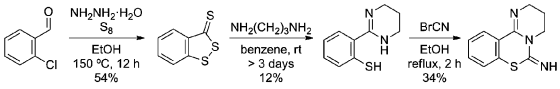
Chapter 2
Development of Divergent Synthetic Methods of Pyrimidobenzothiazine and Related Tricyclic Heterocycles

2.1 Cu(II)-Mediated *Ortho*-Selective Intermolecular C–H Functionalization

3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (PD 404182, **1**, Fig. 2.1) is a promising anti-HIV agent lead discovered by a random screening project. To develop the highly potent derivatives, it is valuable to establish practical and short-step synthetic approaches for the preparation of several derivatives[1,2] .The author planned to develop a diversity-oriented approach to synthesize tricyclic heterocycles related to PD 404182 based on the sp^2-carbon–heteroatom (O, N, and S) bond formations (Scheme 2.1). It was expected that the *ortho*-selective introduction of a heteroatom on 2-phenyl-1,4,5,6-tetrahydropyrimidine derivatives **3** [6], which is easily obtained from the corresponding benzaldehydes **2**, followed by functional group transformations leads to various types of heterocycles **5** including PD 404182.

Directing group-assisted intermolecular C–H functionalization is considered to be one of the most promising approaches for constructions of various heterocycles, providing several biologically active compounds since a new or carbon–heteroatom bond is selectively formed at a non-functionalized position proximal to the directing group. (Scheme 2.2)[3,4]. In general, C–H functionalization proceeds via metallacycle formation by oxidative addition of transition-metal and subsequent coordination of nucleophile and reductive elimination. Recent research has revealed that nitrogen-containing functional groups such as pyridines [14–16],

[1] In the previous reports, compound **1** was obtained via benzo-1,2-dithiole-3-thiones and 2-(1,4,5,6-tetrahydro-2-pyrimidinyl)benzenethiol in 3 % yield from 2-chlorobenzyl chloride, see [1–3]



[2] See [4–5].

[3] For reviews on transition-metal-catalyzed directed C–H activations, See [7–9].

[4] See [10–13].

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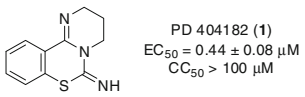
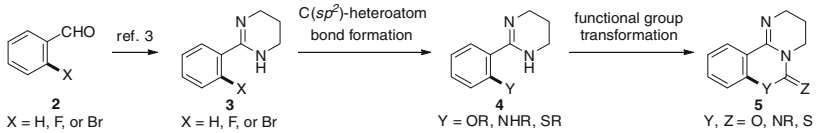
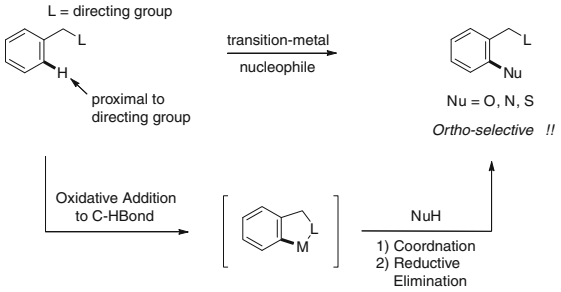


Fig. 2.1 Structure of PD 404182



Scheme 2.1 Synthetic scheme for PD 404182 derivatives via carbon–heteroatom bond formation



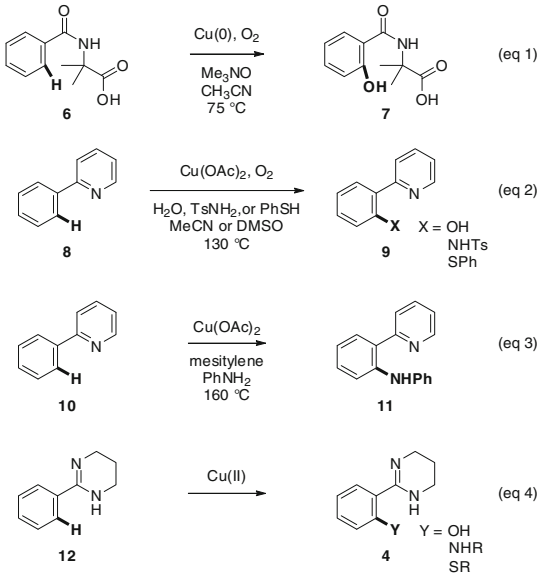
Scheme 2.2 Carbon–heteroatom bond formation by C–H functionalization

imines [17–19], oxazolines [20, 21], and amidines [22] effectively act as directing groups for regioselective C–H functionalization.

Cu-mediated reactions[5] have facilitated the synthesis of biologically active compounds because of its cost, earth abundance, and lower toxicity. Reinaud and co-workers have reported a Cu-mediated *ortho*-hydroxylation reaction of benzamide **6** using a carboxyl group as a directing group (Scheme 2.3, eq 1) [24]. Yu et al. (eq 2) [25] and Chatani et al. (eq 3) [26] have independently reported Cu-mediated oxidative intermolecular C–H functionalization using a pyridine moiety as a directing group. The author designed an experiment for the oxidative introduction of heteroatoms by aromatic C–H functionalization with the assistance of an *ortho*-tetrahydropyrimidinyl group (eq 4).

A few recent reports have revealed that amidine moieties effectively act as directing groups for the *ortho*-selective C–H functionalization (Scheme 2.4). Inoue and co-workers have reported *ortho*-selective arylation of 2-arylimidazolines with aryl halides in the presence of a Ru(II)–phosphine complex [22]. The reaction of

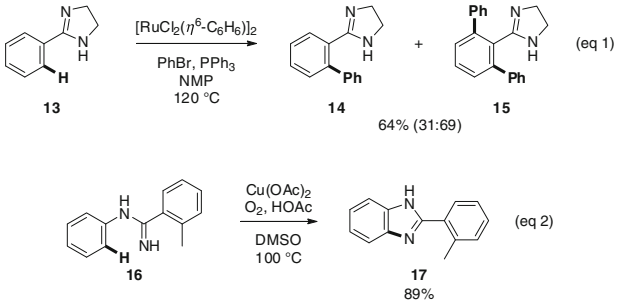
[5] For a review on Cu-mediated C–H functionalization, see [23].



Scheme 2.3 Cu-mediated intermolecular C–H functionalization

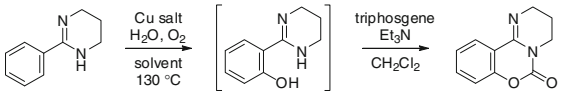
2-phenylimidazoline **13** with 1.2 equiv of bromobenzene using $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ yielded the mono- and diarylated products (**14** and **15**) in a 64 % yield and in 31:69 ratio (eq 1). Buchwald and co-workers have reported the formation of aryl-benzimidazole **17** by $Cu(OAc)_2$-catalyzed oxidative cyclization of amidine **16** [27]. The best result was obtained by using 15 mol % of $Cu(OAc)_2$ and 2–5 equiv of HOAc under an O_2 atmosphere. In this reaction, an amidine moiety acts as a directing group as well as a nucleophile. These contributions prompted the author to investigate a tetrahydropyrimidine group-assisted regioselective C–H functionalization.

The author initially investigated the reaction conditions for C–H hydroxylation (Table 2.1). In the presence of H_2O (1.0 equiv), treatment of 2-phenyl-1,4,5,6-tetrahydropyrimidine (**18a**) with CuO, $Cu(OH)_2$, $Cu(OTf)_2$ or $Cu(tfa)_2$ (1.0 equiv) in DMF at 130 °C under an O_2 atmosphere led to the recovery of unchanged starting material and the desired C–H oxidation did not occur (entries 1–4). Using $Cu(OAc)_2$, [25, 26] however, led to the formation of the desired *ortho*-hydroxylated compound **19a** (ca. 69 % yield) although the product yield of compound **19a** was poorly reproducible because of its high basicity. The author then attempted to isolate **20a** as the tricyclic PD 404182 derivative: after the disappearance of **18a** (monitored by TLC), the solvent was evaporated *in vacuo* and the treatment with triphosgene (1.05 equiv) and triethylamine (4.0 equiv) in CH_2Cl_2 afforded pure **20a** in a yield of 61 % (entry 5, Condition A). When acetonitrile or dioxane was used as the solvent instead of DMF, yields of **20a** decreased considerably (11 %, entries 6 and 7). Lowering the loading of $Cu(OAc)_2$ to 0.2 equiv also resulted in a decreased yield for **20a** (30 %, entry 8), which indicates low catalyst efficiency.



Scheme 2.4 Amidine directed regioselective C–H functionalization

Table 2.1 Optimization of reaction conditions for C–H hydroxylation[a]



Entry	Cu salt (equiv)	Solvent	Time (min)	Yield (%)[b]
1	CuO (1.0)	DMF	20	No reaction
2	$Cu(OH)_2$ (1.0)	DMF	20	No reaction
3	$Cu(OTf)_2$ (1.0)	DMF	20	No reaction
4	$Cu(tfa)_2$ (1.0)	DMF	20	No reaction
5	$Cu(OAc)_2$ (1.0)	DMF	20	61
6	$Cu(OAc)_2$ (1.0)	MeCN	60	11
7	$Cu(OAc)_2$ (1.0)	Dioxane	60	11
8	$Cu(OAc)_2$ (1.0)	DMF	60	30
9	$Cu(OAc)_2$ (2.0)	DMF	15	27
10[c]	$Cu(OAc)_2$ (1.0)	DMF	20	70
11[c,d]	$Cu(OAc)_2$ (1.0)	DMF	20	56

[a] After completion of C–H hydroxylation (monitored by TLC), the reaction mixture was evaporated and treated with triphosgene (1.05 equiv) and Et_3N (4.0 equiv) in CH_2Cl_2 at 0 °C to rt for 1 h (Condition A)

[b] Isolated yields

[c] After completion of C–H hydroxylation (monitored by TLC), the reaction mixture was treated with TMEDA (4.0 equiv) at 130 °C for 1 min. In this case, TMEDA (additional 4.0 equiv) was used for the next step instead of Et_3N (Condition B)

[d] Reaction was carried out under air

TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine

When using 2.0 equiv of $Cu(OAc)_2$, the yield also decreased contrary to the author's expectation (27 %, entry 9).

Considering that the *ortho*-hydroxylated product **19a** may form a complex with the Cu salt, the author further optimized the reaction conditions including the carbonylation procedure. Initially, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)

was added as a bidentate ligand to the oxidative C–H functionalization reaction mixture and this resulted in the complete inhibition of the desired transformation. Similarly, use of TMEDA instead of triethylamine as a base for the carbonylation did not improve the yield of **20a**. On the other hand, treatment with TMEDA (4.0 equiv) at 130 °C for 1 min after the C–H hydroxylation followed by the carbonylation using additional TMEDA (4.0 equiv) increased the yield to 70 % (entry 10, Condition B). The reaction under air resulted in a decreased yield (56 %, entry 11).

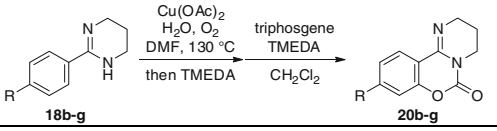
Using the condition B, the author examined the reaction of several substituted substrates (Table 2.2). Substitution with electron-donating groups such as methoxy (**18b**, entry 1) or methyl groups (**18c**, entry 2) was tolerated to afford the desired products **20b** and **20c** in 64 % and 61 % yields, respectively. The chemoselectivity of this reaction was evaluated by a reaction where aryl bromide **18d** was used and the desired product **20d** was obtained in a 45 % yield (entry 3). Methoxycarbonyl (entry 4) and trifluoromethyl groups (entry 5) had relatively small effects on the reactivity of these substrates and the use of the highly electron-deficient arene **18g** bearing a nitro group decreased the yield considerably (19 %, entry 6). These results indicate that this reaction is sensitive to the presence of electron-withdrawing groups on the aromatic ring. In all cases, reactions under condition A gave less favorable results.

To confirm the actual source of *ortho*-hydroxyl group, the author carried out the C–H hydroxylation reaction using $H_2^{18}O$ under an Ar atmosphere (Scheme 2.5). This reaction provided compound **20a** with ^{16}O, suggesting that *ortho*-hydroxyl group was derived from $Cu(OAc)_2$ [25] Notably, the reaction under an Ar atmosphere gave the product in low yield, suggesting that molecular O_2 participates in the reoxidation of the Cu catalyst.

Next, the author investigated the ability of other amidine analogues to function as directing groups (Fig. 2.2). The reaction of the *N*-methylated analog **21** and 2-phenylimidazole **22** did not produce the desired *ortho*-hydroxylated products under the standard reaction conditions and the starting materials were recovered. Unexpectedly, the five-membered ring amidine in **13** was not effective as a directing group either. These results suggest that subtle differences in the intermediate formed by a Cu salt and a directing group strongly affect the reactivity of the substrates.

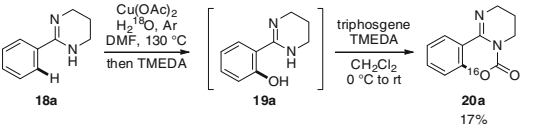
Although the exact mechanism of the *ortho* C–H oxidation is unclear, on the basis of these observations and the seminal work of others, the author proposes the two possible reaction mechanisms (Scheme 2.6): a single electron transfer (SET) pathway (A) [25, 28] and electrophilic substitution pathway (B) [27]. In pathway A, Cu–N adduct **II** is initially formed by the reaction of compound **I** with $Cu(OAc)_2$ [29, 30]. A SET from an aryl ring to the coordinated Cu(II) led to radical cation intermediate **III**. Intramolecular acetate transfer followed by another SET step and transfer of a proton yielded the acetoxylated compound **V**. Subsequent hydrolysis gave an *ortho*-hydroxylated product **VI**. The observed *ortho*-selectivity could be attributed to an intramolecular transfer of the coordinating group on the Cu atom. Alternatively, in pathway B, addition of a π-system to the Cu center yielded metallacycle **VII**. Compound **V** was formed through

Table 2.2 Cu-mediated C–H hydroxylation of *Para*-substituted-2-phenyl-1,4,5,6-tetrahydro-pyrimidines[a]



Entry	Substrate (R)	Product	Yield (%)[b]
1	**18b** (OMe)	20b	64 (53)
2	**18c** (Me)	20c	61 (54)
3	**18d** (Br)	20d	45 (37)
4	**18e** (CO_2Me)	20e	46 (43)
5	**18f** (CF_3)	20f	43 (38)
6	**18g** (NO_2)	20g	19 (16)

[a] These reactions were carried out using the optimized procedure (Condition B, Table 2.1, entry 10)
[b] Isolated yields. Yields in parentheses indicate those of the reactions at condition A (Table 2.1, entry 5)



Scheme 2.5 C–H hydroxylation reaction with $H_2^{18}O$

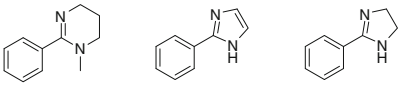
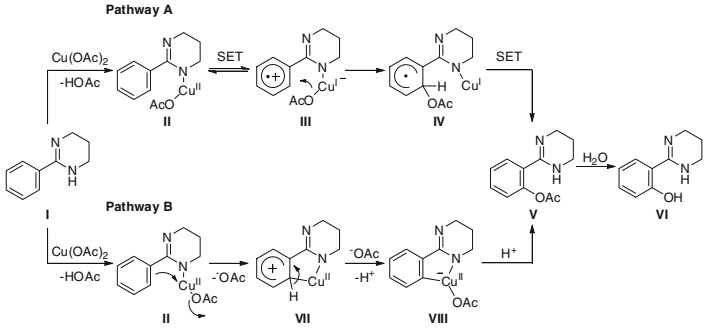
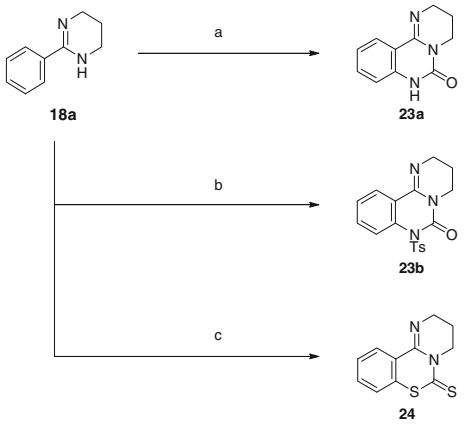


Fig. 2.2 Various amidine analogs used for the *ortho*-hydroxylation experiments



Scheme 2.6 Proposed reaction mechanisms



Scheme 2.7 C–N and C–S bond formations with various nucleophiles. *Reagents and conditions:* (**a**) $Cu(OAc)_2$, $BocNH_2$, O_2, DMF, 100 °C, 53 %; (**b**) (i) $Cu(OAc)_2$, $TsNH_2$, O_2, DMF, 130 °C; (ii) triphosgene, Et_3N, CH_2Cl_2, 0 °C to rt, 47 % (2 steps); (**c**) $Cu(OAc)_2$, CS_2, O_2, 1,4-dioxane, 130 °C, 11 %

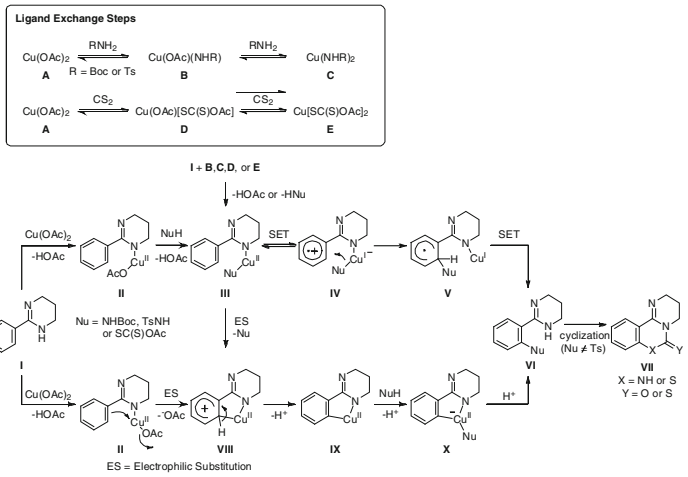
rearomatization and subsequent reductive elimination. These mechanisms are supported by the findings that the presence of an electron-withdrawing group on the benzene ring considerably decreased the product yields. Recently, involvement of Cu(III) species in the C–H oxidation reaction has been demonstrated.[6,7] Therefore, it is possible that this reaction proceeded via the formation of Cu(III)–substrate **I** complex.

Finally, the author investigated C–N and C–S bond formations (Scheme 2.7). The author found that the reaction of amidine **18a** with $Cu(OAc)_2$ (1.0 equiv) and *tert*-butyl carbamate (3.0 equiv) in DMF at 100 °C for 40 min directly afforded the tricyclic aniline derivative (**23a**) in 53 % yield. This reaction occurred by cyclization involving the elimination of *tert*-butoxide. *p*-Toluenesulfonamide [37] also reacted with **18a** under identical condition to afford **23b** in 47 % yield after alumina column chromatography[8] followed by treatment with triphosgene–Et_3N. In addition, the reaction with CS_2 in 1,4-dioxane at 130 °C directly gave pyrimido[1,2-*c*][1,3]benzothiazine derivative **24**. The C–N and C–S bond forming

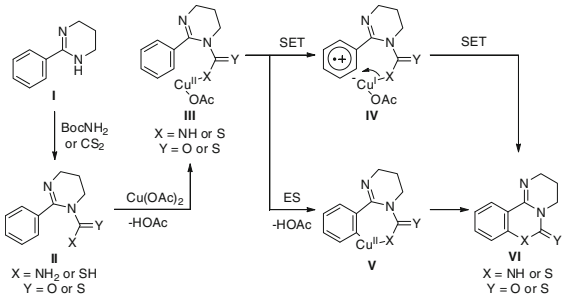
[6] For a review on high-valent Cu(III) species in catalysis, see [31].

[7] See [32–36].

[8] Because the separation of **23b** and the by-product **20a** was difficult, separation by alumina column chromatography was necessary before carbonylation.



Scheme 2.8 Proposed reaction mechanisms of C–N and C–S bond formations



Scheme 2.9 Alternative proposed reaction mechanisms with $BocNH_2$ and CS_2

reactions can be explained by a similar mechanism as depicted in Scheme 2.7 including ligand exchange step.[9,10]

In conclusion, the author has developed a Cu-mediated oxidative *ortho* C–H functionalization using tetrahydropyrimidine as a directing group. This reaction was applied to 2-phenyl-1,4,5,6-tetrahydropyrimidines having an electron-donating or a weak electron-withdrawing group to afford the corresponding pyrimido[1,2-*c*][1,3]benzoxazine derivatives. Use of *tert*-butyl carbamate, *p*-toluenesulfonamide,

[9] Examples for the reaction mechanism including the ligand exchange are shown above (Scheme 2.8).

[10] Different reaction pathways are not excluded at present. Some examples are shown above (Scheme 2.9).

or CS_2 instead of H_2O promotes the introduction of a nitrogen or sulfur functionality to give pyrimido[1,2-*c*]quinazoline or pyrimido[1,2-*c*][1,3]benzothiazine derivative, respectively.

2.1.1 Experimental Section

2.1.1.1 General Methods

All moisture-sensitive reactions were performed using syringe-septum cap techniques under an Ar atmosphere and all glasswares were dried in an oven at 80 °C for 2 h prior to use. Melting points were measured by a hot stage melting point apparatus (uncorrected). For flash chromatography, Wakogel C-300E (Wako) or aluminum oxide 90 standardized (Merck) was employed. ^{1}H-NMR spectra were recorded using a JEOL AL-400 or a JEOL ECA-500 spectrometer, and chemical shifts are reported in δ (ppm) relative to Me_4Si ($CDCl_3$) as internal standards. ^{13}C-NMR spectra were recorded using a JEOL AL-400 or JEOL ECA-500 spectrometer and referenced to the residual $CHCl_3$ signal. ^{19}F-NMR spectra were recorded using a JEOL ECA-500 and referenced to the internal $CFCl_3$ (δ_F 0.00 ppm). ^{1}H-NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s), and number of protons. Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 FT-IR spectrometer with JASCO ATR PRO410-S.

2.1.1.2 General Procedure for Preparation of the Substrates. Synthesis of 2-Phenyl-1,4,5,6-tetrahydropyrimidine (18a)

To a solution of benzaldehyde (5.00 g, 47.1 mmol) in *t*-BuOH (470 mL) was added propylenediamine (3.84 g, 51.8 mmol). After being stirred at 70 °C for 30 min, K_2CO_3 (19.53 g, 141.3 mmol) and I_2 (14.95 g, 58.8 mmol) were added. After being stirred at same temperature for 3 h, the reaction mixture was quenched with sat. Na_2SO_3 until the iodine color disappeared. The organic layer was separated and concentrated *in vacuo*. The resulting solid was dissolved with H_2O, and then pH was adjusted to 12–14 with 2 N NaOH. The whole was extracted with $CHCl_3$ and dried over $MgSO_4$. After concentration, the resulting solid was recrystallized from $CHCl_3$–*n*-hexane to give the title compound **18a** as colorless crystals (6.62 g, 82 %): mp 88–89 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1618 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.83–1.85 (m, 2H, CH_2), 3.49 (t, J = 5.9 Hz, 4H, 2 × CH_2), 5.02 (br s, 1H, NH), 7.34–7.38 (m, 3H, Ar), 7.63–7.66 (m, 2H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.7, 42.3 (2C), 126.0 (2C), 128.2

(2C), 129.6, 137.3, 154.5; *Anal.* calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found; C, 74.79; H, 7.53; N, 17.43.

2.1.1.3 2-(4-Methoxyphenyl)-1,4,5,6-tetrahydropyrimidine (18b)

p-Methoxybenzaldehyde (1.36 g, 10 mmol) was subjected to the general procedure. Colorless crystals (1.40 g, 74 %): mp 132–134 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1611 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.81–1.87 (m, 2H, CH_2), 3.49 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 3.81 (s, 3H, OCH_3), 4.87 (br s, 1H, NH), 6.86 (d, $J = 9.4$ Hz, 2H, Ar), 7.60 (d, $J = 9.4$ Hz, 2H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.9, 42.4 (2C), 55.2, 113.5 (2C), 127.2 (2C), 130.0, 153.9, 160.6; *Anal.* calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.18; H, 7.46; N, 14.58.

2.1.1.4 2-(4-Tolyl)-1,4,5,6-tetrahydropyrimidine (18c)

p-Tolualdehyde (1.20 g, 10 mmol) was subjected to the general procedure. Colorless crystals (1.03 g, 59 %): mp 120–121 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1615 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.82–1.85 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 3.49 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 4.90 (br s, 1H, NH), 7.15 (d, $J = 8.3$ Hz, 2H, Ar), 7.54 (d, $J = 8.3$ Hz, 2H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.8, 21.2, 42.3 (2C), 125.8 (2C), 128.9 (2C), 134.5, 139.5, 154.3; *Anal.* calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.76; H, 8.01; N, 15.91.

2.1.1.5 2-(4-Bromophenyl)-1,4,5,6-tetrahydropyrimidine (18d)

p-Bromobenzaldehyde (1.85 g, 10 mmol) was subjected to the general procedure. Colorless crystals (1.82 g, 76 %): mp 174–175 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1619 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.81–1.88 (m, 2H, CH_2), 3.49 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 4.81 (br s, 1H, NH), 7.48 (d, $J = 8.8$ Hz, 2H, Ar), 7.53 (d, $J = 8.8$ Hz, 2H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.7, 42.4 (2C), 123.8, 127.6 (2C), 131.4 (2C), 136.3, 153.5; *Anal.* calcd for $C_{10}H_{11}BrN_2$: C, 50.23; H, 4.64; N, 11.72. Found: C, 50.20; H, 4.51; N, 11.66.

2.1.1.6 Methyl 4-(1,4,5,6-tetrahydropyrimidin-2-yl)benzoate (18e)

Methyl 4-formylbenzoate (1.00 g, 6.09 mmol) was subjected to the general procedure. Colorless crystals (1.63 g, 80 %): mp 152–153 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1721 (C=O), 1620 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ:

1.83–1.89 (m, 2H, CH_2), 3.52 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 3.92 (s, 3H, OCH_3), 5.04 (br s, 1H, NH), 7.72 (d, $J = 8.5$ Hz, 2H, Ar), 8.02 (d, $J = 8.5$ Hz, 2H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.5, 42.3 (2C), 52.1, 126.0 (2C), 129.5 (2C), 130.8, 141.5, 153.6, 166.6; *Anal.* calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.76; H, 6.28; N, 12.69.

2.1.1.7 2-[4-(Trifluoromethyl)phenyl]-1,4,5,6-tetrahydropyrimidine (18f)

p-(Trifluoromethyl)benzaldehyde (1.74 g, 10 mmol) was subjected to the general procedure. Colorless crystals (1.71 g, 75 %): mp 176–177 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1620 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.83–1.89 (m, 2H, CH_2), 3.51 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 4.92 (br s, 1H, NH), 7.61 (d, $J = 8.3$ Hz, 2H, Ar), 7.76 (d, $J = 8.3$ Hz, 2H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.6, 42.4 (2C), 122.6, 125.2 (q, $J = 3.7$ Hz, 2C), 126.4 (2C), 131.4 (d, $J = 32.3$ Hz), 140.7, 153.3; ^{19}F-NMR (500 MHz, $CDCl_3$) δ: −62.6; *Anal.* calcd for $C_{11}H_{11}F_3N_2$: C, 57.89; H, 4.86; N, 12.28. Found: C, 57.89; H, 4.82; N, 12.29.

2.1.1.8 2-(4-Nitrophenyl)-1,4,5,6-tetrahydropyrimidine (18g)

p-Nitrobenzaldehyde (1.51 g, 10 mmol) was subjected to the general procedure. Yellow crystals (1.63 g, 80 %): mp 169–171 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1623 (C=N), 1519 (NO_2), 1339 (NO_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.85-1.90 (m, 2H, CH_2), 3.54 (t, $J = 5.6$ Hz, 4H, 2 × CH_2), 5.08 (br s, 1H, NH), 7.83 (d, $J = 9.1$ Hz, 2H, Ar), 8.20 (d, $J = 9.1$ Hz, 2H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.4, 42.3 (2C), 123.4 (2C), 127.0 (2C), 143.2, 148.3, 152.7; *Anal.* calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.61; H, 5.45; N, 20.48.

2.1.1.9 1-Methyl-2-phenyl-1,4,5,6-tetrahydropyrimidine (21)

Benzaldehyde (1.06 g, 10 mmol) and *N*-methyl- propandiamine (0.97 g, 11 mmol) was subjected to the general procedure. Product was used to next step without further purification. Yellow oil (1.49 g, 85 %); IR (neat) cm^{-1}: 1600 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.92–1.98 (m, 2H, CH_2), 2.74 (s, 3H, NCH_3), 3.27 (t, $J = 5.6$ Hz, 2H, CH_2), 3.51 (t, $J = 5.2$ Hz, 2H, CH_2), 7.32–7.40 (m, 5H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 22.0, 40.3, 45.0, 49.0, 127.9 (2C), 128.0 (2C), 128.4, 138.1, 159.1; HRMS (EI): *m/z* calcd for $C_{11}H_{13}N_2$ $[M–H]^-$ 173.1084; found: 173.1082.

2.1.1.10 General Procedure for the C–O Bond Formation (Condition B). Synthesis of 3,4-dihydro-2*H*-pyrimido- [1,2-*c*][1,3]benzoxazin-6-one (20a)

DMF (0.83 mL) and water (4.5 μL, 0.25 mmol) were added to a flask containing **18a** (40.1 mg, 0.25 mmol) and $Cu(OAc)_2$ (45.4 mg, 0.25 mmol) under an O_2 atmosphere. After being stirred at 130 °C for 20 min, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA, 150 μL, 1 mmol) was added. After being stirred at same temperature for 1 min, the reaction mixture was concentrated in vacuo. To a solution of residue and TMEDA (150 μL, 1 mmol) in CH_2Cl_2 (16.6 mL) was added dropwise a solution of triphosgene (77.9 mg, 0.26 mmol) in CH_2Cl_2 (1.7 mL) at 0 °C. After being stirred at rt for 1 h under an Ar atmosphere, the mixture was quenched with sat. NH_4Cl, and CH_2Cl_2 was removed in vacuo. The resulting mixture was made basic with 28 % NH_4OH. The whole was extracted with EtOAc and washed with sat. NH_4Cl–28 % NH_4OH, 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 **20a** as colorless solid (35.2 mg, 70 %): mp 146–147 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1730 (C=O), 1647 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.98-2.04 (m, 2H, CH_2), 3.68 (t, $J = 5.6$ Hz, 2H, CH_2), 3.95 (t, $J = 6.0$ Hz, 2H, CH_2), 7.14 (d, $J = 8.3$ Hz, 1H, Ar), 7.23–7.30 (m, 1H, Ar), 7.48–7.51 (m, 1H, Ar), 8.02 (d, $J = 7.8$ Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.3, 42.5, 44.1, 116.2, 125.0, 125.5, 127.8, 129.0, 132.9, 147.5, 150.4; HRMS (FAB): *m/z* calcd for $C_{11}H_{11}N_2O_2$ $[M + H]^+$ 203.0821; found: 203.0813.

2.1.1.11 3,4-Dihydro-2*H*-9-methoxypyrimido[1,2-*c*][1,3]benzoxazin-6-one (20b)

2-(4-Methoxyphenyl)-1,4,5,6-tetrahydropyrimidine **18b** (47.6 mg, 0.25 mmol) was subjected to the general procedure. Pale yellow solid (37.3 mg, 64 %): mp 160–161 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1731 (C=O), 1650 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.97–2.02 (m, 2H, CH_2), 3.64 (t, $J = 5.7$ Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.92 (t, $J = 6.0$ Hz, 2H, CH_2), 6.59 (d, $J = 2.3$ Hz, 1H, Ar), 6.79 (dd, $J = 8.6$, 2.3 Hz, 1H, Ar), 7.90 (d, $J = 8.6$ Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.5, 42.5, 44.0, 55.7, 100.0, 108.8, 112.6, 126.6, 142.7, 147.8, 151.7, 163.3; HRMS (FAB): *m/z* calcd for $C_{12}H_{13}N_2O_3$ $[M + H]^+$ 233.0926; found: 233.0921.

2.1.1.12 3,4-Dihydro-2*H*-9-methylpyrimido[1,2-*c*][1,3]benzoxazin-6-one (20c)

2-(4-Tolyl)-1,4,5,6-tetrahydropyrimidine **18c** (43.6 mg, 0.25 mmol) was subjected to the general procedure. Yellow solid (32.8 mg, 61 %): mp 153–154 °C (from

$CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1736 (C=O), 1650 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.98-2.02 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 3.66 (t, $J = 5.4$ Hz, 2H, CH_2), 3.93 (t, $J = 6.0$ Hz, 2H), 6.93 (s, 1H, Ar), 7.05 (d, $J = 8.0$ Hz, 1H, Ar), 7.88 (d, $J = 8.0$ Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.4, 21.5, 42.5, 44.1, 113.4, 116.2, 125.2, 126.2, 143.0, 144.0, 148.0, 150.4; HRMS (FAB): *m/z* calcd for $C_{12}H_{13}N_2O_2$ $[M + H]^+$ 217.0977; found: 217.0979.

2.1.1.13 9-Bromo-3,4-dihydro-2*H*-pyrimido[1,2-*c*][1,3]benzoxazin-6-one (20d)

2-(4-Bromophenyl)-1,4,5,6-tetrahydropyrimidine **18d** (59.8 mg, 0.25 mmol) was subjected to the general procedure. Pale yellow solid (31.3 mg, 45 %): mp 206–207 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1729 (C=O), 1651 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.98–2.03 (m, 2H, CH_2), 3.65 (t, $J = 5.7$ Hz, 2H, CH_2), 3.93 (t, $J = 6.0$ Hz, 2H, CH_2), 7.31 (d, $J = 1.7$ Hz, 1H, Ar), 7.37 (dd, $J = 8.6$, 1.7 Hz, 1H, Ar), 7.87 (d, $J = 8.6$ Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.3, 42.6, 44.2, 115.2, 119.4, 126.4, 126.8, 128.4, 142.1, 147.0, 150.7; HRMS (FAB): *m/z* calcd for $C_{11}H_{10}BrN_2O_2$ $[M + H]^+$ 280.9926; found: 280.9922.

2.1.1.14 3,4-Dihydro-2*H*-9-(methoxycarbonyl)pyrimido[1,2-*c*][1,3]benzoxazin-6-one (20e)

2-[(4-Methoxycarbonyl)phenyl]-1,4,5,6-tetrahydropyrimidine **18e** (54.6 mg, 0.25 mmol) was subjected to the general procedure. Pale yellow solid (30.2 mg, 46 %): mp 136–137 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1741 (C=O), 1718 (C=O), 1644 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.00–2.05 (m, 2H, CH_2), 3.70 (t, $J = 5.4$ Hz, 2H, CH_2), 3.94–3.96 (m, 5H, CH_2, OMe), 7.78 (d, $J = 1.4$ Hz, 1H, Ar), 7.88 (dd, $J = 8.6$, 1.4 Hz, 1H, Ar), 8.09 (d, $J = 8.6$ Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.2, 42.5, 44.4, 52.6, 117.6, 119.7, 125.6, 125.8, 134.3, 142.2, 147.1, 150.2, 165.4; HRMS (FAB): *m/z* calcd for $C_{13}H_{13}N_2O_4$ $[M + H]^+$ 261.0875; found: 261.0874.

2.1.1.15 3,4-Dihydro-2*H*-9-(trifluoromethyl)pyrimido[1,2-*c*][1,3]benzoxazin-6-one (20f)

2-[4-(Trifluoromethyl)phenyl]-1,4,5,6-tetrahydropyrimidine **18f** (57.1 mg, 0.25 mmol) was subjected to the general procedure. Yellow solid (28.8 mg, 43 %): mp 141–142 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1739 (C=O), 1650 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.00–2.05 (m, 2H, CH_3), 3.70 (t, $J = 5.7$ Hz, 2H, CH_2), 3.95 (t, $J = 6.0$ Hz, 2H, CH_2), 7.40 (d, $J = 1.1$ Hz, 1H, Ar), 7.49 (dd, $J = 8.0$, 1.1 Hz, 1H, Ar), 8.15 (d, $J = 8.0$ Hz, 1H, Ar); ^{13}C-NMR

(100 MHz, $CDCl_3$) δ: 20.3, 42.7, 44.5, 113.9 (q, $J = 4.1$ Hz), 119.3, 121.6 (q, $J = 3.6$ Hz), 124.5, 126.7, 134.7 (q, $J = 33.7$ Hz), 141.8, 146.9, 150.4; ^{19}F-NMR (500 MHz, $CDCl_3$) δ: –63.0; HRMS (FAB): *m/z* calcd for $C_{12}H_{10}F_3N_2O_2$ $[M + H]^+$ 271.0694; found: 271.0692.

2.1.1.16 3,4-Dihydro-2*H*-9-nitropyrimido[1,2-*c*][1,3]benzoxazin-6-one (20g)

2-(4-Nitrophenyl)-1,4,5,6-tetrahydropyrimidine **18g** (51.3 mg, 0.25 mmol) was subjected to the general procedure. Yellow solid (11.9 mg, 19 %): mp 235–236 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1732 (C=O), 1641 (C=N), 1531 (NO_2), 1349 (NO_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.01–2.07 (m, 2H, CH_2), 3.72 (t, $J = 5.6$ Hz, 2H, CH_2), 3.96 (t, $J = 6.0$ Hz, 2H, CH_2), 8.00 (d, $J = 2.2$ Hz, 2H, Ar), 8.08 (dd, $J = 8.8$, 2.2 Hz, 1H, Ar), 8.22 (d, $J = 8.8$ Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.1, 42.6, 44.5, 112.2, 119.4, 121.4, 127.1, 141.3, 146.4, 150.3, 150.5; HRMS (FAB): *m/z* calcd for $C_{11}H_{10}N_3O_4$ $[M + H]^+$ 248.0671; found: 248.0670.

2.1.1.17 C–N Bond Formation with $BocNH_2$. Synthesis of 3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-*c*]quinazolin-6(7*H*)-one (23a)

DMF (0.83 mL) was added to a flask containing **18a** (40.1 mg, 0.25 mmol), $Cu(OAc)_2$ (45.4 mg, 0.25 mmol) and *tert*-butyl carbamate (87.9 mg, 0.75 mmol) under an O_2 atmosphere. After being stirred at 100 °C for 40 min, the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography over aluminum oxide with $CHCl_3$–MeOH (1:0 to 99:1) to give **23a** as colorless solid (26.5 mg, 53 %): mp 250–251 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1682 (C=O), 1616 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.95–2.00 (m, 2H, CH_2), 3.67 (t, $J = 5.6$ Hz, 2H, CH_2), 3.94 (t, $J = 6.0$ Hz, 2H, CH_2), 6.86 (d, $J = 8.0$ Hz, 1H, Ar), 7.09–7.13 (m, 1H, Ar), 7.38–7.42 (m, 1H, Ar), 8.07 (d, $J = 8.0$ Hz, 1H, Ar), 8.30 (br s, 1H, NH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.3, 40.8, 44.5, 114.6, 116.5, 123.0, 125.8, 132.0, 136.5, 145.7, 151.2; HRMS (FAB): *m/z* calcd for $C_{11}H_{12}N_3O$ $[M + H]^+$ 202.0980; found: 202.0988.

2.1.1.18 C–N Bond Formation with $TsNH_2$. Synthesis of 7-Tosyl-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*]quinazolin-6(7*H*)-one (23b)

DMF (0.83 mL) was added to a flask containing **18a** (40.1 mg, 0.25 mmol), $Cu(OAc)_2$ (45.4 mg, 0.25 mmol) and *p*-toluene sulfonamide (85.6 mg, 0.5 mmol) under an O_2 atmosphere. After being stirred at 130 °C for 20 min, the mixture was concentrated *in vacuo*. The residue was subjected to flash chromatography over aluminum oxide with $CHCl_3$–MeOH (95:5) to give crude *ortho*-amidated

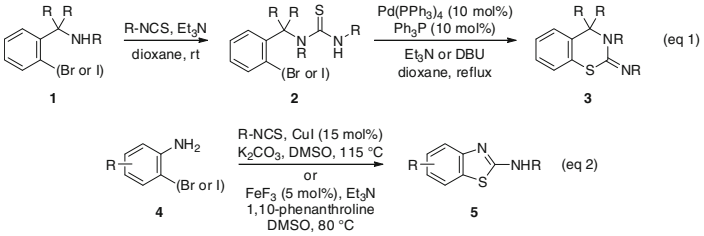
compound. To a solution of the *ortho*-amidated compound and Et_3N (145 μL, 1.0 mmol) in CH_2Cl_2 (16.6 mL) was added dropwise a solution of triphosgene (77.9 mg, 0.26 mmol) in CH_2Cl_2 (1.7 mL) at 0 °C. After being stirred at rt for 1 h under an Ar atmosphere, the mixture was quenched with sat. $NaHCO_3$, and CH_2Cl_2 was removed *in vacuo*. The whole was extracted with EtOAc and 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 **23b** as colorless solid (42.2 mg, 47 %): mp 159–161 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1695 (C=O), 1644 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.85–1.91 (m, 2H, CH_2), 2.46 (s, 3H, CH_3), 3.63 (t, $J = 5.7$ Hz, 2H, CH_2), 3.75 (t, $J = 6.2$ Hz, 2H, CH_2), 7.27–7.31 (m, 1H, Ar), 7.37 (d, $J = 8.3$ Hz, 2H, Ar), 7.48–7.53 (m, 1H, Ar), 7.87 (d, $J = 8.5$ Hz, 1H, Ar), 8.03 (d, $J = 8.3$ Hz, 2H, Ar), 8.07 (dd, $J = 8.0$, 1.7 Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.5, 21.8, 41.8, 44.6, 120.3, 121.0, 125.7, 126.4, 128.4 (2C), 129.8 (2C), 131.3, 134.6, 136.7, 144.5, 145.4, 148.3; HRMS (FAB): *m/z* calcd for $C_{18}H_{18}N_3O_3S$ $[M + H]^+$ 356.1069; found: 356.1074.

2.1.1.19 C–S Bond Formation with CS_2. Synthesis of 3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazine-6-thione (24)

To a solution of **18a** (40.1 mg, 0.25 mmol), $Cu(OAc)_2$ (45.4 mg, 0.25 mmol) in 1,4-dioxane (0.83 mL) was added CS_2 (0.045 mL, 0.75 mmol) under an 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 **24** as pale yellow solid (6.6 mg, 11 %): mp 139–141 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1624 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.01–2.07 (m, 2H, CH_2), 3.76 (t, $J = 5.6$ Hz, 2H, CH_2), 4.45 (t, $J = 6.2$ Hz, 2H, CH_2), 7.03 (dd, $J = 7.8$, 1.5 Hz, 1H, Ar), 7.28–7.33 (m, 1H, Ar), 7.41 (ddd, $J = 8.0$, 7.6, 1.5 Hz, 1H, Ar), 8.20 (dd, $J = 8.0$, 1.2 Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.6, 45.5, 48.6, 121.6, 126.5, 127.5, 128.9, 131.1, 131.8, 144.2, 189.8; *Anal.* calcd for $C_{11}H_{10}N_2S_2$: C, 56.38; H, 4.30; N, 11.95. Found: C, 56.23; H, 4.44; N, 11.85.

2.2 S_NAr-Type C–S, C–N, or C–O Bond Formation with Heterocumulenes

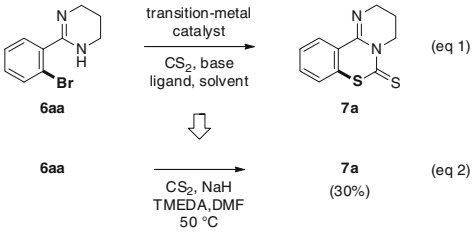
The C–H functionalization methodology described in Chap 2.1 provides a facile access to tricyclic heterocycles related to PD 404182; however, C–S bond formation failed to synthesize several derivatives with the pyrimido[1,2-*c*][1,3]benzothiazin-6-imine scaffold because of the low yield.



Scheme 2.10 Examples of transition-metal-catalyzed coupling of haloarene and heterocumulene

The transition-metal-catalyzed carbon–heteroatom bond formations such as Ullmann–Goldberg reactions and Buchwald–Hartwig cross coupling are becoming a powerful methods for construction of various heterocycles.[11,12] Orain and co-workers have reported a Pd-catalyzed intramolecular *S*-arylation of thioureas **2** to yield 3,4-dihydro-2*H*-benzo[*e*][1,3]thiazin-2-imine derivatives **3** (Scheme 2.10, eq 1) [43] Thioureas were easily obtained by the reaction of 2-halobenzyl-amine derivatives **1** and isothiocyanates. Bao and co-workers have reported the formation of 2-amino-benzothiazoles **5** by CuI-catalyzed coupling of 2-haloanilines **4** and isothiocyanates (eq 2) [44] Li and co-workers have revealed that thses 2-amino-benzothiazole formation reactions were assisted by an Fe(III) catalyst [45]. These reactions proceed via nucleophilic addition of aniline to isothiocyanate followed by transition-metal-catalyzed intramolecular *S*-arylation.

With these findings [38–53], the author investigated the transition-metal (Pd, Cu, Fe, etc.) catalyzed coupling of haloarenes **6aa** and heterocumulenes. During examination of the coupling reaction of **6aa** with CS_2 (Scheme 2.11, eq 1), the author noticed that the desired compound **7a** was formed without using a transition-metal catalyst (eq 2).



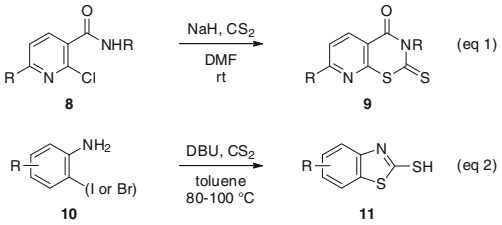
Scheme 2.11 Synthesis of PD 404182 Derivatives **7a** by the coupling of haloarene and heterocumulene. TMEDA N,N,N′,N′-tetramethylethylenediamine

[11] For reviews on transition-metal-catalyzed carbon–heteroatom bond formation, see [38– 41].

[12] For recent examples of the transition-metal-catalyzed coupling reaction of haloarene and hetelocumulenes, see [41–53].

There are several reports of transition-metal-free C–S bond formation. Kobayashi and co-workers have reported the coupling reaction of 2-chloropyridine derivatives **8** with CS_2 (Scheme 2.12, eq 1) [57]. In this reaction, *S*-functionality is introduced at electronically activated C-2 position through the aromatic nucleophilic substitution (S_NAr) reaction. This report encouraged the author to examine the coupling of haloarenes **6aa** and heterocumulenes by S_NAr reaction for the synthesis of PD 404182 derivatives [54–61].[13] After the authors' report, [59] Xi and co-workers reported [59] DBU-promoted tandem reaction of 2-haloanilines **10** and CS_2 (eq 2) [60].

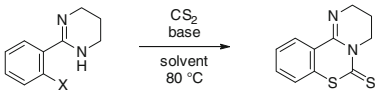
The author initially examined the reaction of **6aa** [6] with 5 equiv of sodium hydride and CS_2 (Table 2.3). The desired reaction efficiently proceeded in DMF to give **7a** in 75 % yield (entry 1). In contrast, when acetonitrile or THF was used as



8 **9** **10** **11**

Scheme 2.12 Examples of transition-metal-free coupling of haloarene and heterocumulene

Table 2.3 Optimization of reaction conditions with CS_2[a]



6aa (X = Br)
6ab (X = F)

7a

Entry	X	Base (equiv)	Solvent	Time (h)	Yield (%)[b]
1	Br	NaH (5)	DMF	6	75
2	Br	NaH (5)	MeCN	4	Trace
3	Br	NaH (5)	THF	4	Trace
4	Br	NaH (2)	DMF	12	88
5	Br	None	DMF	12	12
6	Br	Et_3N (2)	DMF	12	Trace
7	Br	KH (2)	DMF	6	Trace
8	Br	NaO*t*-Bu (2)	DMF	6	27
9	F	NaH (2)	DMF	12	86

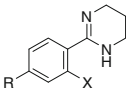
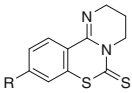
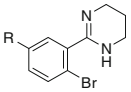
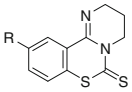
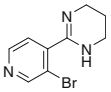
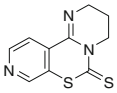
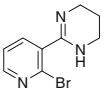
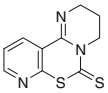
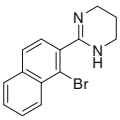
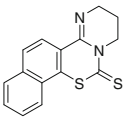
[a] All reactions were carried out at 80 °C with 2 or 5 equiv of CS_2 (corresponding to the base loading)
[b] Isolated yields

[13] For examples of the transition-metal-free coupling reaction of haloarene and hetelocumulenes, see [58–61].

the solvent instead of DMF, yields of **7a** decreased considerably (entries 2 and 3). A decreasing amount of sodium hydride and CS_2 (2.0 equiv) slightly improved the yield of **7a** (88 %) under the reaction for 12 h (entry 4). The reaction in the absence of sodium hydride provided a yield of **7a** of only 12 % (entry 5). The author next screened several bases such as triethylamine, potassium hydride[14] and sodium *tert*-butoxide (entries 6-8): sodium hydride was the most effective (entry 4). The fluoride **6ab** gave a comparable result with the bromide **6aa** to afford **7a** in 86 % yield under optimized conditions (entry 9).

With knowledge of the optimized conditions, the author examined the reaction of several substituted substrates (Table 2.4). Substrates **6b–d** having a methoxy, methyl, or fluoro group at the 4-position provided the corresponding cyclized

Table 2.4 Reaction of substituted 2-(2-halophenyl)-1,4,5,6-tetrahydropyrimidines[a]

Entry	Substrate	Product	Yield (%)[b]
			
1	**6b** (R = OMe, X = F)	**7b** (R = OMe)	95
2	**6c** (R = Me, X = Br)	**7c** (R = Me)	88
3	**6d** (R = F, X = Br)	**7d** (R = F)	76
4	**6e** (R = NO_2, X = F)	**7e** (R = NO_2)	(73)[c]
			
5	**6f** (R = OMe)	**7f** (R = OMe)	17
6	**6g** (R = NO_2)	**7g** (R = NO_2)	(57)[c]
7	 **12**	 **13**	18
8	 **14**	 **15**	71
9	 **16**	 **17**	>99

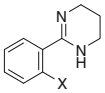
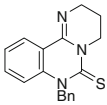
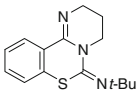
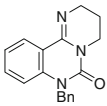
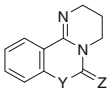
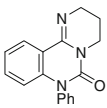
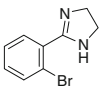
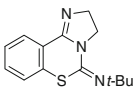
[a] Unless otherwise stated, reactions were carried out with CS_2 (2.0 equiv) and NaH (2.0 equiv) in DMF at 80 °C for 12 h

[b] Isolated yields

[c] Yields in parentheses indicate those of the reactions at rt

[14] A reason for the significant countercation effect (NaH vs. KH) on the reactivity is unclear.

Table 2.5 Reaction with isothiocyanates or isocyanates[a]

Entry	Substrate	R-NCX	Product	Yield (%)[b]
				
1	**6aa** (X = Br)	BnNCS	**18**	82
2	**6ab** (X = F)			97
3[c]	**6ab**	*t*-BuNCS	 **19**	62[d,e]
4	**6ab**	BnNCO	 **20**	>99
5[c]	**6ab**	*t*-BuNCO	 **21** (Y = N*t*-Bu, Z = O)	54
			22 (Y = O, Z = N*t*-Bu)	18[e]
6	**6ab**	PhNCO	 **23**	>99
7	 **24**	*t*-BuNCS	 **25**	49[e]

[a] Unless otherwise stated, reactions were carried out with R-NCX (2.0 equiv) and NaH (2.0 equiv) in DMF at rt for 2–3 h
[b] Isolated yields
[c] These reactions were carried out at 80 °C
[d] A trace amount of regioisomeric *N*-arylation product was also formed
[e] Isolated as a single isomer

products 7**b–d** in good-to-excellent yields (76–95 %, entries 1–3). Whereas the reaction of **6e** bearing the 4-nitro group at 80 °C resulted in the formation of a complex mixture, the reaction at room temperature gave the cyclization product **7e** in 73 % yield (entry 4). A methoxy group on the 5-position considerably diminished the reactivity, affording **7f** in only 17 % yield (entry 5). This was presumably due to increased electron density at the carbon substituted by a bromine atom. In the case of **6g** bearing a 5-nitro group, the corresponding product **7g** was obtained by the reaction at room temperature (entry 6), similarly to **6e** (entry 4). Pyridine derivatives **12** and **14** showed different reactivity depending on the position of the

nitrogen atom: the 2-bromopyridine derivative **14** gave a better result (71 %, entry 8) than the 3-bromopyridine derivative **12** (18 %, entry 7). The naphthalene derivative **16** afforded the tetracyclic compound **17** in quantitative yield (entry 9).

To further expand this methodology for the construction of other heterocyclic frameworks, the author investigated the reaction using isothiocyanates or isocyanates[15] as heterocumulene (Table 2.5). When benzylisothiocyanate was employed, the reaction of **6aa** or **6ab** efficiently proceeded to give the corresponding *N*-arylated product **18** in 82 % or 97 % yields, respectively (entries 1 and 2). The reaction with *tert*-butylisothiocyanate exclusively furnished an *S*-arylated product **19** as a single isomer (entry 3). These results indicate that the regioselectivity of the reaction can be perfectly switched by changing a substituent on the nitrogen atom. As expected, the reaction of **6ab** with benzylisocyanate provided an *N*-arylated product **20** in quantitative yield (entry 4) as in the case with isothiocyanate (entries 1 and 2). Interestingly, *tert*-butylisocyanate showed moderate selectivity to mainly afford an *N*-arylation product **21** (54 %), formed by the arylation at the more bulky position, as well as an *O*-arylation product **22** (18 %, entry 5). Phenylisocyanate also provided an *N*-arylated product **23** (entry 6). The 2-phenylimidazoline derivative **24** (a 5-membered-ring amidine congener) also provided the corresponding *S*-arylated product **25** in a slightly decreased yield (49 %, entry 7).

This reaction would proceed via a nucleophilic addition of the amidine moiety to heterocumulene followed by an intramolecular S_NAr reaction[16,17] of the resulting adducts such as **B** (Scheme 2.13). Nonactivated aromatic rings efficiently reacted under relatively mild conditions, so two molecules of the heterocumulene may be involved in the reaction to form the intermediate **C** in which the amidine moiety can be a more powerful electron-withdrawing group suitable for the S_NAr-type reaction. The regioselectivity in the nucleophilic attack on the aromatic ring (Y vs. Z) is controlled by a subtle balance of inherent nucleophilicity and steric hindrance of these functionalities.

The author finally focused on the synthesis of PD 404182 (**26**) (Scheme 2.14). Hydrolysis of the carbamodithioate derivative **7a** followed by treatment with cyanogen bromide [3] readily afforded the desired compound **26**. The same compound was also obtained in a single step by heating compound **19** in trifluoroacetic acid in the presence of molecular sieves.

In conclusion, the author developed a simple and practical synthetic method for tricyclic heteroarenes related to PD 404182. This reaction provides divergent access to several related heterocycles under mild conditions without a powerful activating group.

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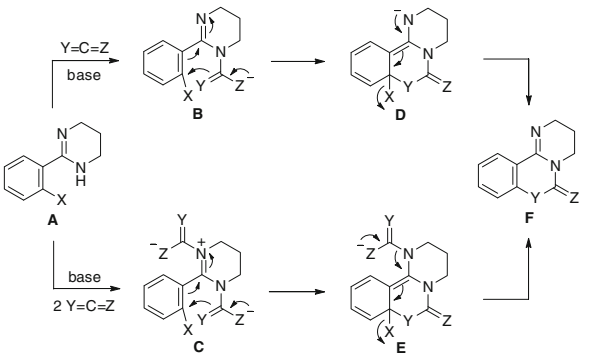
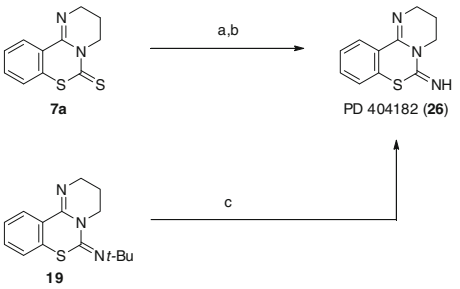
[15] For related reactions of electron-deficient (haloaryl)isothiocyanates, see [62–64].

[16] For reviews on nucleophilic aromatic substitution reaction, see [65, 66].

[17] For examples on nucleophilic aromatic substitution reaction, see [67–73].



Scheme 2.13 Proposed reaction mechanisms



Scheme 2.14 Synthesis of PD 404182. Reagents and conditions: (**a**) NaOH, MeOH-H_2O (9:1), reflux; (**b**) BrCN, EtOH, reflux, 61 % (2 steps); (**c**) TFA, MS4Å, $CHCl_3$, reflux, 85 %

2.2.1 Experimental Section

2.2.1.1 General Methods

All moisture-sensitive reactions were performed using syringe-septum cap techniques under an Ar atmosphere and all glasswares were dried in an oven at 80 °C for 2 h prior to use. Melting points were measured by a hot stage melting point apparatus (uncorrected). For flash chromatography, Wakogel C-300E (Wako) or aluminum oxide 90 standardized (Merck) was employed. ^{1}H-NMR spectra were recorded using a JEOL AL-400 or a JEOL ECA-500 spectrometer, and chemical shifts are reported in δ (ppm) relative to Me_4Si ($CDCl_3$) as internal standards. ^{13}C-NMR spectra were recorded using a JEOL AL-400 or JEOL ECA-500 spectrometer and referenced to the residual $CHCl_3$ signal. ^{19}F–NMR spectra were recorded using a JEOL ECA-500 and referenced to the internal $CFCl_3$ (δ_F 0.00 ppm). ^{1}H-NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet),

coupling constant(s), and number of protons. Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 FT-IR spectrometer with JASCO ATR PRO410-S.

2.2.1.2 General Procedure for Preparation of the Substrates. 2-(2-Bromophenyl)-1,4,5,6-tetrahydropyrimidine (6aa)

To a solution of 2-bromobenzaldehyde (5.55 g, 30.0 mmol) in *t*-BuOH (280 mL) was added propylenediamine (2.45 g, 33.0 mmol). The mixture was stirred at 70 °C for 30 min, and then K_2CO_3 (12.4 g, 90.0 mmol) and I_2 (9.52 g, 37.5 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 *in vacuo*. The resulting solid was dissolved with H_2O, and then pH was adjusted to 12–14 with 2 N NaOH. The whole was extracted with $CHCl_3$. The extract was dried over Na_2SO_4. After concentration, the resulting solid was recrystallized from $CHCl_3$–*n*-hexane to give the compound **6aa** as colorless crystals (6.63 g, 92 %): mp 136–137 °C; IR (neat) cm^{-1}: 1625 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.81-1.86 (m, 2H, CH_2), 3.42 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 4.83 (br s, 1H, NH), 7.18 (ddd, $J = 8.0$, 7.7, 1.7 Hz, 1H, Ar), 7.27-7.31 (m, 1H, Ar), 7.41 (dd, $J = 7.7$, 1.7 Hz, 1H, Ar), 7.53 (d, $J = 8.0$ Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.5, 42.2 (2C), 120.7, 127.3, 129.9, 130.2, 132.7, 139.3, 155.3; HRMS (FAB): *m/z* calcd for $C_{10}H_{12}BrN_2$ $[M + H]^+$ 239.0184; found: 239.0185.

2.2.1.3 2-(2-Fluorophenyl)-1,4,5,6-tetrahydropyrimidine (6ab)

2-Fluorobenzaldehyde (1.24 g, 10.0 mmol) was subjected to the general procedure. Colorless crystals (1.28 g, 71 %): mp 112–113 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1629 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.82–1.88 (m, 2H, CH_2), 3.49 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 5.33 (br s, 1H, NH), 7.03 (ddd, $J = 11.9$, 8.2, 1.1 Hz, 1H, Ar), 7.14 (ddd, $J = 7.8$, 7.8, 1.1 Hz, 1H, Ar), 7.29–7.34 (m, 1H, Ar), 7.80 (ddd, $J = 7.8$, 7.8, 2.0 Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.6, 42.2 (2C), 115.8 (d, $J = 23.2$ Hz), 124.2 (d, $J = 3.3$ Hz), 124.5 (d, $J = 11.6$ Hz), 130.5 (d, $J = 3.3$ Hz), 130.7 (d, $J = 8.3$ Hz), 151.5, 160.1 (d, $J = 247.5$ Hz); ^{19}F-NMR (500 MHz, $CDCl_3$) δ: –116.1; *Anal.* calcd for $C_{10}H_{11}FN_2$: C, 67.40; H, 6.22; N, 15.72. Found: C, 67.15; H, 6.32; N, 15.63.

2.2.1.4 2-(2-Fluoro-4-methoxyphenyl)-1,4,5,6-tetrahydropyrimidine (6b)

2-Fluoro-4-methoxybenzaldehyde (0.77 g, 5.0 mmol) was subjected to the general procedure. Pale yellow crystals (0.70 g, 67 %): mp 77 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1623 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.82-1.88 (m, 2H, CH_2), 3.48 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 3.79 (s, 3H, OCH_3), 5.13 (br s, 1H, NH), 6.56 (dd, $J = 13.8$, 2.6 Hz, 1H, Ar), 6.69 (dd, $J = 8.8$, 2.6 Hz, 1H, Ar), 7.77 (dd, $J = 8.8$, 8.8 Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.8, 42.2 (2C), 55.5, 101.5 (d, $J = 27.6$ Hz), 110.2 (d, $J = 2.4$ Hz), 116.7 (d, $J = 10.8$ Hz), 131.3 (d, $J = 6.0$ Hz), 151.4 (d, $J = 2.4$ Hz), 160.7 (d, $J = 205.1$ Hz), 161.7 (d, $J = 30.0$ Hz); ^{19}F-NMR (500 MHz, $CDCl_3$) δ: –113.8; *Anal.* calcd for $C_{11}H_{13}FN_2O$: C, 63.45; H, 6.29; N, 13.45. Found: C, 63.38; H, 6.29; N, 13.49.

2.2.1.5 2-(2-Bromo-4-methylphenyl)-1,4,5,6-tetrahydropyrimidine (6c)

2-Bromo-4-methylbenzaldehyde (1.00 g, 5.0 mmol) was subjected to the general procedure. Colorless crystals (1.11 g, 88 %): mp 128–129 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1639 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.83-1.89 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 3.46 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 4.65 (br s, 1H, NH), 7.07–7.10 (m, 1H, Ar), 7.27–7.35 (m, 2H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.7, 20.8, 42.3 (2C), 120.4, 128.1, 130.1, 133.2, 136.5, 140.3, 155.3; *Anal.* calcd for $C_{11}H_{13}BrN_2$: C, 52.19; H, 5.18; N, 11.07. Found: C, 52.37; H, 5.21; N, 11.12.

2.2.1.6 2-(2-Bromo-4-fluorophenyl)-1,4,5,6-tetrahydropyrimidine (6d)

2-Bromo-4-fluorobenzaldehyde (1.02 g, 5.0 mmol) was subjected to the general procedure. Colorless crystals (1.25 g, 97 %): mp 130 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1623 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.83-1.87 (m, 2H, CH_2), 3.44 (t, $J = 6.0$ Hz, 4H, 2 × CH_2), 4.42 (br s, 1H, NH), 7.01 (ddd, $J = 8.6$, 8.3, 2.7 Hz, 1H, Ar), 7.27 (dd, $J = 8.3$, 2.7 Hz, 1H, Ar), 7.40 (dd, $J = 8.6$, 5.7 Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.5, 42.3 (2C), 114.6 (d, $J = 20.4$ Hz), 120.0 (d, $J = 24.0$ Hz), 121.1 (d, $J = 9.6$ Hz), 131.4 (d, $J = 8.4$ Hz), 135.6 (d, $J = 3.6$ Hz), 154.5, 162.2 (d, $J = 251.9$ Hz); ^{19}F-NMR (500 MHz, $CDCl_3$) δ: –116.1. *Anal.* calcd for $C_{10}H_{10}BrFN_2$: C, 46.72; H, 3.92; N, 10.90. Found: C, 46.64; H, 3.87; N, 10.97.

2.2.1.7 2-(2-Fluoro-4-nitrophenyl)-1,4,5,6-tetrahydropyrimidine (6e)

2-Fluoro-4-nitrobenzaldehyde (0.68 g, 4.0 mmol) was subjected to the general procedure. Yellow crystals (0.69 g, 77 %): mp 141–142 °C (from $CHCl_3$–*n*-

hexane); IR (neat) cm^{-1}: 1625 (C=N), 1603 (NO_2), 1519 (NO_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.84-1.90 (m, 2H, CH_2), 3.50 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 5.51 (br s, 1H, NH), 7.90–8.02 (m, 3H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.4, 44.8 (2C), 112.0 (d, $J = 30.0$ Hz), 119.2 (d, $J = 3.6$ Hz), 130.5 (d, $J = 12.0$ Hz), 131.9 (d, $J = 3.6$ Hz), 148.8 (d, $J = 9.6$ Hz), 149.8, 159.4 (d, $J = 251.9$ Hz); ^{19}F-NMR (500 MHz, $CDCl_3$) δ: –111.8; *Anal.* calcd for $C_{10}H_{10}FN_3O_2$: C, 53.81; H, 4.52; N, 18.83. Found: C, 54.05; H, 4.53; N, 19.05.

2.2.1.8 2-(2-Bromo-5-methoxyphenyl)-1,4,5,6-tetrahydropyrimidine (6f)

2-Bromo-5-methoxybenzaldehyde (0.86 g, 4.0 mmol) was subjected to the general procedure. Colorless crystals (0.98 g, 91 %): mp 124 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1626 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.84–1.89 (m, 2H, CH_2), 3.46 (t, $J = 6.0$ Hz, 4H, 2 × CH_2), 3.79 (s, 3H, OCH_3), 4.63 (br s, 1H, NH), 6.76 (dd, $J = 9.2$, 3.2 Hz, 1H, Ar), 6.98 (d, $J = 3.2$ Hz, 1H, Ar), 7.39 (d, $J = 9.2$ Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 20.6, 42.3 (2C), 55.5, 110.9, 115.0, 116.9, 133.5, 140.0, 155.3, 158.9; *Anal.* calcd for $C_{11}H_{13}BrN_2O$: C, 49.09; H, 4.87; N, 10.41. Found: C, 49.21; H, 4.84; N, 10.44.

2.2.1.9 2-(2-Bromo-5-nitrophenyl)-1,4,5,6-tetrahydropyrimidine (6g)

2-Bromo-5-nitrobenzaldehyde (0.58 g, 2.5 mmol) was subjected to the general procedure. Yellow crystals (0.41 g, 58 %): mp 139–141 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1631 (C=N), 1608 (NO_2), 1524 (NO_2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.87–1.93 (m, 2H, CH_2), 3.50 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 4.59 (br s, 1H, NH), 7.72 (d, $J = 8.8$ Hz, 1H, Ar), 8.03 (dd, $J = 8.8$, 2.7 Hz, 1H, Ar), 8.27 (d, $J = 2.7$ Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.5, 42.4 (2C), 124.4, 125.3, 128.3, 134.0, 140.5, 147.1, 153.4; *Anal.* calcd for $C_{10}H_{10}BrN_3O_2$: C, 42.27; H, 3.55; N, 14.79. Found: C, 42.55; H, 3.80; N, 14.52.

2.2.1.10 2-(3-Bromopyridin-4-yl)-1,4,5,6-tetrahydropyrimidine (12)

3-Bromoisonicotinaldehyde (0.93 g, 5.0 mmol) was subjected to the general procedure. Yellow solid (0.73 g, 61 %): mp 141 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1630 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.84-1.90 (m, 2H, CH_2), 3.46 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 4.93 (br s, 1H, NH), 7.35 (d, $J = 4.6$ Hz, 1H, Ar), 8.50 (d, $J = 4.6$ Hz, 1H, Ar), 8.70 (s, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.3, 42.3 (2C), 118.8, 124.5, 145.9, 148.5, 152.4, 153.0; *Anal.* calcd for $C_9H_{10}BrN_3$: C, 45.02; H, 4.20; N, 17.50. Found: C, 44.74; H, 4.13; N, 17.43.

2.2.1.11 2-(2-Bromopyridin-3-yl)-1,4,5,6-tetrahydropyrimidine (14)

2-Bromonicotinaldehyde (0.93 g, 5.0 mmol) was subjected to the general procedure. Yellow solid (1.14 g, 95 %): mp 106–108 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1626 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.84–1.89 (m, 2H, CH_2), 3.44 (t, $J = 5.9$ Hz, 4H, 2 × CH_2), 4.89 (br s, 1H, NH), 7.27–7.30 (m, 1H, Ar), 7.72 (dd, $J = 7.6$, 2.0 Hz, 1H, Ar), 8.35 (d, $J = 4.8$, 2.0 Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.3, 42.3 (2C), 122.7, 136.1, 138.7, 140.1, 150.1, 153.8; HRMS (FAB): *m/z* calcd for $C_9H_{11}BrN_3$ $[M + H]^+$ 240.0136; found: 240.0139.

2.2.1.12 2-(1-Bromonaphthalen-2-yl)-1,4,5,6-tetrahydropyrimidine (16)

1-Bromo-2-naphthaldehyde (0.94 g, 4.0 mmol) was subjected to the general procedure. Colorless crystals (1.04 g, 90 %): mp 151–153 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1625 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.89–1.95 (m, 2H, CH_2), 3.52 (t, $J = 5.7$ Hz, 4H, 2 × CH_2), 4.72 (br s, 1H, NH), 7.47-7.62 (m, 3H, Ar), 7.77–7.82 (m, 2H, Ar), 8.33 (d, $J = 8.5$ Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.7, 42.5 (2C), 121.2, 126.8, 126.9, 127.6, 127.6, 127.9, 128.1, 132.1, 134.2, 137.5, 156.1; *Anal.* calcd for $C_{14}H_{13}BrN_2$: C, 58.15; H, 4.53; N, 9.69. Found: C, 58.02; H, 4.47; N, 9.71.

2.2.1.13 2-(2-Bromophenyl)-4,5-dihydro-1*H*-imidazole (24)

2-Bromobenzaldehyde (0.93 g, 5.0 mmol) was subjected to the general procedure using ethylenediamine (0.33 g, 5.5 mmol) instead of propylenediamine. Colorless crystals (0.77 g, 68 %): mp 98–99 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1619 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.79 (s, 4H, 2 × CH_2), 4.99 (br s, 1H, NH), 7.25 (ddd, $J = 8.0$, 7.5, 1.7 Hz, 1H, Ar), 7.33 (ddd, $J = 8.0$, 7.5, 1.1 Hz, 1H, Ar), 7.58 (dd, $J = 8.0$, 1.1 Hz, 1H, Ar), 7.64 (d, $J = 8.0$, 1.7 Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 50.6 (2C), 120.8, 127.4, 131.0, 131.2, 133.0, 133.2, 164.4; HRMS (FAB): *m/z* calcd for $C_9H_{10}BrN_2$ $[M + H]^+$ 225.0027; found: 225.0030.

2.2.1.14 General Procedure for Cyclization Using CS_2. 3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzo- thiazine-6-thione (7a)

To a mixture of **6aa** (59.8 mg, 0.25 mmol) and NaH (20.0 mg, 0.50 mmol; 60 % oil suspension) in DMF (0.83 mL) was added CS_2 (30.5 μL, 0.50 mmol) under an Ar atmosphere. After being stirred at 80 °C for 12 h, the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel with *n*-

hexane–EtOAc (9:1) to give the compound **7a** as a pale-yellow solid (51.4 mg, 88 %). Spectral data were in good agreement with compound **24** in Chap. 2.

2.2.1.15 3,4-Dihydro-9-methoxy-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazine-6-thione (7b)

The fluoride **6b** (52.1 mg, 0.25 mmol) was subjected to the general procedure. Pale yellow solid (62.6 mg, 95 %): mp 120–122 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1624 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.00–2.05 (m, 2H, CH_2), 3.71 (t, $J = 5.4$ Hz, 2H, CH_2), 3.83 (m, 3H, OCH_3), 4.42 (t, $J = 6.3$ Hz, 2H, CH_2), 6.46 (d, $J = 2.3$ Hz, 1H, Ar), 6.83 (dd, $J = 9.0$, 2.3 Hz, 1H, Ar), 8.12 (d, $J = 9.0$ Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.6, 45.3, 48.7, 55.6, 104.9, 114.9, 119.2, 130.7, 133.3, 143.9, 161.6, 189.7; *Anal.* calcd for $C_{12}H_{12}N_2OS_2$: C, 54.52; H, 4.58; N, 10.60. Found: C, 54.22; H, 4.62; N, 10.47.

2.2.1.16 3,4-Dihydro-9-methyl-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazine-6-thione (7c)

The bromide **6c** (63.3 mg, 0.25 mmol) was subjected to the general procedure. Colorless solid (54.6 mg, 88 %): mp 146–147 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1620 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.99–2.06 (m, 2H, CH_2), 2.35 (m, 3H, CH_3), 3.73 (t, $J = 5.6$ Hz, 2H, CH_2), 4.43 (t, $J = 6.2$ Hz, 2H, CH_2), 6.82 (d, $J = 1.0$ Hz, 1H, Ar), 7.10 (dd, $J = 8.3$, 1.0 Hz, 1H, Ar), 8.07 (d, $J = 8.3$ Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.2, 21.6, 45.4, 48.7, 121.6, 123.8, 128.7, 128.7, 131.6, 141.8, 144.2, 190.0; *Anal.* calcd for $C_{12}H_{12}N_2S_2$: C, 58.03; H, 4.87; N, 11.28. Found: C, 57.84; H, 4.85; N, 11.19.

2.2.1.17 9-Fluoro-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazine-6-thione (7d)

The bromide **6d** (64.3 mg, 0.25 mmol) was subjected to the general procedure. Colorless solid (47.9 mg, 76 %): mp 185 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1630 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.01–2.06 (m, 2H, CH_2), 3.73 (t, $J = 5.7$ Hz, 2H, CH_2), 4.42 (t, $J = 6.0$ Hz, 2H, CH_2), 6.73 (dd, $J = 8.0$, 2.9 Hz, 1H, Ar), 6.98 (ddd, $J = 8.9$, 8.9, 2.9 Hz, 1H, Ar), 8.22 (dd, $J = 8.9$, 5.4 Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.5, 45.4, 48.7, 108.1 (d, $J = 24.0$ Hz), 115.1 (d, $J = 22.8$ Hz), 122.7 (d, $J = 3.6$ Hz), 131.7 (d, $J = 9.6$ Hz), 134.0 (d, $J = 8.4$ Hz), 143.4, 163.9 (d, $J = 255.5$ Hz), 188.9; ^{19}F-NMR (500 MHz, $CDCl_3$) δ: –106.9; *Anal.* calcd for $C_{11}H_9FN_2S_2$: C, 52.36; H, 3.60; N, 11.10. Found: C, 52.10; H, 3.48; N, 11.15.

2.2.1.18 3,4-Dihydro-9-nitro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazine-6-thione (7e)

Using the general procedure, the fluoride **6e** (55.8 mg, 0.25 mmol) was allowed to react with CS_2 at rt for 12 h. Pale yellow solid (50.7 mg, 73 %): mp 192–193 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1620 (C=N), 1598 (NO_2), 1520 (NO_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.05-2.09 (m, 2H, CH_2), 3.81 (t, $J = 5.7$ Hz, 2H, CH_2), 4.44 (t, $J = 6.0$ Hz, 2H, CH_2), 7.90 (d, $J = 1.7$ Hz, 1H, Ar), 8.06 (dd, $J = 9.0$, 1.7 Hz, 1H, Ar), 8.40 (d, $J = 9.0$ Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.4, 45.8, 48.5, 117.0, 121.4, 130.7, 131.2, 133.8, 142.9, 149.0, 187.9; *Anal.* calcd for $C_{11}H_9N_3O_2S_2$: C, 47.30; H, 3.25; N, 15.04. Found: C, 47.07; H, 3.19; N, 14.99.

2.2.1.19 3,4-Dihydro-10-methoxy-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazine-6-thione (7f)

The bromide **6f** (67.3 mg, 0.25 mmol) was subjected to the general procedure. Pale yellow solid (11.3 mg, 17 %): mp 136 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1625 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.99–2.07 (m, 2H, CH_2), 3.76 (t, $J = 5.7$ Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.46 (t, $J = 6.2$ Hz, 2H, CH_2), 6.94 (d, $J = 8.8$ Hz, 1H, Ar), 7.02 (dd, $J = 8.8$, 2.7 Hz, 1H, Ar), 7.75 (d, $J = 2.7$ Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.6, 45.5, 48.6, 55.6, 111.6, 119.8, 123.0, 123.4, 127.6, 144.2, 159.2, 189.9; HRMS (FAB): *m/z* calcd for $C_{12}H_{13}N_2OS_2$ $[M + H]^+$ 265.0469; found: 265.0461.

2.2.1.20 3,4-Dihydro-10-nitro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazine-6-thione (7g)

Using the general procedure, the bromide **6g** (71.0 mg, 0.25 mmol) was allowed to react with CS_2 at rt for 12 h. Yellow solid (39.6 mg, 57 %): mp 176–177 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1627 (C=N), 1605 (NO_2), 1523 (NO_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.05-2.10 (m, 2H, CH_2), 3.81 (t, $J = 5.4$ Hz, 2H, CH_2), 4.44 (t, $J = 6.0$ Hz, 2H, CH_2), 7.18 (d, $J = 8.9$ Hz, 1H, Ar), 8.23 (dd, $J = 8.9$, 2.9 Hz, 1H, Ar), 9.09 (d, $J = 2.9$ Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.3, 45.6, 48.6, 122.7, 124.6, 125.4, 127.4, 139.2, 142.4, 146.9, 187.3; HRMS (FAB): *m/z* calcd for $C_{11}H_{10}N_3O_2S_2$ $[M + H]^+$ 280.0214; found: 280.0211.

2.2.1.21 3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-*c*]pyrido[4,3-*e*][1,3]thiazine-6-thione (13)

The bromide **12** (60.0 mg, 0.25 mmol) was subjected to the general procedure. Orange solid (10.8 mg, 18 %): mp 205–207 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1619 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.03–2.09 (m, 2H, CH_2), 3.79 (t, $J = 5.6$ Hz, 2H, CH_2), 4.44 (t, $J = 6.1$ Hz, 2H, CH_2), 8.01 (d, $J = 5.4$ Hz, 1H, Ar), 8.36 (s, 1H, Ar), 8.51 (d, $J = 5.4$ Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.4, 45.7, 48.4, 121.3, 128.2, 132.9, 142.6, 143.2, 148.3, 188.5; HRMS (FAB): *m/z* calcd for $C_{10}H_{10}N_3S_2$ $[M + H]^+$ 236.0316; found: 236.0311.

2.2.1.22 3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-*c*]pyrido[3,2-*e*][1,3]thiazine-6-thione (15)

The bromide **14** (60.0 mg, 0.25 mmol) was subjected to the general procedure. Colorless solid (41.9 mg, 71 %): mp 141–142 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm-1: 1621 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.02–2.08 (m, 2H, CH_2), 3.76 (t, $J = 5.6$ Hz, 2H, CH_2), 4.45 (t, $J = 6.2$ Hz, 2H, CH_2), 7.22 (dd, $J = 8.0$, 4.5 Hz, 1H, Ar), 8.46 (dd, $J = 8.0$, 1.6 Hz, 1H, Ar), 8.54 (dd, $J = 4.5$, 1.6 Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.3, 45.7, 48.6, 122.2, 124.0, 136.5, 143.8, 151.9, 153.3, 190.8; *Anal.* calcd for $C_{10}H_9N_3S_2$: C, 51.04; H, 3.85; N, 17.86. Found: C, 50.88; H, 3.95; N, 17.82.

2.2.1.23 2,3-Dihydronaphtho[2,1-*e*]pyrimido[1,2-*c*][1,3]thiazine-12(1*H*)-thione (17)

The bromide **16** (72.3 mg, 0.25 mmol) was subjected to the general procedure. Pale yellow solid (73.4 mg, >99 %): mp 230–231 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1620 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.06-2.12 (m, 2H, CH_2), 3.82 (t, $J = 5.5$ Hz, 2H, CH_2), 4.50 (t, $J = 6.2$ Hz, 2H, CH_2), 7.58-7.63 (m, 2H, Ar), 7.75 (d, $J = 9.0$ Hz, 1H, Ar), 7.83-7.86 (m, 1H, Ar), 7.96-8.00 (m, 1H, Ar), 8.26 (d, $J = 8.8$ Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.5, 45.7, 48.7, 123.0, 124.0, 124.7, 126.0, 127.1, 127.3, 128.3, 128.4, 129.7, 133.9, 144.8, 188.4; *Anal.* calcd for $C_{15}H_{12}N_2S_2$: C, 63.35; H, 4.25; N, 9.85. Found: C, 63.36; H, 4.03; N, 9.70.

2.2.1.24 General Procedure for Cyclization Using Isothiocyanates or Isocyanates. *N*-Benzyl-3,4-dihydro-2*H*-pyrimido[1,2-*c*]quinazolin-6(7*H*)-thione (18)

To a mixture of the fluoride **6ab** (44.6 mg, 0.25 mmol) and NaH (20.0 mg, 0.50 mmol; 60 % oil suspension) in DMF (0.83 mL) was added

benzylisothiocyanate (66.0 μL, 0.50 mmol) under an Ar atmosphere. After being stirred at rt for 2 h, EtOAc was added. The resulting solution 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 (29:1) to give the title compound **18** as a colorless solid (74.7 mg, 97 %): mp 137 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1635 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.02-2.07 (m, 2H, CH_2), 3.67 (t, $J = 5.2$ Hz, 2H, CH_2), 4.43 (t, $J = 6.0$ Hz, 2H, CH_2), 6.01 (br s, 2H, CH_2), 6.99 (d, $J = 8.6$ Hz, 1H, Ar), 7.15–7.36 (m, 7H, Ar), 8.18 (d, $J = 7.4$ Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.7, 44.8, 50.3, 54.5, 115.6, 119.6, 124.4, 126.0, 126.2 (2C), 127.2, 128.8 (2C), 132.2, 135.6, 137.5, 143.2, 177.6; *Anal.* calcd for $C_{18}H_{17}N_3S$: C, 70.33; H, 5.57; N, 13.67. Found: C, 70.31; H, 5.66; N, 13.69.

2.2.1.25 *N*-(*tert*-Butyl)-3,4-dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (19)

Using the general procedure, the fluoride **6ab** (44.6 mg, 0.25 mmol) was allowed to react with *tert*-butylisothiocyanate (63.4 μL, 0.50 mmol) at 80 °C for 2 h and purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1). Pale yellow solid (42.7 mg, 62 %): mp 62 °C (from *n*-hexane): IR (neat) cm^{-1}: 1622 (C=N), 1598 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.39 (s, 9H, $3 \times CH_3$), 1.88–1.94 (m, 2H, CH_2), 3.62 (t, $J = 5.6$ Hz, 2H, CH_2), 3.87 (t, $J = 6.2$ Hz, 2H, CH_2), 7.11 (dd, $J = 8.0$, 1.2 Hz, 1H, Ar), 7.20 (ddd, $J = 8.0$, 7.3, 1.2 Hz, 1H, Ar), 7.31 (ddd, $J = 8.0$, 7.3, 1.4 Hz, 1H, Ar), 8.18 (dd, $J = 8.0$, 1.4 Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.9, 30.0 (3C), 45.1, 45.4, 54.1, 124.5, 126.0, 127.8, 128.4, 129.0, 130.1, 138.3, 148.0; HRMS (FAB): *m/z* calcd for $C_{15}H_{20}N_3S$ $[M + H]^+$ 274.1378; found: 274.1375.

2.2.1.26 *N*-Benzyl-3,4-dihydro-2*H*-pyrimido[1,2-*c*]quinazolin-6-one (20)

Using the general procedure, the fluoride **6ab** (44.6 mg, 0.25 mmol) was allowed to react with benzylisocyanate (61.6 μL, 0.50 mmol) at rt for 2 h and purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1). White solid (74.8 mg, >99 %): mp 105–107 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1672 (C=O), 1625 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.97–2.03 (m, 2H, CH_2), 3.67 (t, $J = 5.5$ Hz, 2H, CH_2), 3.99 (t, $J = 6.0$ Hz, 2H, CH_2), 5.29 (s, 2H, CH_2), 6.93 (d, $J = 8.3$ Hz, 1H, Ar), 7.09 (dd, $J = 8.0$, 7.3 Hz, 1H, Ar), 7.23–7.35 (m, 6H, Ar), 8.18 (d, $J = 8.0$ Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.6, 41.8, 44.5, 47.0, 114.1, 117.8, 122.7, 126.1, 126.4, 127.3, 127.3, 128.6, 128.8, 132.0, 136.4, 138.0, 145.3, 150.8; *Anal.* calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 73.90; H, 6.04; N, 14.12.

2.2.1.27 *N*-(*tert*-Butyl)-3,4-dihydro-2*H*-pyrimido[1,2-*c*]quinazolin-6-one (21) and *N*-(*tert*-Butyl)-3,4-dihydro-2*H*- pyrimido [1,2-*c*][1,3]benzoxazin-6-imine (22)

Using the general procedure, the fluoride **6ab** (44.6 mg, 0.25 mmol) was allowed to react with *tert*-butylisocyanate (57.1 μL, 0.50 mmol) at 80 °C for 2 h and purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1).

Compound **21**: pale yellow oil (34.9 mg, 54 %): IR (neat) cm^{-1}: 1679 (C=O), 1631 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.68 (s, 9H, 3 × CH_3), 1.86–1.92 (m, 2H, CH_2), 3.61 (t, J = 5.5 Hz, 2H, CH_2), 3.77 (t, J = 6.2 Hz, 2H, CH_2), 7.07-7.11 (m, 1H, Ar), 7.25–7.27 (m, 1H, Ar), 7.33-7.37 (m, 1H, Ar), 7.95 (dd, J = 7.8, 1.2 Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.9, 30.4 (3C), 41.3, 44.6, 59.6, 119.5, 122.5, 122.6, 125.9, 129.3, 138.8, 147.3, 151.7; HRMS (FAB): *m/z* calcd for $C_{15}H_{20}N_3O$ $[M + H]^+$ 258.1606; found: 258.1604.

Compound **22**: colorless crystals (11.4 mg, 18 %): mp 53–55 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1637 (C=N), 1613 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.35 (s, 9H, 3 × CH_3), 1.91–1.96 (m, 2H, CH_2), 3.59 (t, J = 5.7 Hz, 2H, CH_2), 3.79 (t, J = 6.0 Hz, 2H, CH_2), 7.01 (d, J = 8.0 Hz, 1H, Ar), 7.12 (dd, J = 7.7, 7.4 Hz, 1H, Ar), 7.40 (ddd, J = 8.0, 7.4, 1.4 Hz, 1H, Ar), 8.00 (dd, J = 7.7, 1.4 Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.0, 30.8 (3C), 43.4, 44.3, 52.5, 115.1, 116.6, 123.5, 125.5, 132.0, 139.1, 143.8, 150.6; HRMS (FAB): *m/z* calcd for $C_{15}H_{20}N_3O$ $[M + H]^+$ 258.1606; found: 258.1602.

2.2.1.28 *N*-Phenyl-3,4-dihydro-2*H*-pyrimido[1,2-*c*]quinazolin-6-one (23)

Using the general procedure, the fluoride **6ab** (44.6 mg, 0.25 mmol) was allowed to react with phenylisocyanate (54.5 μL, 0.50 mmol) at rt for 2 h and purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1). White solid (69.6 mg, >99 %): mp 225–226 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1684 (C=O), 1629 (C=N); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.97-2.03 (m, 2H, CH_2), 3.69 (t, J = 5.6 Hz, 2H, CH_2), 3.95 (t, J = 6.0 Hz, 2H, CH_2), 6.37 (d, J = 8.3 Hz, 1H, Ar), 7.08–7.12 (m, 1H, Ar), 7.22–7.34 (m, 3H, Ar), 7.46-7.61 (m, 3H, Ar), 8.19 (dd, J = 7.9, 1.6 Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.5, 41.5, 44.6, 115.1, 117.2, 122.8, 125.9, 128.8, 129.3 (2C), 130.1 (2C), 131.6, 137.2, 139.6, 145.4, 150.2; *Anal.* calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.41; H, 5.27; N, 15.11.

2.2.1.29 *N*-(*tert*-Butyl)-2,3-dihydroimidazo[1,2-*c*][1,3]benzothiazin-5-imine (25)

Using the general procedure, the bromide **24** (112.5 mg, 0.50 mmol) was allowed to react with *tert*-butylisothiocyanate (126.8 μL, 1.00 mmol) at rt for 3 h and purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (1:0 to 9:1). White solid (63.0 mg, 49 %): mp 140–142 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1625 (C=N), 1604 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.37 (s, 9H, 3 × CH_3), 3.93–4.03 (m, 4H, 2 × CH_2), 7.17 (d, J = 8.0 Hz, 1H, Ar), 7.22 (dd, J = 8.0, 7.7 Hz, 1H, Ar), 7.37 (dd, J = 7.7, 7.4 Hz, 1H, Ar), 8.19 (d, J = 7.4 Hz, 1H, Ar); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 30.1 (3C), 49.2, 52.2, 53.9, 121.8, 124.5, 126.0, 128.5, 131.5, 132.9, 134.6, 154.5; HRMS (FAB): *m/z* calcd for $C_{14}H_{18}N_3S$ $[M + H]^+$ 260.1221; found: 260.1219.

2.2.1.30 3,4-Dihydro-2*H*,6*H*-pyrimido[1,2-*c*][1,3]benzothiazin-6-imine (26)

Synthesis from **7a**: 0.1 M solution of NaOH in a mixed solvent of MeOH/H_2O (9:1; 5 mL) was added to a flask containing **7a** (58.6 mg, 0.25 mmol). After being stirred under reflux for 12 h, the mixture was concentrated *in vacuo* [azeotroped with MeOH (×2) and $CHCl_3$ (×2)]. The residue was suspended with anhydrous EtOH (1 mL), and BrCN (53.0 mg, 0.50 mmol) was added under an Ar atmosphere. After being stirred under reflux for 2 h, 2 N NaOH was added to the mixture. The whole was extracted with $CHCl_3$, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) to give the title compound **26** as white solid (33.2 mg, 61 % in 2 steps).

Synthesis from **19**: TFA (2 mL) was added to a mixture of **19** (54.7 mg, 0.20 mmol) in small amount of $CHCl_3$ (1 or 2 drops) and MS4Å (300 mg, powder, activated by heating with Bunsen burner). After being stirred under reflux for 1 h, the mixture was concentrated *in vacuo*. To a stirring mixture of this 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. $NaHCO_3$ (×2), brine, and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography over aluminum oxide with *n*-hexane–EtOAc (9:1) to give the title compound **26** as white solid (36.9 mg, 85 %).

Compound **26**: mp 105 °C (from $CHCl_3$–*n*-hexane); IR (neat) cm^{-1}: 1621 (C=N), 1578 (C=N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.95-2.00 (m, 2H, CH_2), 3.69 (t, J = 5.5 Hz, 2H, CH_2), 4.02 (t, J = 6.1 Hz, 2H, CH_2), 7.04 (dd, J = 7.5, 1.1 Hz, 1H, Ar), 7.17 (br s, 1H, NH), 7.21–7.24 (m, 1H, Ar), 7.34 (ddd, J = 7.5, 7.5, 1.4 Hz, 1H, Ar), 8.22 (dd, J = 7.5, 1.4 Hz, 1H, Ar); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.1, 43.8, 44.9, 123.5, 126.2, 126.8, 128.8, 128.9, 130.5, 146.6, 153.4; *Anal.* calcd for $C_{11}H_{11}N_3S$: C, 60.80; H, 5.10; N, 19.34.

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