Polycyclic *N*-Heterocyclic Compounds, Part 72: Reaction of *N*-([1]Benzofuro (or Benzothieno)[3,2-*d*]pyrimidin-4-yl)formamidine and *N*-(Pyrido[2,3-*d*] pyrimidin-4-yl)formamidine Derivatives with Hydroxylamine Hydrochloride

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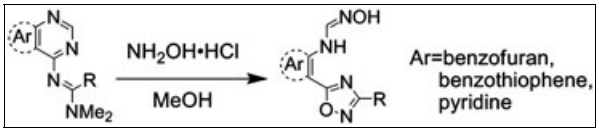

The reactions of *N*-([1]benzofuro[3,2-*d*]pyrimidin-4-yl)formamidines with hydroxylamine hydrochloride gave rearranged cyclization products via ring cleavage of the pyrimidine component accompanied by a ring closure of the 1,2,4-oxadiazole to give *N*-[2-([1,2,4]oxadiazol-5-yl)[1]benzofuran-3-yl)formamide oximes. *N*-([1]Benzothieno[3,2-*d*]pyrimidin-4-yl)formamidines and *N*-(pyrido[2,3-*d*]pyrimidin-4-yl)formamidines with hydroxylamine hydrochloride gave similar results.

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INTRODUCTION

Addition of a nucleophile to an electron poor heterocycle can initiate a ring-opening/ring-closure (ANRORC)-like rearrangement, which has proven to be a useful strategy in organic synthesis [1]. Hydroxylamines are often utilized as 1,2-bidentate nucleophiles for this type of conversion [2]. Recently, we reported that reaction of *N*-(quinazolin-4-yl)formamidines (**1**) with hydroxylamine hydrochloride results in a pyrimidine ring-opening reaction and formation of the 1,2,4-oxadiazole ring to give *N*-[2-([1,2,4]oxadiazol-5-yl)phenyl]formamide oximes (**2**) (Fig. 1) [3]. As this unusual reaction should be applicable to other fused aromatic derivatives such as electron rich benzofuro (or benzothieno) [3,2-*d*]pyrimidines and electron deficient pyrido[2,3-*d*]pyrimidine, we have explored extension of this process to such systems. Herein, we report in detail the results of these studies.

RESULTS AND DISCUSSIONS

First, we examined ([1]benzofuro[3,2-*d*]pyrimidin-4-yl)amidines (**4**). As shown in Scheme 1, the requisite amidine starting materials **4** were synthesized by previously reported methods [4]. Amidines **4a**,**b** were prepared by the reaction of 4-amino[1]benzofuro[3,2-*d*]pyrimidine (**3**) [5] with commercially available *N*,*N*-dimethylformamide (or acetamide) dimethyl acetal in refluxing toluene. Other amidines **4c**–**g** were produced by the reaction of compound **3** with the Vilsmeier reagent prepared from the corresponding *N*,*N*-dimethylamide and phosphoryl chloride in the presence of triethylamine.

When a hydrogen is attached to the amidine moiety (R = H) the reaction of **4a** with 1.2 equiv of hydroxylamine hydrochloride in methanol at room temperature gave the amide oxime (**5a**) in 87% yield. Reaction of **5a** with 10 equiv of hydroxylamine hydrochloride in a refluxing methanol containing dioxane to increase the solubility of **5a** produced the 1,2,4-oxadiazole derivative (**6a**) in 34% yield.

In the ^{1}H NMR spectrum of **6a**, a characteristic formamide oxime one-proton doublet (J = 10.5 Hz) appeared at 8.01 ppm coupled with an adjacent NH proton (J = 10.5 Hz). This NH is exchangeable and, thus, the formamide oxime signal changed to a singlet in the presence of deuterium oxide. The one-proton singlet at 8.74 ppm (pyrimidine ring proton) present in **5a** was absent in the product. One 1,2,4-oxadiazole ring proton was observed in the product at 9.24 ppm as a singlet. These NMR data indicate that pyrimidine ring cleavage and 1,2,4-oxadiazole ring formation occurred during reaction of **5a** with hydroxylamine hydrochloride [6].

In similar fashion, we carried out the reaction of **4b** (R = Me) with 1.2 equiv of hydroxylamine hydrochloride in methanol at room temperature. TLC analysis suggested the formation of a mixture of **5b** and **6b**, but we were unable to isolate the product. However, reaction of **4b** with 6.0 equiv of hydroxylamine hydrochloride in methanol under reflux gave the 1,2,4-oxadiazole derivative (**6b**) in 50% yield. The

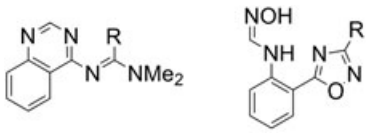


Figure 1. Substrates (**1**) and their rearranged products (**2**).

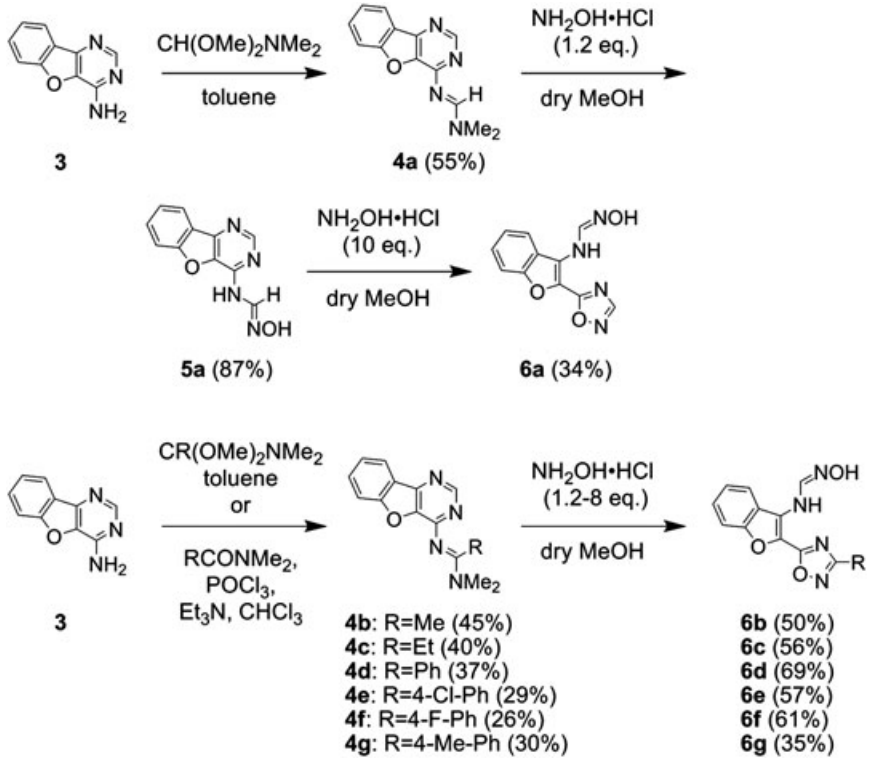
reaction of **4c** (R = Et) with 1.2 equiv of hydroxylamine hydrochloride in methanol at room temperature gave the 1,2,4-oxadiazole derivative (**6c**) in 56% yield instead of the amide oxime **5c**.

Reactions of other amidines **4d**–**g** having an aryl group substituted in the amidine moiety required an excess amount of hydroxylamine hydrochloride to consume starting materials completely. In such cases, the reaction did not produce amide oximes (**5d**–**g**) but instead gave the oxadiazole **6d**–**g** in reactions with 5–8 equiv of hydroxylamine hydrochloride.

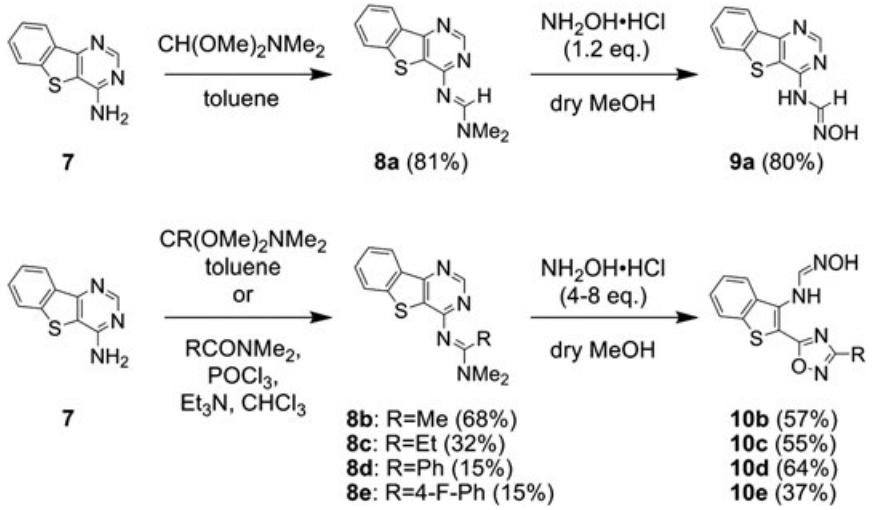
Next, we focused our attention on the ([1]benzothieno[3,2-*d*]pyrimidin-4-yl)amidines (**8**). As shown in Scheme 2, the requisite amidines **8** starting materials were synthesized by the same method as described above for amidines **4**. The reactivity of each **8** with hydroxylamine hydrochloride was same as that of **4**. In the case of **8a** (R = H), amide oxime **9a** was isolated. Other amidines **8b-e** did not afford isolable amide oxime but produced 1,2,4-oxadiazole derivatives (**10b-e**) directly by using excess hydroxylamine hydrochloride. However, conversion of **9a** to 1,2,4-oxadiazole derivative (**10a**) was not successful in contrast to the behavior of **5a**. Reaction with 14 equiv of hydroxylamine hydrochloride in refluxing methanol was necessary to consume **9a** completely, but this produced a complex mixture of compounds that could not be isolated. This was probably due to the fact that **10a** appears to be contaminated in the reaction mixture with partly hydrolyzed 5-(3-amino[1]benzothiophen-2-yl)-1,2,4-oxadiazole and/or 4-amino[1]benzothieno[3,2-*d*]pyrimidine (**7**) [7], as judged the ^{1}H NMR spectrum.

The above reactions were done for fused pyrimidines that posses electron-rich aromatics such as benzofuran and benzothiophene. It is quite interesting that formamide oximes (**5a** and **9a**) alone were stable and could be isolated. We speculated that fused electron-deficient aromatics such as pyridine could affect this amide oxime stability. To test this, the requisite formamidine (**12a**) [8] and acetamidine (**12b**) starting materials were synthesized by the same method as described above from amine **11** (Scheme 3). We examined the reaction of **12a** with 1.2 equiv of hydroxylamine hydrochloride in methanol at room temperature. We observed a possible mixture of

Scheme 1. Synthesis of **6**.



Scheme 2. Synthesis of **10**.



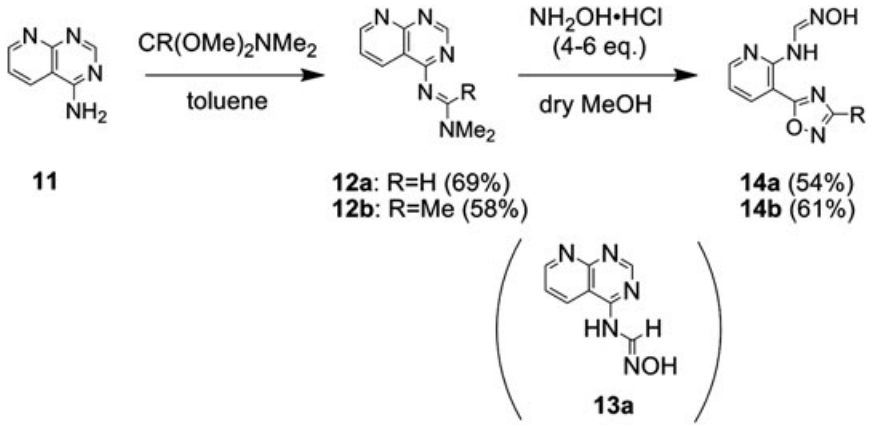
formamide oxime (**13a**) and 1,2,4-oxadiazole derivative (**14a**) as indicated by TLC analysis, but no product could be isolated. In contrast, reaction of **12a** with 6.0 equiv of hydroxylamine hydrochloride in methanol at room temperature gave the 1,2,4-oxadiazole derivative (**14a**) in 54% yield.

This result was quite different compared to the reactions of *N*-(electron rich aromatics-fused pyrimidin-4-yl)formamidines (**4a** and **8a**) described above. In those cases, the amide oximes were isolable when a hydrogen is attached to the amidine moiety. From these results, we conclude that the fused pyridine moiety of pyrido[2,3-*d*]pyrimidine affects the reactivity by facilitating the nucleophilic attack of amide oxime (**13a**) on the pyrimidine ring. This increased reactivity toward nucleophilic should promote the ring-cleavage and ring-closure reactions that give the 1,2,4-oxadiazole derivatives (**14a**). This assumption is supported by LUMO energy level comparison of **5a**, **9a**, and **13a**. The calculated LUMO energy of **5a** is −1.543 eV, and **9a** is −1.474 eV while that of **13a** is −1.929 eV [9]. Therefore, increased reactivity toward nucleophilic attack is a reasonable explanation for our inability to isolate **13a**.

Compound **12b** displayed behavior similar to **12a**. Thus, reaction of **12b** with 1.2 equiv of hydroxylamine hydrochloride in methanol at room temperature did not consume starting material completely while reaction with 4.0 equiv of hydroxylamine hydrochloride in methanol at room temperature gave the 1,2,4-oxadiazole derivative (**14b**) in 61% yield.

Many 1,2,4-oxadiazoles are known to be bioactive compounds [10]. In this regard, we found that 3,5-disubstituted 1,2,4-oxadiazoles, the structures of which are related to the products (**6**, **10**, and **14**), have considerable activity as inhibitors of arachidonic acid-induced platelet aggregation [3,11] and pentosidine formation [12]. We are currently exploring

Scheme 3. Synthesis of **14**.



the biological properties of the products prepared in this study with the goal of developing new pharmaceutical agents.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The FAB-mass and EI-mass spectra were obtained on a VG 70 mass spectrometer and *m*-nitrobenzyl alcohol was used as the matrix. The IR spectra were recorded on a Japan Spectroscopic FTIR-200 spectrophotometer with potassium bromide, and frequencies are expressed in cm^{-1}. The ^1H NMR spectra were recorded on a Varian VXR-200 instrument operating at 200 MHz with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ) and *J* values in Hz, and the signals are designated as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; br, broad; m, multiplet. Column chromatography was performed on silica gel (IR-60–63-210-W, Daiso) or aluminum oxide 90 active neutral (101077, 70–230 mesh ASTM, Merck). TLC was carried out on Kieselgel 60F254 (Merck).

***N*¹,*N*¹-Dimethyl-*N*²-([1]benzofuro[3,2-*d*]pyrimidin-4-yl) formamidine (4a).** To a solution of 4-amino[1]benzofuro [3,2-*d*]pyrimidine [5] (**3**, 1.00 g, 5.40 mmol) in dry toluene (80 mL), *N*,*N*-dimethylformamide dimethyl acetal (900 μL, 6.77 mmol) was added, and the mixture was refluxed for 2 h. After the removal of solvent *in vacuo*, the residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane, 3:2) and recrystallized from cyclohexane to give **4a** (710 mg, 55%) as colorless prisms, mp 130–133°C; ^1H NMR (deuterochloroform): δ 3.28 and 3.33 (each s, each 3H, 2 × NMe), 7.47 (td, 1H, *J* = 7.9, 1.5 Hz, H8), 7.60–7.73 (m, 2H, H6 and 7), 8.24 (d, 1H, *J* = 7.9 Hz, H9), 8.76 (s, 1H, H2), 8.98 (s, 1H, N C*H*NMe_2); FAB-ms: *m/z* 241 (MH^+). *Anal*. Calcd. for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.13; H, 5.04; N, 23.26.

***N*¹,*N*¹-Dimethyl-*N*²-([1]benzofuro[3,2-d]pyrimidin-4-yl) acetamidine (4b).** To a solution of **3** (300 mg, 1.62 mmol) in dry toluene (30 mL), *N*,*N*-dimethylacetamide dimethyl acetal (310 μL, 2.12 mmol) was added, and the mixture was refluxed for 20 h. After the removal of solvent *in vacuo*, the residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane, 2:1), and recrystallized from cyclohexane to give **4b** (187 mg, 45%) as a white powder, mp 84–86°C; ^1H NMR (deuterochloroform): δ 2.32 (s, 3H, CMe), 3.23 and 3.32 (each s, each 3H, 2 × NMe), 7.42–7.52 (m, 1H, H8), 7.62–7.68 (m, 2H, H6 and 7), 8.23 (d, 1H, *J* = 7.7 Hz, H9), 8.80 (s, 1H, H2); FAB-ms: *m/z* 255 (MH^+). *Anal*. Calcd. for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.11; H, 5.79; N, 22.03.

General procedure for the preparation of 4c–g. To a solution of **3** (500 mg, 2.70 mmol) in dry chloroform (200 mL), *N*,*N*-dimethylamide, phosphoryl chloride, and triethylamine were added sequentially, and the mixture was then refluxed. After the removal of solvent *in vacuo*, water (150 mL) was added, and the mixture was made basic with sodium carbonate and then extracted with ethyl acetate (150 mL × 3). The combined organic phase was washed with sat. brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The residue was purified by column chromatography and/or recrystallization to give **4**.

***N*¹,*N*¹-Dimethyl-*N*²-([1]benzofuro[3,2-d]pyrimidin-4-yl) propionamidine (4c).** A mixture of **3** (500 mg, 2.70 mmol), *N*,*N*-dimethylpropionamide (360 μL, 3.27 mmol), phosphoryl chloride (1.50 mL, 16.1 mmol), and triethylamine (2.20 mL, 15.8 mmol) was refluxed for 23 h. After the workup procedure described above, the brown oily residue was purified by neutral alumina column chromatography (ethyl acetate/*n*-hexane, 1:5), and the product was recrystallized from *n*-hexane to give **4c** (288 mg, 40%) as colorless needles, mp 69–72°C; ^1H NMR (deuterochloroform): δ 1.25 (t, 3H, *J* = 7.5 Hz, Me), 3.03 (q, 2H, *J* = 7.5 Hz, CH_2Me), 3.38 and 3.42 (each br s, each 3H, 2 × NMe), 7.49–7.58 (m, 1H, H8), 7.69–7.72 (m, 2H, H7 and 9), 8.35 (br d, 1H, *J* = 7.5, H9), 8.57 (s, 1H, H2); FAB-ms: *m/z* 269 (MH^+). *Anal*. Calcd. for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.88. Found: C, 67.19; H, 6.30; N, 20.64.

***N*¹,*N*¹-Dimethyl-*N*²-([1]benzofuro[3,2-d]pyrimidin-4-yl) benzamidine (4d).** A mixture of **3** (500 mg, 2.70 mmol), *N*,*N*-dimethylbenzamide (483 mg, 3.24 mmol), phosphoryl chloride (1.25 mL, 13.4 mmol), and triethylamine (3.10 mL, 22.2 mmol) was refluxed for 23 h. After the workup procedure described above, the brown oily residue was purified by neutral alumina column chromatography (ethyl acetate/*n*-hexane, 1:5), and the product was recrystallized from *n*-hexane to give **4d** (319 mg, 37%) as colorless needles, mp 137–139°C; ^1H NMR (deuterochloroform): δ 2.99 and 3.41 (each br s, each 3H, 2 × NMe), 7.17–7.33 (m, 5H, phenyl-H), 7.35–7.46 (m, 1H, H8), 7.58–7.64 (m, 2H, H6 and 7), 8.11 (d, 1H, *J* = 7.6 Hz, H9), 8.58 (s, 1H, H2); FAB-ms: *m/z* 317 (MH^+). *Anal*. Calcd. for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71. Found: C, 72.18; H, 5.45; N, 17.67.

***N*¹,*N*¹-Dimethyl-*N*²-([1]benzofuro[3,2-d]pyrimidin-4-yl)-4-chlorobenzamidine (4e).** A mixture of **3** (500 mg, 2.70 mmol), *N*,*N*-dimethyl-4-chlorobenzamide (596 mg, 3.25 mmol), phosphoryl chloride (2.00 mL, 21.5 mmol), and triethylamine (2.70 mL, 19.4 mmol) was refluxed for 28 h. After the workup procedure described above, the brown oily residue was purified by neutral alumina column chromatography (ethyl acetate/*n*-hexane,1:5) to give **4e** (275 mg, 29%) as colorless oil; ^1H NMR (deuterochloroform): δ 3.25 and 3.54 (each s, each 3H, 2 × NMe), 7.36 (d, 2H, *J* = 8.5 Hz, H3′ and 5′), 7.50–7.80 (m, 5H, H6, 7, 8, 2′ and 6′), 8.42 (d, 1H, *J* = 7.8 Hz, H9), 8.45 (s, 1H, H2); FAB-ms: *m/z* 351 (MH^+), 353 ($MH^+ + 2$). HR-FAB-ms: *m/z* 351.0981 (Calcd. for $C_{19}H_{16}ClN_4O$: 351.1013) [13].

***N*¹,*N*¹-Dimethyl-*N*²-([1]benzofuro[3,2-d]pyrimidin-4-yl)-4-fluorobenzamidine (4f).** A mixture of **3** (500 mg, 2.70 mmol), *N*,*N*-dimethyl-4-fluorobenzamide (542 mg, 3.24 mmol), phosphoryl chloride (2.00 mL, 21.5 mmol), and triethylamine (3.30 mL, 23.7 mmol) was refluxed for 28 h. After the workup procedure described above, the brown oily residue was purified by neutral alumina column chromatography (ethyl acetate/*n*-hexane, 1:5) to give **4f** (240 mg, 26%) as pale yellow oil; ^1H NMR (deuterochloroform): δ 3.14 and 3.48 (each br s, each 3H, 2 × NMe), 6.99 (t, 2H, *J* = 8.7 Hz, H3′ and 5′), 7.42–7.56 (m, 3H, H8, 2′ and 6′), 7.64–7.70 (m, 2H, H6 and 7), 8.27 (d, 1H, *J* = 8.2 Hz, H9), 8.52 (s, 1H, H2); FAB-ms: *m/z* 335 (MH^+). *Anal*. Calcd. for $C_{19}H_{15}FN_4O{\cdot}0.5H_2O$: C, 66.46; H, 4.70; N, 16.32. Found: C, 66.65; H, 4.84; N, 15.97.

***N*¹,*N*¹-Dimethyl-*N*²-([1]benzofuro[3,2-d]pyrimidin-4-yl)-4-methylbenzamidine (4g).** A mixture of **3** (500 mg, 2.70 mmol), *N*,*N*-dimethyl-4-methylbenzamide (530 mg, 3.25 mmol), phosphoryl chloride (2.00 mL, 21.5 mmol), and triethylamine (4.00 mL, 28.7 mmol) was refluxed for 31 h. After the workup

procedure described above, the brown oily residue was purified by neutral alumina column chromatography (ethyl acetate/*n*-hexane, 1:5) to give **4g** (270 mg, 30%) as pale yellow oil; ^{1}H NMR (deuterochloroform): δ 2.28 (s, 3H, CMe), 3.18 and 3.49 (each br s, each 3H, 2 × NMe), 7.10 (d, 2H, *J* = 8.0 Hz, H3′ and 5′), 7.38 (d, 2H, *J* = 8.0 Hz, H2′ and 6′), 7.44–7.52 (m, 1H, H8), 7.64–7.69 (m, 2H, H6, and 7), 8.32 (d, 1H, *J* = 7.6 Hz, H9), 8.48 (s, 1H, H2); FAB-ms: *m/z* 331 (MH^+). HR-FAB-ms: *m/z* 331.1525 (Calcd. for $C_{20}H_{19}N_4O$: 331.1559) [13].

***N*-([1]Benzofuro[3,2-d]pyrimidin-4-yl)formamide oxime (5a).** To a solution of **4a** (500 mg, 2.08 mmol) in dry methanol (10 mL), hydroxylamine hydrochloride (173 mg, 2.49 mmol) was added, and the reaction mixture was stirred at room temperature for 10 min. The precipitate was filtered and then recrystallized from dioxane to give **5a** (412 mg, 87%) as colorless needles, mp 215–217°C; IR (potassium bromide): 3040, 3130, and 3180 (NH, OH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.51–7.61 (m, 1H, H8), 7.73–7.84 (m, 1H, H7), 7.89 (d, 1H, *J* = 8.3 Hz, H6), 8.09 (d, 1H, *J* = 9.6 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.18 (dd, 1H, *J* = 7.8, 1.3 Hz, H9), 8.74 (s, 1H, H2), 9.56 (d, 1H, *J* = 9.6 Hz, deuterium oxide exchangeable, NH), 10.79 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 229 (MH^+). *Anal*. Calcd. for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53; N, 24.55. Found: C, 57.78; H, 3.77; N, 24.50.

***N*-[2-([1,2,4]oxadiazol-5-yl)[1]benzofuran-3-yl)formamide oxime (6a).** To a solution of **5a** (200 mg, 0.876 mmol) in dry methanol (100 mL) and dry dioxane (20 mL), hydroxylamine hydrochloride (610 mg, 8.78 mmol) was added, and the reaction mixture was refluxed for 3 h. After the removal of solvent *in vacuo*, the residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane, 1:4) and then recrystallized from methanol to give **6a** (72.0 mg, 34%) as colorless needles, mp 178–180°C; IR (potassium bromide): 3120, 3200, and 3300 (NH, OH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.42 (br t, 1H, *J* = 7.6 Hz, H5), 7.63 (br t, 1H, *J* = 7.6 Hz, H6), 7.77 (d, 1H, *J* = 8.3 Hz, H7), 8.01 (d, 1H, *J* = 10.5 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.25 (d, 1H, *J* = 8.3 Hz, H4), 9.22 (d, 1H, *J* = 10.5 Hz, deuterium oxide exchangeable, NH), 9.24 (s, 1H, H3′), 10.66 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 245 (MH^+). *Anal*. Calcd. for $C_{11}H_8N_4O_3$: C, 54.10; H, 3.30; N, 22.94. Found: C, 54.26; H, 3.36; N, 22.83.

***N*-[2-(3-Methyl[1,2,4]oxadiazol-5-yl)[1]benzofuran-3-yl) formamide oxime (6b).** To a solution of **4b** (100 mg, 0.393 mmol) in dry methanol (50 mL), hydroxylamine hydrochloride (165 mg, 2.37 mmol) was added, and the reaction mixture was refluxed for 2 h. After the removal of solvent *in vacuo*, water was added, and then the solution was made basic with sat. sodium bicarbonate aq. The precipitate was filtered and then recrystallized from methanol to give **6b** (51.0 mg, 50%) as colorless needles, mp 221°C (dec.); IR (potassium bromide): 3130, 3190, and 3280 (NH, OH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.45 (s, 3H, Me), 7.41 (br t, 1H, *J* = 7.6 Hz, H5), 7.62 (br t, 1H, *J* = 7.8 Hz, H6), 7.76 (d, 1H, *J* = 8.3 Hz, H7), 8.00 (d, 1H, *J* = 10.5 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.24 (d, 1H, *J* = 7.8 Hz, H4), 9.14 (d, 1H, *J* = 10.5 Hz, deuterium oxide exchangeable, NH), 10.63 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 259 (MH^+). *Anal*. Calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.60; H, 4.11; N, 21.83.

General procedure for the reaction of 4c–g with hydroxylamine hydrochloride to give 6c–g. To a solution of amidine (**4**) in dry methanol, hydroxylamine hydrochloride was added, and the reaction mixture was stirred at room temperature. The precipitate was filtered and then recrystallized to give **6**.

***N*-[2-(3-Ethyl[1,2,4]oxadiazol-5-yl)[1]benzofuran-3-yl)formamide oxime (6c).** Compound **4c** (220 mg, 0.820 mmol) was allowed to react with hydroxylamine hydrochloride (69.0 mg, 0.993 mmol) in dry methanol (5.0 mL) for 2 h. Compound **6c** (124 mg, 56%) was obtained as colorless needles from methanol, mp 220–221°C (dec.); IR (potassium bromide): 3110, 3190, and 3280 (NH and OH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.31 (t, 3H, *J* = 7.5 Hz, Me), 2.83 (q, 2H, *J* = 7.5 Hz, C*H*$_2$Me), 7.41 (br t, 1H, *J* = 7.6 Hz, H5), 7.62 (br t, 1H, *J* = 7.6 Hz, H6), 7.76 (d, 1H, *J* = 8.2 Hz, H7), 8.00 (d, 1H, *J* = 10.5 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.25 (d, 1H, *J* = 8.2 Hz, H4), 9.26 (d, 1H, *J* = 10.5 Hz, deuterium oxide exchangeable, NH), 10.62 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 273 (MH^+). *Anal*. Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.21; H, 4.40; N, 20.49.

***N*-[2-(3-Phenyl[1,2,4]oxadiazol-5-yl)[1]benzofuran-3-yl) formamide oxime (6d).** Compound **4d** (320 mg, 1.01 mmol) was allowed to react with hydroxylamine hydrochloride (420 mg, 6.04 mmol) in dry methanol (20 mL) for 2 h. Compound **6d** (253 mg, 69%) was obtained as colorless needles from dioxane, mp 219°C (dec.); IR (potassium bromide): 3100, 3200, and 3280 (NH and OH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.43 (br t, 1H, *J* = 7.8 Hz, H5), 7.56–7.72 (m, 4H, H6, 3′, 4′, and 5′), 7.79 (d, 1H, *J* = 8.3 Hz, H7), 8.07 (d, 1H, *J* = 10.7 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.08–8.17 (m, 2H, H2′and 6′), 8.29 (d, 1H, *J* = 7.8 Hz, H4), 9.53 (d, 1H, *J* = 10.7 Hz, deuterium oxide exchangeable, NH), 10.77 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 321 (MH^+). *Anal*. Calcd. for $C_{17}H_{12}N_4O_3$·0.5dioxane: C, 62.63; H, 4.43; N, 15.38. Found: C, 62.40; H, 4.61; N, 15.28.

***N*-[2-[3-(4-Chlorophenyl)[1,2,4]oxadiazol-5-yl][1]benzofuran-3-yl]formamide oxime (6e).** Compound **4e** (470 mg, 1.34 mmol) was allowed to react with hydroxylamine hydrochloride (745 mg, 10.7 mmol) in dry methanol (40 mL) for 2 h. Compound **6e** (271 mg, 57%) was obtained as colorless needles from methanol, mp 223–226°C (dec.); IR (potassium bromide): 3140, 3200, and 3320 (NH and OH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.43 (br t, 1H, *J* = 7.6 Hz, H5), 7.60–7.73 (m, 3H, H6, 3′ and 5′), 7.79 (d, 1H, *J* = 8.0 Hz, H7), 8.06 (d, 1H, *J* = 10.3 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.10 (dd, 2H, *J* = 8.6 Hz, H2′ and 6′), 8.28 (d, 1H, *J* = 7.8 Hz, H4), 9.45 (d, 1H, *J* = 10.3 Hz, deuterium oxide exchangeable, NH), 10.76 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 355 (MH^+), 357 (MH^+ + 2). *Anal*. Calcd. for $C_{17}H_{11}ClN_4O_3$: C, 57.56; H, 3.13; N, 15.79. Found: C, 57.45; H, 3.37; N, 15.82.

***N*-[2-[3-(4-Fluorophenyl)[1,2,4]oxadiazol-5-yl][1]benzofuran-3-yl]formamide oxime (6f).** Compound **4f** hemihydrate (230 mg, 0.670 mmol) was allowed to react with hydroxylamine hydrochloride (380 mg, 5.47 mmol) in dry methanol (5.0 mL) for 2 h. Compound **6f** (157 mg, 61%) was obtained as colorless needles from methanol–dioxane, mp 219–221°C (dec.); IR (potassium bromide): 3080, 3200, and 3270 (NH and OH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.37–7.52 (m, 3H, H5, 3′and 5′), 7.65 (br t, 1H, *J* = 7.2 Hz, H6), 7.79 (d, 1H, *J* = 8.2 Hz, H7), 8.07 (d,

1H, *J* = 10.5 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.11–8.21 (m, 2H, H2′ and 6′), 8.29 (d, 1H, *J* = 8.3 Hz, H4), 9.47 (d, 1H, *J* = 10.5 Hz, deuterium oxide exchangeable, NH), 10.76 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 339 (MH^+). *Anal*. Calcd. for $C_{17}H_{11}FN_4O_3 \cdot 0.5$dioxane: C, 59.69; H, 3.95; N, 14.65. Found: C, 59.67; H, 3.83; N, 14.92.

***N*-{2-[3-(4-Methylphenyl)[1,2,4]oxadiazol-5-yl][1]benzofuran-3-yl}formamide oxime (6g).** Compound **4g** (260 mg, 0.787mmol) was allowed to react with hydroxylamine hydrochloride (275 mg, 3.96 mmol) in dry methanol (25 mL) for 2 h. Compound **6g** (93.0 mg, 35%) was obtained as colorless needles from dioxane, mp 216–218°C (dec.); IR (potassium bromide): 3100, 3190, and 3300 (NH and OH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.42 (s, 3H, Me), 7.37–7.48 (m, 3H, H5, 3′and 5′), 7.65 (t, 1H, *J* = 7.3 Hz, H6), 7.79 (br d, 1H, *J* = 8.3 Hz, H7), 8.00 (d, 2H, *J* = 8.2 Hz, H2′ and 6′), 8.08 (d, 1H, *J* = 10.6 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.29 (br d, 1H, *J* = 8.0 Hz, H4), 9.56 (d, 1H, *J* = 10.6 Hz, deuterium oxide exchangeable, NH), 10.77 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 335 (MH^+). *Anal*. Calcd. for $C_{18}H_{14}N_4O_3$: C, 64.66; H, 4.22; N, 16.76. Found: C, 65.05; H, 4.09; N, 16.74.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-([1]benzothieno[3,2-*d*]pyrimidin-4-yl) formamidine (8a).** To a solution of 4-amino[1]benzothieno [3,2-*d*]pyrimidine [7] (**7**, 450 mg, 2.24 mmol) in dry toluene (40 mL), *N*,*N*-dimethylformamide dimethyl acetal (330 μL, 2.48 mmol) was added, and the mixture was refluxed for 2 h. After the removal of solvent *in vacuo*, the residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane, 3:2), and the product was recrystallized from cyclohexane to give **8a** (467 mg, 81%) as colorless prisms, mp 124–125°C; ^1H NMR (deuterochloroform): δ 3.26 and 3.28 (each s, each 3H, 2 × NMe), 7.54–7.67 (m, 2H, H7 and 8), 7.93 (br d, 1H, *J* = 7.2 Hz, H6), 8.51 (br d, 1H, *J* = 7.2 Hz, H9), 8.86 (s, 1H, H2), 9.01 (s, 1H, N C*H*NMe_2); FAB-ms: *m/z* 257 (MH^+). *Anal*. Calcd. for $C_{13}H_{12}N_4S$: C, 60.91; H, 4.72; N, 21.86. Found: C, 60.86; H, 4.91; N, 22.25.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-([1]benzothieno[3,2-*d*]pyrimidin-4-yl) acetamidine (8b).** To a solution of **7** (300 mg, 1.49 mmol) in dry toluene (30 mL), *N*,*N*-dimethylacetamide dimethyl acetal (240 μL, 1.64 mmol) was added, and the mixture was refluxed for 20 h. After the removal of solvent *in vacuo*, the residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane, 5:1) and recrystallized from cyclohexane to give **8b** (275 mg, 68%) as a white powder, mp 108–110°C; ^1H NMR (deuterochloroform): δ 2.33 (s, 3H, CMe), 3.19 (s,6H, NMe_2), 7.53–7.73 (m, 2H, H7 and 8), 8.10 (d, 1H, *J* = 7.9 Hz, H6), 8.34 (dd, 1H, *J* = 7.9, 1.0 Hz, H9), 8.80 (s, 1H, H2); FAB-ms: *m/z* 271 (MH^+). *Anal*. Calcd. for $C_{14}H_{14}N_4S$: C, 62.20; H, 5.22; N, 20.72. Found: C, 62.44; H, 4.83; N, 20.62.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-([1]benzothieno[3,2-d]pyrimidin-4-yl) propionamidine (8c).** To a solution of **7** (300 mg, 1.49 mmol) in dry chloroform (130 mL), *N*,*N*-dimethylpropionamide (200 μL, 1.82 mmol), phosphoryl chloride (1.12 mL, 12.0 mmol), and triethylamine (3.20 mL, 23.0 mmol) were added sequentially, and the mixture was then refluxed for 25 h. After the removal of solvent *in vacuo*, water (100 mL) was added, and the mixture was made basic with sodium carbonate and then extracted with ethyl acetate (100 mL × 3). The combined organic phase was washed with sat. brine, dried over anhydrous sodium sulfate, then evaporated *in vacuo*. The brown oily residue was purified by neutral alumina column chromatography (ethyl acetate/*n*-hexane, 1:5) to give **8c** (135 mg, 32%) as colorless oil; ^1H NMR (deuterochloroform): δ 1.19 (t, 3H, *J* = 7.6 Hz, Me), 2.77 (q, 2H, *J* = 7.6 Hz, CH_2Me), 3.22 (br s, 6H, NMe_2), 7.49–7.67 (m, 2H, H7 and 8), 7.90 (dd, 1H, *J* = 6.8, 1.5 Hz, H6), 8.48 (dd, 1H, *J* = 7.7, 1.6 Hz, H9), 8.89 (s, 1H, H2); FAB-ms: *m/z* 285 (MH^+). HR-FAB-ms: *m/z* 285.1127 (Calcd. for $C_{15}H_{17}N_4S$: 285.1174) [13].

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-([1]benzothieno[3,2-d]pyrimidin-4-yl) benzamidine (8d).** To a solution of **7** (500 mg, 2.48 mmol) in dry chloroform (200 mL), *N*,*N*-dimethylbenzamide (445 mg, 2.98 mmol), phosphoryl chloride (2.00 mL, 21.5 mmol), and triethylamine (3.00 mL, 21.5 mmol) were added sequentially, and the reaction was then refluxed for 27 h. After the removal of solvent *in vacuo*, water (150 mL) was added, and the mixture was made basic with sodium carbonate and then extracted with ethyl acetate (150 mL × 3). The combined organic phase was washed with sat. brine, dried over anhydrous sodium sulfate and then evaporated *in vacuo*. The brown oily residue was purified by neutral alumina column chromatography (ethyl acetate/*n*-hexane, 1:5) to give **8d** (121 mg, 15%) as colorless oil; ^1H NMR (deuterochloroform): δ 3.23 and 3.51 (each br s, each 3H, 2 × NMe), 7.33–7.45 (m, 3H, H3′, 4′, and 5′), 7.53–7.74 (m, 4H, H7, 8, 2′ and 6′), 7.97 (br d, 1H, *J* = 7.4 Hz, H6), 8.44 (s, 1H, H2), 8.58 (br d, *J* = 7.7 Hz, H9); FAB-ms: *m/z* 333 (MH^+). HR-FAB-ms: *m/z* 333.1161 (Calcd. for $C_{19}H_{17}N_4S$: 333.1174) [13].

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-([1]benzothieno[3,2-d]pyrimidin-4-yl)-4-fluorobenzamidine (8e).** To a solution of **7** (400 mg, 1.99 mmol) in dry chloroform (170 mL), *N*,*N*-dimethyl-4-fluorobenzamide (400 mg, 2.39 mmol), phosphoryl chloride (1.10 mL, 11.8 mmol), and triethylamine (2.70 mL, 19.4 mmol) were added sequentially, and the reaction was then refluxed for 24 h. After the removal of solvent *in vacuo*, water (150 mL) was added, the mixture was made basic with sodium carbonate, and then extracted with ethyl acetate (150 mL × 3). The combined organic phase was washed with sat. brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The brown oily residue was purified by neutral alumina column chromatography (ethyl acetate/*n*-hexane, 1:5) to give **8e** (104 mg, 15%) as colorless oil; ^1H NMR (deuterochloroform): δ 3.06 and 3.40 (each br s, each 3H, 2 × NMe), 6.96 (t, 2H, *J* = 8.8 Hz, H3′ and 5′), 7.36 (dd, 2H, *J* = 8.8, 5.3 Hz, H2′ and 6′), 7.50–7.68 (m, 2H, H7 and 8), 7.93 (br d, 1H, *J* = 7.5 Hz, H6), 8.48 (br d, 1H, *J* = 7.5 Hz, H9), 8.57 (s, 1H, H2); FAB-ms: *m/z* 351 (MH^+). HR-FAB-ms: *m/z* 351.1042 (Calcd. for $C_{19}H_{16}FN_4S$: 351.1080) [13].

***N*-([1]Benzothieno[3,2-d]pyrimidin-4-yl)formamide oxime (9a).** To a solution of **8a** (300 mg, 1.17 mmol) in dry methanol (30 mL), hydroxylamine hydrochloride (97.0 mg, 1.40 mmol) was added, and the reaction mixture was stirred at room temperature for 10 min. The precipitate was filtered and then recrystallized from methanol to give **9a** (228 mg, 80%) as colorless needles, mp 205–211°C; IR (potassium bromide): 3000, 3050, and 3130 (NH and OH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.57–7.81 (m, 2H, H7 and 8), 8.13 (d, 1H, *J* = 9.2 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.20 (d, 1H, *J* = 8.0 Hz, H6), 8.40 (br d, 1H, *J* = 7.5 Hz, H9), 8.84 (s, 1H, H2), 9.96 (d, 1H, *J* = 9.2 Hz, deuterium oxide exchangeable, NH), 10.78 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 245 (MH^+). *Anal*.

Calcd. for $C_{11}H_8N_4OS$: C, 54.09; H, 3.30; N, 22.94. Found: C, 53.90; H, 3.54; N, 23.22.

***N*-[2-(3-Methyl[1,2,4]oxadiazol-5-yl)[1]benzothiophen-3-yl] formamide oxime (10b).** To a solution of **8b** (100 mg, 0.370mmol) in dry methanol (50 mL), hydroxylamine hydrochloride (154 mg, 2.22 mmol) was added, and the reaction mixture was refluxed for 2 h. Water was added, and the mixture was then made basic with sat. sodium bicarbonate aq. The precipitate was filtered, washed with water, and then recrystallized from methanol to give **10b** (58.0 mg, 57%) as colorless needles, mp 220–222°C; IR (potassium bromide): 3050, 3110, and 3200 (NH and OH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.44 (s, 3H, Me), 7.53 (br t, 1H, *J* = 7.7 Hz, H5), 7.63 (br t, 1H, *J* = 7.7 Hz, H6), 7.84 (d, 1H, *J* = 9.8 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.11 (br d, 1H, *J* = 7.9 Hz, H7), 8.20 (br d, 1H, *J* = 7.9 Hz, H4), 9.72 (d, 1H, *J* = 9.8 Hz, deuterium oxide exchangeable, NH), 10.55 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 275 (MH^+). *Anal*. Calcd. for $C_{12}H_{10}N_4O_2S$: C, 52.54; H, 3.67; N, 20.43. Found: C, 52.72; H, 3.65; N, 20.07.

General procedure for the reaction of 8c–e with hydroxylamine hydrochloride to give 10c–e. To a solution of amidine (**8**) in dry methanol, hydroxylamine hydrochloride was added, and the reaction mixture was stirred at room temperature. The precipitate was filtered and then recrystallized to give **10**.

***N*-[2-(3-Ethyl[1,2,4]oxadiazol-5-yl)[1]benzothiophen-3-yl] formamide oxime (10c).** Compound **8c** (200 mg, 0.704 mmol) was allowed to react with hydroxylamine hydrochloride (391 mg, 5.63 mmol) in dry methanol (5.0 mL) for 2 h. Compound **10c** (112 mg, 55%) was obtained as colorless needles from methanol/dioxane, mp 220–221°C (dec.); IR (potassium bromide): 3050, 3120, and 3200 (NH and OH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.32 (t, 3H, *J* = 7.5 Hz, Me), 2.81 (q, 2H, *J* = 7.5 Hz, CH_2Me), 7.48–7.69 (m, 2H, H5 and 6), 7.89 (d, 1H, *J* = 10.3 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.10 (d, 1H, *J* = 7.7 Hz, H7), 8.22 (d, 1H, *J* = 8.1 Hz, H4), 9.50 (d, 1H, *J* = 10.3 Hz, deuterium oxide exchangeable, NH), 10.58 (1H, s, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 289 (MH^+). *Anal*. Calcd. for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.20; N, 19.43. Found: C, 53.76; H, 3.97; N, 19.26.

***N*-[2-(3-Phenyl[1,2,4]oxadiazol-5-yl)[1]benzothiophen-3-yl] formamide oxime (10d).** Compound **8d** (110 mg, 0.331 mmol) was allowed to react with hydroxylamine hydrochloride (94.0 mg, 1.35 mmol) in dry methanol (5.0 mL) for 2 h. Compound **10d** (73.0 mg, 64%) was obtained as colorless needles from methanol, mp 207–209°C (dec.); IR (potassium bromide): 3040, 3130, and 3220 (NH and OH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.20–7.35 (m, 2H, H5 and 6), 7.55–7.73 (m, 4H, H7, 3′, 4′, and 5′), 8.03 (d, 1H, *J* = 10.1 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.15 (m, 2H, H2′ and 6′), 8.29 (br d, 1H, *J* = 7.8 Hz, H4), 10.34 (br d, 1H, *J* = 10.1 Hz, deuterium oxide exchangeable, NH), 10.79 (s, 1H, OH); FAB-ms: *m/z* 337 (MH^+). *Anal*. Calcd. for $C_{17}H_{12}N_4O_2S{\cdot}0.5H_2O$: C, 59.12; H, 3.79; N, 16.22. Found: C, 59.30; H, 3.67; N, 15.96.

***N*-{2-[3-(4-Fluorophenyl)[1,2,4]oxadiazol-5-yl][1]benzothiophen-3-yl}formamide oxime (10e).** Compound **8e** (80.0 mg, 0.228 mmol) was allowed to react with hydroxylamine hydrochloride (67.0 mg, 0.964 mmol) in dry methanol (2.0mL) for 2 h. Compound **10e** (30.0 mg, 37%) was obtained as colorless needles from dioxane, mp 219–222°C (dec.); IR (potassium bromide): 3060, 3130, and 3220 (NH and OH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.45 (t, 2H, *J* = 8.8 Hz, H3′ and 5′), 7.56–7.69 (m, 2H, H5 and 6), 8.02 (d, 1H, *J* = 9.8 Hz, changed to singlet with addition of deuterium oxide, NC*H* NOH), 8.14 (d, 1H, *J* = 7.8 Hz, H7), 8.11–8.24 (m, 2H, H2′ and 6′), 8.28 (br d, 1H, *J* = 7.4 Hz, H4), 10.30 (d, 1H, *J* = 9.8 Hz, deuterium oxide exchangeable, NH), 10.79 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 355 (MH^+). *Anal*. Calcd. for $C_{17}H_{11}FN_4O_2S$: C, 57.62; H, 3.13; N, 15.81. Found: C, 57.31; H, 3.37; N, 15.79.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[2,3-*d*]pyrimidin-4-yl)formamidine (12a).** To a suspension of 4-aminopyrido[2,3-*d*]pyrimidine [8] (**11**, 300 mg, 2.05 mmol) in dry toluene (30 mL), *N*,*N*-dimethylformamide dimethyl acetal (340 mg, 2.85 mmol) was added, and the mixture was refluxed for 3 h. The solution was evaporated *in vacuo*, and the residue was recrystallized from benzene to give **12a** (286 mg, 69%) as a white granule, mp 162–164°C (lit. [8] 164–166°C); ^1H NMR (DMSO-d_6): δ 3.24 (s, 3H, NMe), 3.27 (s, 3H, NMe), 7.58 (dd, 1H, *J* = 8.2, 4.4 Hz, H6), 8.82 (s, 1H, N C*H*NMe$_2$), 8.83 (dd, 1H, *J* = 8.2, 2.0 Hz, H5), 8.98 (s, 1H, H-2), 9.09 (dd, 1H, *J* = 4.4, 2.0 Hz, H7); FAB-ms: *m/z* 202 (MH^+).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[2,3-*d*]pyrimidin-4-yl)acetamidine (12b).** To a suspension of **11** (200 mg, 1.37 mmol) in dry toluene (20 mL), *N*,*N*-dimethylacetamide dimethyl acetal (310 mg, 2.33 mmol) was added, and the mixture was refluxed for 3 h. After the solution was evaporated *in vacuo*, the residue was recrystallized from cyclohexane/benzene to give **12b** (170 mg, 58%) as a brown powder, mp 149–151°C; ^1H NMR (DMSO-d_6): δ 2.31 (s, 3H, C Me), 3.21 (s, 6H, NMe$_2$), 7.53 (dd, 1H, *J* = 8.0, 4.4 Hz, H6), 8.61 (dd, 1H, *J* = 8.0, 2.0 Hz, H5), 8.80 (s, 1H, H2), 9.13 (dd, 1H, *J* = 4.4, 2.0 Hz, H7); FAB-ms: *m/z* 216 (MH^+). *Anal*. Calcd. for $C_{11}H_{13}N_5$: C, 61.38; H, 6.09; N, 32.54. Found: C, 61.30; H, 6.00; N, 32.56.

***N*-[3-([1,2,4]Oxadiazol-5-yl)-2-pyridyl]formamide oxime (14a).** Compound **12a** (100 mg, 0.497 mmol) was allowed to react with hydroxylamine hydrochloride (210 mg, 3.02 mmol) in dry methanol (10 mL) for 4 h. Compound **14a** (54.0 mg, 54%) was obtained as a colorless feather, mp 170–172°C (dec.); IR (potassium bromide): 3080, 3160, and 3230 (NH and OH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.16 (dd, 1H, *J* = 7.8, 4.8 Hz, H5), 8.14 (d, 1H, *J* = 9.4 Hz, changed to singlet after addition of deuterium oxide, NC*H* NOH), 8.31 (dd, 1H, *J* = 4.8, 2.0 Hz, H6), 8.49 (dd, 1H, *J* = 7.8, 2.0 Hz, H4), 9.36 (s, 1H, H3′), 10.67 (s, 1H, deuterium oxide exchangeable, OH), 10.80 (d, 1H, *J* = 9.4 Hz, deuterium oxide exchangeable, NH); FAB-ms: *m/z* 206 (MH^+). *Anal*. Calcd. for $C_8H_7N_5O_2$: C, 46.83; H, 3.44; N, 34.13. Found: C, 46.61; H, 3.81; N, 34.22.

***N*-[3-(3-Methyl[1,2,4]oxadiazol-5-yl)-2-pyridyl]formamide oxime (14b).** Compound **12b** (100 mg, 0.464 mmol) was allowed to react with hydroxylamine hydrochloride (129 mg, 1.86 mmol) in dry methanol (10 mL) for 3 h. Compound **14b** (62.0 mg, 61%) was obtained as a yellow grain crystal, mp 228–230°C; IR (potassium bromide): 3040, 3140, and 3270 (NH and OH) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.47 (s, 3H, Me), 7.14 (dd, 1H, *J* = 7.8, 4.8 Hz, H5), 8.13 (d, 1H, *J* = 9.3 Hz, changed to singlet after addition of deuterium oxide, NC*H* NOH), 8.43 (dd, 1H, *J* = 7.8, 1.7 Hz, H4), 8.51 (dd, 1H, *J* = 4.8, 1.7 Hz, H6), 10.63 (s, 1H, deuterium oxide exchangeable, OH), 10.77 (d, 1H, *J* = 9.3 Hz, deuterium oxide exchangeable, NH); FAB-ms: *m/z* 220 (MH^+). *Anal*. Calcd. for

$C_9H_9N_5O_2$: C, 49.31; H, 4.14; N, 31.95. Found: C, 49.42; H, 4.46; N, 32.19.

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