1572 (C=N); δ_H (400 MHz, $CDCl_3$) 1.98-2.04 (2H, m, CH_2), 3.75 (2H, t, J = 5.5

Hz, CH_2), 4.06 (2H, t, J = 6.2 Hz, CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{15}H_{14}N_3S$ $[M + H]^+$ 268.0908; found: 268.0909.

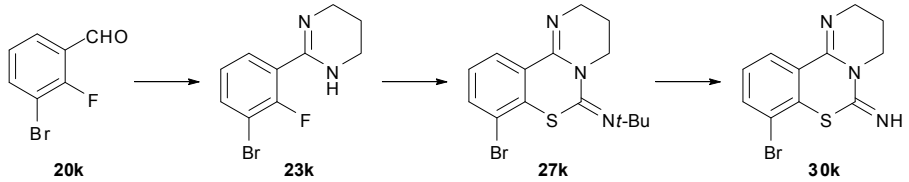
Synthesis of 3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*]pyrido[3,2-*e*][1,3]thiazine-6-imine (30s)



23s **24s** **30s**

Using general procedure as described for **28f**, reaction of **24s** (58.8 mg, 0.25 mmol) and purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (7:3) gave the title compound **30s** as colorless solid (17.4 mg, 32%): mp 181–183 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1624 (C=N), 1582 (C=N); δ_H (500 MHz, $CDCl_3$) 1.96-2.01 (2H, m, CH_2), 3.70 (2H, t, J = 5.7 Hz, CH_2), 4.05 (2H, t, J = 6.3 Hz, CH_2), 7.17 (1H, dd, J = 8.0, 4.6 Hz, Ar), 7.39 (1H, br s, NH), 8.46-8.50 (2H, m, Ar). δ_C (125 MHz, $CDCl_3$) 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 $C_{10}H_{11}N_4S$ $[M + H]^+$ 219.0704; found: 219.0703.

Synthesis of compound 30k



20k **23k** **27k** **30k**

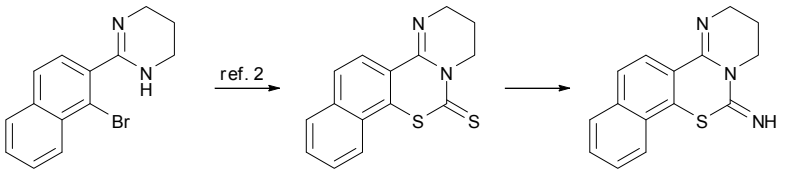
2-(3-Bromo-2-fluoro-phenyl)-1,4,5,6-tetrahydropyrimidine (23k). Compound **20k** (0.71 g, 3.5 mmol) was subjected to general procedure as described for **21j** to give the title compound **23k** as colorless crystals (0.62 g, 69%): mp 99 °C; IR (neat) ν_{max}/cm^{-1}: 1624 (C=N); δ_H (400 MHz, $CDCl_3$) 1.84-1.89 (2H, m, CH_2), 3.50 (4H, t, J = 5.7 Hz, 2 × 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). δ_C (100 MHz, $CDCl_3$) 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); δ_F (500 MHz, $CDCl_3$) –110.7; *Anal.* calcd for $C_{10}H_{10}BrFN_2$: C, 46.72; H, 3.92; N, 10.90. Found: C, 46.64; H, 4.10; N, 10.93.

8-Bromo-*N*-(*tert*-butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (27k). Using the general procedure as described for **25e**, compound **23k** (257.1 mg, 1.00 mmol) was allowed to react at room temperature overnight. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (10:0 to 9:1) gave the title compound **27k** as colorless solid (335.3 mg, 95%): mp 89 °C (from *n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1595 (C=N); δ_H (500 MHz, $CDCl_3$) 1.42 (9H, s, 3 × 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). δ_C (125 MHz, $CDCl_3$) 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

$C_{15}H_{18}BrN_3S$: C, 51.14; H, 5.15; N, 11.93. Found: C, 50.89; H, 5.06; N, 11.83.

8-Bromo-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (30k). Using the general procedure as described for **28a**, compound **27k** (52.8 mg, 0.15 mmol) was allowed to react for 2 h with TFA (1.5 cm^3) and MS4Å (225 mg). Purification by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) gave the title compound **30k** as colorless solid (31.6 mg, 71%): mp 138–139 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1567 (C=N); δ_H (500 MHz, $CDCl_3$) 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{11}H_{10}BrN_3S$: C, 44.61; H, 3.40; N, 14.19. Found: C, 44.36; H, 3.64; N, 13.96.

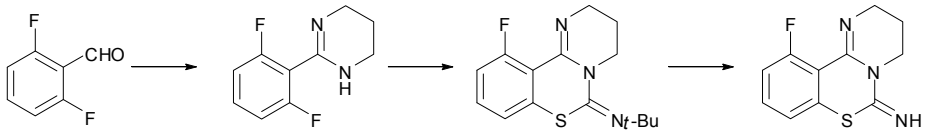
Synthesis of 3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*]naphtho[2,1-*e*][1,3]thiazine-6-imine (30t)



23t **24t** **30t**

Compound **24t** (71.1 mg, 0.25 mmol) was subjected to general procedure as described for **28f** to give the title compound **30t** as colorless solid (42.3 mg, 63%): mp 157 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1615 (C=N), 1572 (C=N); δ_H (500 MHz, $CDCl_3$) 1.99-2.03 (2H, m, CH_2), 3.75 (2H, t, J = 5.4 Hz, CH_2), 4.07 (2H, t, J = 6.0 Hz, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{15}H_{14}N_3S$ $[M + H]^+$ 268.0908; found: 268.0906.

Synthesis of compound 30i



20i **23i** **27i** **30i**

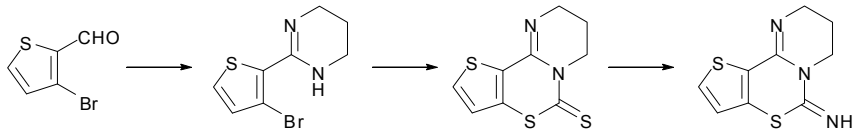
2-(2,6-Difluorophenyl)-1,4,5,6-tetrahydropyrimidine (23i). Compound **20i** (1.00 g, 7.04 mmol) was subjected to general procedure as described for **21j** to give the title **23i** as colorless crystals (1.08 g, 78%): mp 165–166 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1620 (C=N); δ_H (500 MHz, $CDCl_3$) 1.85-1.90 (2H, m, CH_2), 3.47 (4H, t, J = 5.7 Hz, 2 × CH_2), 4.77 (1H, br s, NH), 6.86-6.91 (2H, m, Ar), 7.24-7.30 (1H, m, Ar). δ_C (100 MHz, $CDCl_3$) 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). δ_F (500 MHz, $CDCl_3$) –114.4; *Anal.* calcd for $C_{10}H_{10}F_2N_2$: 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-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (27i).** Using

the general procedure as described for **25e**, compound **23i** (196.2 mg, 1.0 mmol) was allowed to react at rt overnight. Purification by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (10:0 to 9:1) gave the title compound **27i** as colorless solid (212.6 mg, 73%): mp 81 °C (from *n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1592 (C=N); δ_H (500 MHz, $CDCl_3$) 1.37 (9H, s, 3 × 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). δ_C (125 MHz, $CDCl_3$) 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); δ_F (500 MHz, $CDCl_3$) –110.8. HRMS (FAB): *m/z* calcd for $C_{15}H_{19}FN_3S$ $[M + H]^+$ 292.1284; found: 292.1288.

11-Fluoro-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (30i). Using the general procedure as described for **28a**, compound **27i** (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 **30i** as colorless solid (42.3 mg, 90%): mp 142.5 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1624 (C=N), 1585 (C=N); δ_H (500 MHz,$CDCl_3$) 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). δ_C (125 MHz, $CDCl_3$) 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) δ_F (500 MHz, $CDCl_3$) –110.0. *Anal.* calcd for $C_{11}H_{10}FN_3S$: C, 56.15; H, 4.28; N, 17.86. Found: C, 56.05; H, 4.28; N, 17.71.

Synthesis of compound 30u



20u **23u** **24u** **30u**

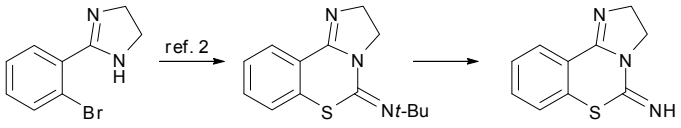
2-(3-Bromothiophen-2-yl)-1,4,5,6-tetrahydropyrimidine (23u). Compound **20u** (1.29 g, 6.75 mmol) was subjected to general procedure as described for **21j** to give the title compound **23u** as pale yellow crystals (1.11 g, 67%): mp 61–63 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1611 (C=N); δ_H (400 MHz, $CDCl_3$) 1.83-1.88 (2H, m, CH_2), 3.48 (4H, t, J = 5.9 Hz, 2 × CH_2), 6.07 (1H, br s, NH), 6.92 (1H, d, J = 5.4 Hz, Ar), 7.24 (1H, d, J = 5.4 Hz, Ar). δ_C (100 MHz, $CDCl_3$) 20.5, 42.0 (2C), 105.8, 127.3, 131.4, 135.6, 149.3; HRMS (FAB): *m/z* calcd for $C_8H_{10}BrN_2S$ $[M + H]^+$ 244.9748; found: 244.9742.

3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-*c*]thieno[2,3-*e*][1,3]thiazin-6-thione (24u). To a mixture of **23u** (122.6 mg, 0.50 mmol) and NaH (40.0 mg, 1.0 mmol; 60% oil suspension) in DMF (1.7 cm^3) was added carbon disulfide (0.060 cm^3, 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 **24u** as pale yellow solid (80.5 mg, 67%): mp 167 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1624 (C=N); δ_H (400 MHz, $CDCl_3$) 2.04-2.10 (2H, m, CH_2), 3.68 (2H, t, J = 5.5 Hz, CH_2), 4.42 (2H, t, J = 6.1 Hz, CH_2), 6.76 (1H, d, J = 5.4 Hz, Ar), 7.49 (1H, d, J = 5.4 Hz, Ar). δ_C (100 MHz, $CDCl_3$) 21.5, 45.0, 48.5, 122.3, 128.4, 130.8, 131.0, 141.7, 189.7; HRMS

(FAB): *m/z* calcd for $C_9H_9N_2S_3$ $[M + H]^+$ 240.9928; found: 240.9936.

3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-*c*]thieno[2,3-*e*][1,3]thiazin-6-imine (30u). Compound **24u** (60.1 mg, 0.25 mmol) was subjected to general procedure as described for **28f** to give the title compound **30u** as colorless solid (19.4 mg, 35%): mp 100–101 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1616 (C=N), 1567 (C=N); δ_H (400 MHz, $CDCl_3$) 1.99-2.05 (2H, m, CH_2), 3.62 (2H, t, J = 5.6 Hz, CH_2), 3.99 (2H, t, J = 6.1 Hz, CH_2), 6.74 (1H, d, J = 5.4 Hz, Ar), 7.28 (1H, br s, NH), 7.41 (1H, d, J = 5.4 Hz, Ar). δ_C (100 MHz, $CDCl_3$) 21.2, 43.5, 44.5, 123.3, 125.9, 127.0, 129.9, 143.7, 153.7; *Anal.* calcd for $C_9H_9N_3S_2$: C, 48.40; H, 4.06; N, 18.82. Found: C, 48.38; H, 3.98; N, 18.75.

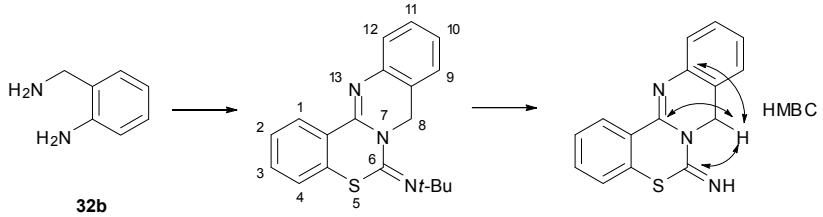
Synthesis of 2,3-dihydro-5*H*-imidazo[1,2-*c*][1,3]benzothiazin-5-imine (359a)



33a **34a** **35a**

Using the general procedure as described for **27a**, compound **34a** (18.4 mg, 0.07 mmol) was allowed to react for 12 h with TFA (1.0 cm^3) and MS4Å (150 mg). Purification by flash chromatography over silica gel with *n*-hexane–EtOAc (1:1) gave the title compound **35a** as colorless solid (11.1 mg, 78%): mp 176–178 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1621 (C=N), 1585 (C=N); δ_H (500 MHz, $CDCl_3$) 4.11 (4H, s, 2 × CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{10}H_{10}N_3S$ $[M + H]^+$ 204.0595; found: 204.0600.

Synthesis of compound 35b



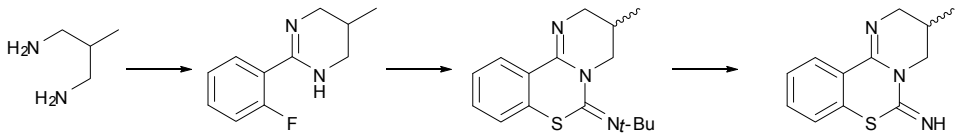
32b **34b** **35b**

***N*-(*tert*-Butyl)-6*H*,8*H*-quinazolino[3,2-*c*][1,3]benzothiazin-6-imine (34b).** To a solution of 2-fluorobenzaldehyde (1.41 g, 11.39 mmol) in *t*-BuOH (38 cm^3) was added 2-aminobenzylamine **32b** (1.53 g, 12.53 mmol). The mixture was stirred at 80 °C for 30 min, and then K_2CO_3 (4.73 g, 34.18 mmol) and I_2 (3.61 g, 14.24 mmol) were added. After being stirred at same temperature for 4 h, the mixture was quenched with sat. Na_2SO_3. The organic layer was separated and concentrated. The resulting solid was dissolved with H_2O and $CHCl_3$, and then pH was adjusted to 12–14 with 5N NaOH. The whole was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4. To a mixture of resulting residue in DMAc (7.4 cm^3) was added KO*t*-Bu (496 mg, 4.42 mmol) and *tert*-butylisothiocyanate (0.56 cm^3, 4.42 mmol) under an N_2 atmosphere. After being stirred at 80 °C for 2.5 h, sat. NH_4Cl was added.

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 (10:0 to 9:1) to give the title compound **34b** as yellow solid (114.1 mg, 3.1% over 2 steps): mp 92.2 °C; IR (neat) ν_{max}/cm^{-1}: 1588 (C=N); δ_H (300 MHz, $CDCl_3$) 1.42 (9H, s, 3 × CH_3), 5.10 (2H, s, CH_2), 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). δ_C (75 MHz, $CDCl_3$) 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 $C_{19}H_{19}N_3S$: C, 70.99; H, 5.96; N, 13.07. Found: C, 71.05; H, 5.99; N, 12.91.

6*H*,8*H*-Quinazolino[3,2-*c*][1,3]benzothiazin-6-imine (35b). TFA (0.5 cm^3) was added to **34b** (100 mg, 0.311 mmol). After being stirred under reflux for 30 min, 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. $NaHCO_3$ aq., brine, and dried over Na_2SO_4. After concentration, the residue was purified by preparative TLC over aluminium oxide with *n*-hexane–EtOAc (9:1) to give the title compound **35b** as colorless crystals (13 mg, 16%): Colorless solid (42.1 mg, 87%): mp 133-135 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1594 (C=N), 1541 (C=N); δ_H (500 MHz, $CDCl_3$) 5.27 (2H, s, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{15}H_{12}N_3S$ $[M + H]^+$ 266.0752; found: 266.0750.

Synthesis of compound 35c



32c **33c** **34c** **35c**

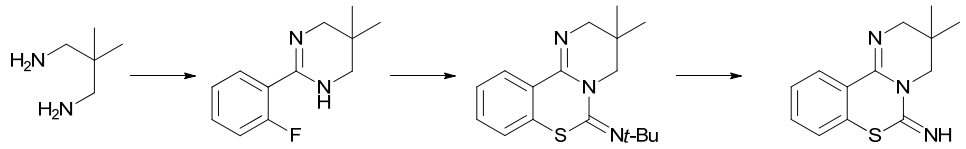
2-(2-Fluorophenyl)-5-methyl-1,4,5,6-tetrahydropyrimidine (33c). 2-Fluorobenzaldehyde (0.62 g, 5.0 mmol) was subjected to general procedure for **21j** using 2-methylpropylenediamine **32c** (0.48 g, 5.5 mmol) to give the title compound **33c** as colorless crystals (0.72 g, 75%): mp 98–99 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1628 (C=N); δ_H (500 MHz, $CDCl_3$) 1.01 (3H, d, J = 6.9 Hz, CH_3), 1.92-1.99 (1H, m, CH), 3.06 (2H, dd, J = 13.2, 9.7 Hz, 2 × CH), 3.52 (2H, dd, J = 13.2, 3.4 Hz, 2 × 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). δ_C (125 MHz, $CDCl_3$) 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); δ_F (500 MHz, $CDCl_3$) –117.1. HRMS (FAB): *m/z* calcd for $C_{11}H_{14}FN_2$ $[M + H]^+$ 193.1141; found: 193.1136.

(±)-*N*-(*tert*-Butyl)-3,4-dihydro-3-methyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (34c). Using the general procedure as described for **25e**, compound **33c** (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 (10:0 to 95:5) gave the title compound **34c** as colorless solid (288.4 mg, 50%): mp 60–62 °C (from

n-hexane); IR (neat) ν_{max}/cm^{-1}: 1598 (C=N), 1570 (C=N); δ_H (500 MHz, $CDCl_3$) 1.05 (3H, d, *J* = 6.3 Hz, CH_3), 1.39 (9H, s, 3 × CH_3), 1.91-1.99 (1H, m, CH), 3.09-3.17 (2H, m, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{16}H_{22}N_3S$ $[M + H]^+$ 288.1534; found: 288.1535.

(±)-3,4-Dihydro-3-methyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (35c). Using the general procedure as described for **28a**, compound **34c** (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 **35c** as colorless solid (36.7 mg, 79%): mp 82–84 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1621 (C=N), 1574 (C=N); δ_H (500 MHz, $CDCl_3$) 1.09 (3H, d, *J* = 6.3 Hz, CH_3), 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{12}H_{13}N_3S$: C, 62.31; H, 5.66; N, 18.17. Found: C, 62.04; H, 5.75; N, 17.88.

Synthesis of compound 35d



32d **33d** **34d** **35d**

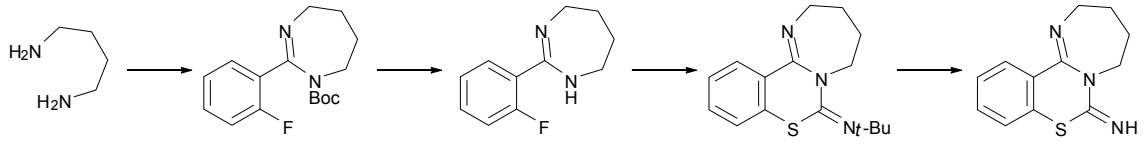
2-(2-Fluorophenyl)-5,5-dimethyl-1,4,5,6-tetrahydropyrimidine (33d). 2-Fluorobenzaldehyde (0.62 g, 5.0 mmol) was subjected to general procedure for **21j** using 2,2-dimethylpropylenediamine **32d** (0.56 g, 5.5 mmol) to give the title compound **33d** as colorless crystals (0.82 g, 79%): mp 150–153 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1629 (C=N); δ_H (400 MHz, $CDCl_3$) 1.02 (6H, s, 2 × CH_3), 3.13 (4H, s, 2 × CH_2), 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). δ_C (100 MHz, $CDCl_3$) 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); δ_F (500 MHz, $CDCl_3$) –117.3. HRMS (FAB): *m/z* calcd for $C_{12}H_{16}FN_2$ $[M + H]^+$ 207.1298; found: 207.1299.

***N*-(*tert*-Butyl)-3,4-dihydro-3,3-dimethyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (34d).** Using the general procedure as described for **25e**, compound **33d** (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 (10:0 to 9:1) gave the title compound **34d** as colorless solid (236.6 mg, 39%): mp 70–72 °C (from *n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1602 (C=N), 1570 (C=N); δ_H (500 MHz, $CDCl_3$) 1.01 (6H, s, 2 × CH_3), 1.39 (9H, s, 3 × CH_3), 3.33 (2H, s, CH_2), 3.58 (2H, s, CH_2), 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). δ_C (125 MHz, $CDCl_3$)

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 $C_{17}H_{24}N_3S$ $[M + H]^+$ 302.1691; found: 302.1695.

3,4-Dihydro-3,3-dimethyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (35d). Using the general procedure as described for **28a**, compound **34d** (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 **35d** as colorless solid (42.0 mg, 86%): mp 113–114 °C (from $CHCl_3$–*n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1627 (C=N), 1575 (C=N); δ_H (500 MHz, $CDCl_3$) 1.05 (6H, s, 2 × CH_3), 3.41 (2H, s, CH_2), 3.74 (2H, s, CH_2), 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); δ_C (125 MHz, $CDCl_3$) 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 $C_{13}H_{16}N_3S$ $[M + H]^+$ 246.1065; found: 246.1069.

Synthesis of compound 35e



32e **36** **33e** **34e** **35e**

***N*-(*tert*-Butoxycalbonyl)-2-(2-fluorophenyl)-4,5,6,7-tetrahydro-1,3-diazepine (36).** To a solution of 2-fluorobenzaldehyde (2.48 g, 20.0 mmol) in *t*-BuOH (188 cm^3) was added 1,4-diaminobutane **32e** (2.21 cm^3, 22.0 mmol). The mixture was stirred at 70 °C for 30 min, and then K_2CO_3 (8.29 g, 60.0 mmol) and I_2 (6.35 g, 25 mmol) were added. After being stirred at same temperature for 3 h, the mixture was quenched with sat. Na_2SO_3. The organic layer was separated and concentrated. The resulting solid was dissolved with H_2O, and then pH was adjusted to 12–14 with 2N NaOH. The whole was extracted with $CHCl_3$, and dried over Na_2SO_4. After concentration, Et_3N (8.67 cm^3, 60.0 mmol) and Boc_2O (13.8 cm^3, 60.0 mmol) were added to the solution of residue in CH_2Cl_2 (100 cm^3). After being stirred for 30 min at rt, sat. $NaHCO_3$ was added. After being stirred at rt for 1 h, the whole was extracted with $CHCl_3$. The extract was washed with brine, and dried over $MgSO_4$. After concentration, the residue was purified by column chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give the title compound **36** as colorless solid (2.18 g, 37%): mp 63–65 °C (from *n*-hexane); IR (neat) ν_{max}/cm^{-1}: 1710 (C=O), 1631 (C=N); δ_H (500 MHz, $CDCl_3$) 1.14 (9H, s, 3 × CH_3), 1.66-1.70 (2H, m, CH_2), 1.78-1.83 (2H, m, CH_2), 3.61 (2H, br s, CH_2), 3.76 (2H, t, *J* = 5.2 Hz, CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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). δ_F (500 MHz, $CDCl_3$) –118.9; HRMS (FAB) *m/z* calcd for $C_{16}H_{22}FN_2O_2$ $[M + H]^+$ 293.1665; found: 293.1669.

2-(2-Fluorophenyl)-4,5,6,7-tetrahydro-1*H*-1,3-diazepine (33e). To a solution of **36** (877.1 mg, 3.0 mmol) in CH_2Cl_2 (6.0 cm^3) was added TFA (6.0 cm^3). The mixture was stirred under reflux for 2 h, mixture was washed with 2N NaOH. The organic phase was dried over $MgSO_4$. After concentration, the

residue was recrystallized from $CHCl_3$–*n*-hexane to give the title compound **33e** as colorless crystals (461.2 mg, 80%): mp 92 °C; IR (neat) ν_{max}/cm^{-1}: 1627 (C=N); δ_H (500 MHz, $CDCl_3$) 1.80-1.83 (4H, m, 2 × CH_2), 3.48 (4H, br s, 2 × CH_2), 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). δ_C (125 MHz, $CDCl_3$) 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). δ_F (500 MHz, $CDCl_3$) –117.7; HRMS (FAB) *m*/*z* calcd for $C_{11}H_{14}FN_2$ $[M + H]^+$ 193.1141; found: 193.1140.

***N*-(*tert*-Butyl)-7*H*-2,3,4,5-tetrahydro-1,3-diazepino[1,2-*c*][1,3]benzothiazin-7-imine (34e).** Using the general procedure as described for **25e**, compound **33e** (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 **34e** as a yellow oil (50.3 mg, 18%): IR (neat) ν_{max}/cm^{-1}: 1588 (C=N); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, 3 × CH_3), 1.87-1.93 (4H, m, 2 × 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). δ_C (100 MHz, $CDCl_3$) 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 $C_{16}H_{22}N_3S$ $[M + H]^+$ 288.1534; found: 288.1540.

2,3,4,5-Tetrahydro-7*H*-1,3-diazepino[1,2-*c*][1,3]benzothiazin-7-imine (35e). Using the general procedure as described for **28a**, compound **34e** (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 **35e** as a colorless oil (11.3 mg, 27%): IR (neat) ν_{max}/cm^{-1}: 1638 (C=N), 1578 (C=N); δ_H (400 MHz, $CDCl_3$) 1.94-2.01 (4H, m, 2 × 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). δ_C (125 MHz, $CDCl_3$) 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 $C_{12}H_{14}N_3S$ $[M + H]^+$ 232.0908; found: 232.0906.

^1H and ^{13}C NMR spectra of
3,4-dihydro-2*H,*6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (**4**, Scheme 2)[2],
3,4-dihydro-2*H,*6*H*-pyrimido[1,2-*c*][1,3]benzoxazin-6-one (**7**, Scheme 2)[1],
3,4-dihydro-2*H,*6*H*-pyrimido[1,2-*c*]quinazolin-6(7*H*)-one (**10**, Scheme 2:)[1],
2-phenyl-1,4,5,6-tetrahydropyrimidine derivatives (**21e-g**, **21i**, **22e**, **23s** and **23t**, Scheme 4)[2],
3,4-dihydro-2*H,*6*H*-pyrimido[1,2-*c*][1,3]benzthiazine-6-thione derivatives (**24f**, **24g**, **24i**, **24s** and **24t**, Scheme 4:)[2],
2-(2-bromophenyl)-4,5-dihydro-1*H*-imidazole (**33a**)[2], and
N-*tert*-butyl-2,3-dihydroimidazo[1,2-*c*][1,3]benzothiazin-5-imine (**34a**)[2]
were in good agreement with those previously reported.

References

(1) T. Mizuhara, S. Inuki, S. Oishi, N. Fujii, H. Ohno, *Chem Commun.* 2009, 3413–3415.
(2) T. Mizuhara, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* 2010, **75**, 265–268.