Polycyclic *N*-Heterocyclic Compounds. Part 84: Reaction of *N*-(pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-yl)amidines or *N*-(pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidin-4-yl)amidines with Hydroxylamine Hydrochloride

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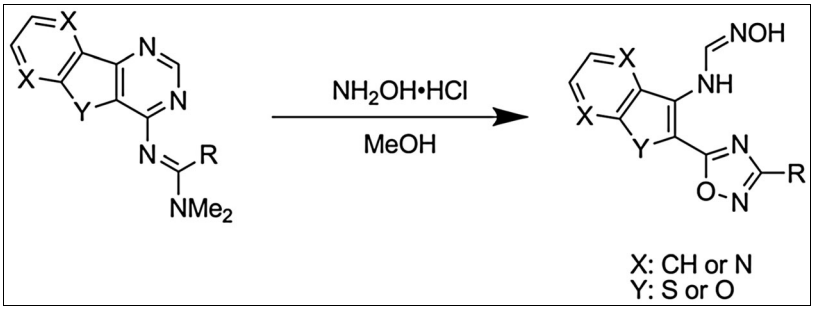

The reactions of nine *N*-(pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-yl)amidines (**3**) with hydroxylamine hydrochloride produced new cyclization products. These were formed via ring cleavage of the pyrimidine component followed by a 1,2,4-oxadiazole-forming ring closure to give *N*-[2-([1,2,4]oxadiazol-5-yl)thieno[2,3-*b*]pyridin-3-yl]formamide oximes (**11**). Reaction of six *N*-(pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidin-4-yl) amidines (**12**) with hydroxylamine hydrochloride gave similar results. Effects of the newly synthesized compounds on pentosidine formation were also evaluated.

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INTRODUCTION

Addition of a nucleophile to an electron poor heterocycle can initiate a ring opening/ring closure-like rearrangement that 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 [2–4]. Recently, we have reported that reaction of *N*-(quinazolin-4-yl)amidines (**2**) with hydroxylamine hydrochloride leads to a pyrimidine ring opening reaction followed by formation of the 1,2,4-oxadiazole ring to produce *N*-[2-([1,2,4]oxadiazol-5-yl)phenyl]formamide oximes (**1**) (Figure 1) [5,6]. We also reported that some of the products (**1**) showed significant inhibitory effects on the formation of pentosidine, which is one of the representatives of advanced glycation end products [5,6]. Recognizing that other fused aromatic derivatives in addition to quinazolines should be susceptible to this transformation [7], we decided to explore reactions of hydroxylamine hydrochloride with pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines and pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidines as an approach to potential pharmaceutics. These are aza-analogs of [1]benzofuro[3,2-*d*]pyrimidines and [1]benzothieno[3,2-*d*]pyrimidines [7], products of rearrangement from which also showed some inhibitory effects on pentosidine formation. Here, we report in detail the results of our present investigation.

RESULTS AND DISCUSSIONS

First, we examined *N*-(pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4-yl)amidines (**3**). As shown in Scheme 1, the requisite amidine **3** starting materials were synthesized from 2-chloropyridin-3-carbonitrile (**4**) by several steps. First, the chlorine substituent was converted to a sulfanyl group by nucleophilic displacement to give (**5**), which was then alkylated by bromoacetonirile to give 2-(cyanomethylsulfanyl)pyridin-3-carbonitrile (**6**). Base-induced cyclization afforded 3-aminothieno[2,3-*b*]pyridin-2-carbonitrile (**7**) [8], which was converted to *N*,*N*-dimethylformamidine derivative (**8**) by reaction with *N*,*N*-dimethylformamide dimethyl acetal. Cyclization of **8** with ammonium acetate gave 4-aminopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**9**) [9]. Amidine **3a** was prepared by the reaction of **9** with commercially available *N*,*N*-dimethylacetamide dimethyl acetal in refluxing toluene. Other amidines **3b–j** were produced by the reaction of compound **9** with the Vilsmeier reagent prepared from the corresponding *N*,*N*-dimethylamide and phosphoryl chloride. Because **3b–j** were subjects to decomposition during purification by column chromatography, they were used as crude amidines for the next reaction.

First, we carried out the reaction of **3a** with 1.2 equiv of hydroxylamine hydrochloride in methanol at room

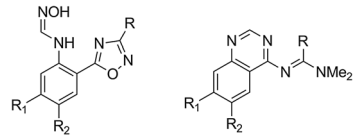
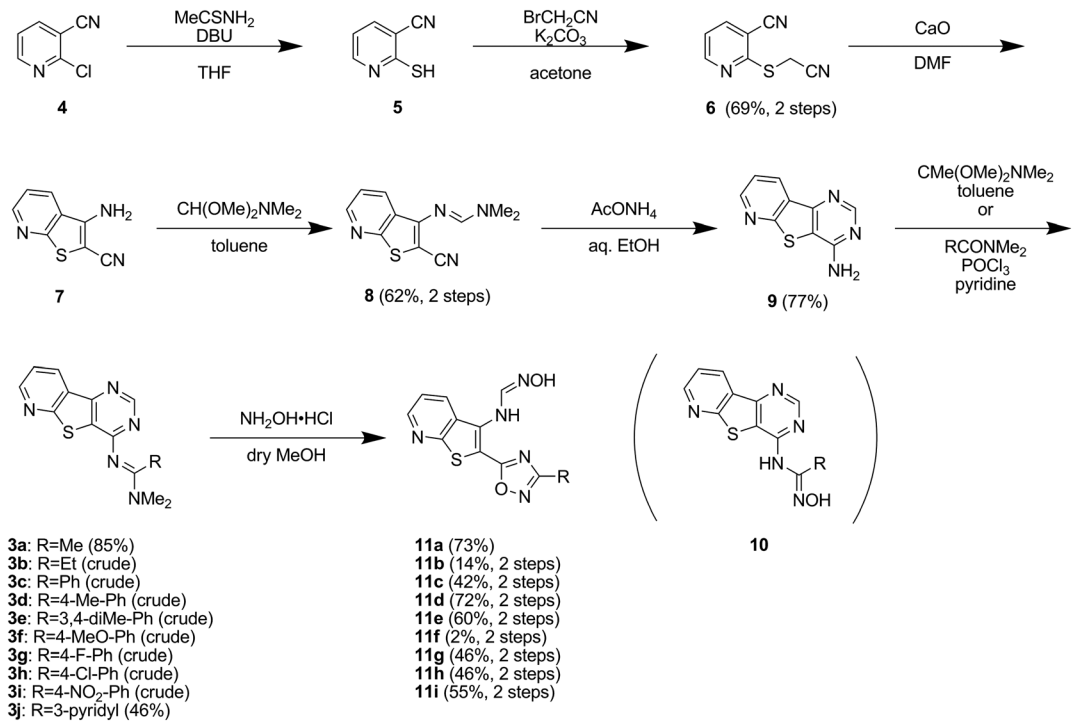


Figure 1. Substrates (2) and their rearranged products (1).

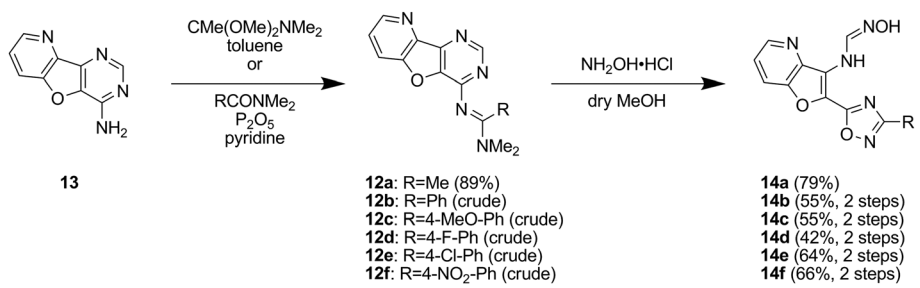
temperature. We observed incomplete consumption of **3a** on TLC. However, reaction of **3a** with 4.0 equiv of hydroxylamine hydrochloride in methanol led to complete consumption of **3a** and gave the 1,2,4-oxadiazole derivative (**11a**) in 73% yield. In the ^{1}H NMR spectrum of **11a**, a characteristic formamide oxime one-proton doublet ($J = 10.2$ Hz) appeared at 7.88 ppm coupled with an adjacent NH proton ($J = 10.2$ 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 8.83 ppm (pyrimidine ring proton) present in **3a** was absent in the product. These NMR data indicate that pyrimidine ring cleavage, and 1,2,4-oxadiazole ring formation occurred during reaction of **3a** with hydroxylamine hydrochloride [10]. Other amidines **3b–i** having ethyl group or aryl group substituted in the amidine moiety needed reflux conditions with an excess amount of hydroxylamine hydrochloride to consume starting materials completely. In every case, we did not observe **10**, which one can assume is the probable intermediate in the conversion of **3** to **11** [5,6]. In contrast, reaction of **3j** under the same conditions did not give **11j** but led to a decomposition product **9**, which was observed in the reaction mixture by TLC analysis.

Next, we focused our attention on *N*-(pyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidin-4-yl)amidines (**12**). As shown in Scheme 2, the requisite amidine starting materials **12** were prepared from 4-aminopyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidine (**13**) [11] by

Scheme 1. Synthesis of **11**.



Scheme 2. Synthesis of **14**.



the same method as described earlier for amidines **3** except that phosphorus pentoxide instead of phosphoryl chloride was employed. The reactivity of each **12** with hydroxylamine hydrochloride was the same as that of **3**. Amidines **12a–f** did not afford isolable amide oximes such as **10** but produced 1,2,4-oxadiazole derivatives (**14a–f**) directly by using excess hydroxylamine hydrochloride.

Finally, preliminary evaluation of the products on pentosidine formation was evaluated *in vitro*. *N*-[4-Nitro-2-([1,2,4] oxadiazol-5-yl)phenyl]formamide oxime (**1**, R=H, R_1=H, R_2=NO_2) [5,6] was used as a positive control. We found that **11a** and **11h** had some inhibitory activity (33.8% and 36.7%, respectively) against pentosidine formation; however, their potency was lower than **1** (R=H, R_1=H, R_2=NO_2) (94.5%). We are currently exploring their structure–activity relationships for further elucidation of anti-advanced glycation end products compounds.

EXPERIMENTAL

All melting points were determined on a Yanagimoto (Kyoto, Japan) micro-melting point apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto (Kyoto, Japan) MT-5 CHN Corder elemental analyzer. The ESI-mass spectra were obtained on a Waters (Milford, MA, USA) ZMD mass spectrometer. FAB mass spectra were obtained on a Micromass (Manchester, UK) Autspec-OA-Tof spectrometer and *m*-nitrobenzyl alcohol was used as the matrix. The IR spectra were recorded on a Japan Spectroscopic (Hachioji, Japan) FT/IR-200 spectrophotometer with potassium bromide and frequencies are expressed in cm^{-1}. The ^1H NMR spectra were recorded on a Varian (Palo Alto, CA, USA) VXR-200 instrument operating at 200 MHz or VXR-300 instrument operating at 300 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; and m, multiplet. Column chromatography was performed on silica gel (IR-60-63-210-W, Daiso, Osaka, Japan). TLC was carried out on Kieselgel 60 F254 (Merck, Darmstadt, Germany).

2-(Cyanomethylsulfanyl)pyridin-3-carbonitrile (6). To a solution of 2-chloropyridin-3-carbonitrile (**4**, 10.0 g, 72.1 mmol) in dry THF (100 mL) were added thioacetamide (16.3 g, 217 mmol) and DBU (32.4 mL, 217 mmol), and the mixture was then refluxed for 5 h. After evaporation *in vacuo*, ice water was added, and the solution was made acidic (pH 1) by addition of 10% hydrochloric acid. The precipitated solid was filtrated to yield 2-sulfanylpyridin-3-carbonitrile (**5**) as a yellow solid (9.70 g). This intermediate was used without further purification.

To a suspension of this crude **5** in dry acetone (150 mL) were added bromoacetonitrile (6.0 mL, 86.1 mmol) and potassium carbonate (20.0 g, 145 mmol), the reaction mixture was then stirred at room temperature for 1 h. After filtration to remove insoluble inorganic material followed by evaporation *in vacuo*, the residue was extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The residue was purified by column chromatography (ethyl acetate/*n*-hexane, 1:10) to give a white solid, which was recrystallized from ethyl acetate-*n*-hexane to give **6** (8.70 g, 69% (2 steps)) as colorless needles, mp 134–135 °C; IR (potassium bromide) cm^{-1}: 2224, 2249 (CN); ^1H NMR (200 MHz, DMSO-d_6): δ 4.39 (s, 2H, CH_2), 7.46 (dd, 1H, *J* = 7.8, 5.0 Hz, H5), 8.34 (dd, 1H, *J* = 7.8, 1.8 Hz, H4), 8.82 (dd, 1H, *J* = 5.0, 1.8 Hz, H6); FAB-ms *m/z*: 176 (MH^+). *Anal*. Calcd. for $C_8H_5N_3S$: C, 54.84; H, 2.88; N, 23.98. Found: C, 54.99; H, 3.11; N, 24.36.

N^1,N^1-Dimethyl-N^2-(2-cyanothieno[2,3-b]pyridin-3-yl) formamidine (8). To a solution of **6** (100 mg, 0.571 mmol) in dry DMF (5.0 mL) was added calcium oxide (64.4 mg, 1.15 mmol), and the mixture was stirred at 80 °C for 1 h. After filtration to remove insoluble inorganic material followed by evaporation *in vacuo*, the residue was partially purified by recrystallization from ethyl acetate-*n*-hexane to give 3-aminothieno[2,3-*b*]pyridin-2-carbonitrile (**7**) [8] (88.6 mg, 89%) as yellow feathers, mp 218–219 °C; This compound **7** was used without further purification. IR (potassium bromide) cm^{-1}: 2199 (CN), 3211, 3344, 3398 (NH); ^1H NMR (200 MHz, DMSO-d_6): δ 7.35 (2H, br s, deuterium oxide exchangeable, NH_2), 7.53 (dd, 1H, *J* = 6.2, 4.4 Hz, H5), 8.51 (dd, 1H, *J* = 6.2, 1.6 Hz, H4), 8.71 (dd, 1H, *J* = 4.4, 1.6 Hz, H6).

To a suspension of **7** (100 mg, 0.571 mmol) in dry toluene (5.0 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (90.0 μL, 0.677 mmol), and the mixture was refluxed for 2 h. After removal of solvent *in vacuo*, the residue was recrystallized from ethyl acetate-*n*-hexane to give **8** (92.6 mg, 62% (2 steps)) as yellow feathers, mp 101–102 °C; IR (potassium bromide) cm^{-1}: 2198 (CN); ^1H NMR (300 MHz, deuterochloroform): δ 3.18 and 3.22 (each s, each 3H, NMe_2), 7.35 (dd, 1H, *J* = 8.1, 4.8 Hz, H5), 8.07 (s, 1H, NCH), 8.24 (dd, 1H, *J* = 8.1, 1.8 Hz, H4), 8.68 (dd, 1H, *J* = 4.8, 1.8 Hz, H6); ESI-ms *m/z*: 231 (MH^+). *Anal*. Calcd. for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38; N, 24.33. Found: C, 57.27; H, 4.77; N, 24.31.

4-Aminopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (9) [9]. To a solution of **8** (1.00 g, 4.34 mmol) in ethanol (15 mL) were added ammonium acetate (3.70 g, 47.8 mmol) and water (1.0 mL), and the mixture was then refluxed for 3 h. After cooling to room temperature, it was made basic with sat. sodium bicarbonate aq. The precipitate was filtered, washed with water, and then recrystallized from DMF to give **9** (676.2 mg, 77%) as colorless granules, mp > 300 °C; IR (potassium bromide) cm^{-1}: 3124, 3294, 3360 (NH); ^1H NMR (200 MHz, DMSO-d_6): δ 7.63 (dd, 1H, *J* = 8.0, 4.6 Hz, H8), 7.67 (br s, 2H, deuterium oxide exchangeable, NH_2), 8.56 (s, 1H, H2), 8.63 (dd, 1H, *J* = 8.0, 1.8 Hz, H9), 8.83 (dd, 1H, *J* = 4.6, 1.8 Hz, H7); ESI-ms *m/z*: 203 (MH^+). *Anal*. Calcd. for $C_9H_6N_4S$: C, 53.45; H, 2.99; N, 27.70. Found: C, 53.26; H, 3.18; N, 28.02.

N^1,N^1-Dimethyl-N^2-(pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-yl)acetamidine (3a). Compound **9** (200 mg, 0.989 mmol) and *N*,*N*-dimethylacetamide dimethyl acetal (220 μL, 1.50 mmol) in dry toluene (5.0 mL) was refluxed for 1.5 h. After removal of solvent, the residue was recrystallized from ethyl acetate-*n*-hexane to give **3a** (228.1 mg, 85%) as colorless needles, mp 127–128 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 2.36 (s, 3H, CMe), 3.20 (s, 6H, NMe_2), 7.64 (dd, 1H, *J* = 7.8, 4.5 Hz, H8), 8.66 (dd, 1H, *J* = 7.8, 1.8 Hz, H9), 8.82 (dd, 1H, *J* = 4.5, 1.8 Hz, H7), 8.83 (s, 1H, H2); FAB-ms *m/z*: 272 (MH^+). *Anal*. Calcd. for $C_{13}H_{13}N_5S$: C, 57.54; H, 4.83, N, 25.81. Found: C, 57.20; H, 4.88; N, 25.95.

N^1,N^1-Dimethyl-N^2-(pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-yl)propionamidine (3b). To a solution of **9** (300 mg, 1.48 mmol) in dry pyridine (40 mL) were added *N*,*N*-dimethylpropionamide (0.200 mL, 1.82 mmol) and phosphoryl chloride (2.10 g, 13.7 mmol), and the mixture was then refluxed for 5 h. After

removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous sodium sulfate and then evaporated *in vacuo*. The brown oily residue (crude **3b**) was used without further purification. ^{1}H NMR (300 MHz, deuterochloroform): δ 1.22 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.84 (q, 2H, J = 7.5 Hz, CH_2CH_3), 3.26 (s, 6H, NMe_2), 7.48 (dd, 1H, J = 8.1, 4.5 Hz, H8), 8.72 (br d, 1H, J = 8.1 Hz, H9), 8.78 (dd, 1H, J = 4.5, 1.8 Hz, H7), 8.83 (s, 1H, H2).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-yl)benzamidine (3c).** To a solution of **9** (300 mg, 1.48 mmol) in dry pyridine (40 mL) were added *N*,*N*-dimethylbenzamide (265.6 mg, 1.78 mmol) and phosphoryl chloride (2.10 g, 13.7 mmol), and the mixture was then refluxed for 18 h. After removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The brown oily residue (crude **3c**) was used without further purification. ^{1}H NMR (300 MHz, deuterochloroform): δ 2.99 and 3.37 (each br s, each 3H, NMe_2), 7.22–7.26 (m, 5H, Ph), 7.44 (dd, 1H, J = 8.1, 4.8 Hz, H8), 8.58 (dd, 1H, J = 8.1, 1.8 Hz, H9), 8.59 (s, 1H, H2), 8.76 (dd, 1H, J = 4.8, 1.8 Hz, H7).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-yl)-4-methylbenzamidine (3d).** To a solution of **9** (300 mg, 1.48 mmol) in dry pyridine (40 mL) were added *N*,*N*-dimethyl-4-methylbenzamide [12] (290.5 mg, 1.78 mmol) and phosphoryl chloride (2.10 g, 13.7 mmol), and the mixture was then refluxed for 12 h. After removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The brown oily residue (crude **3d**) was used without further purification. ^{1}H NMR (300 MHz, deuterochloroform): δ 2.26 (s, 3H, CMe), 2.99 and 3.35 (each br s, each 3H, NMe_2), 7.02 (br d, 2H, J = 7.8 Hz, H3′ and 5′), 7.13 (br d, 2H, J = 7.8 Hz, H2′ and 6′), 7.44 (dd, 1H, J = 7.8, 4.8 Hz, H8), 8.59 (dd, 1H, J = 7.8, 1.5 Hz, H9), 8.61 (s, 1H, H2), 8.76 (dd, 1H, J = 4.8, 1.5 Hz, H7).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-yl)-3,4-dimethylbenzamidine (3e).** To a solution of **9** (300 mg, 1.48 mmol) in dry pyridine (40 mL) were added *N*,*N*-dimethyl-3,4-dimethylbenzamide [13] (315.5 mg, 1.78 mmol) and phosphoryl chloride (2.10 g, 13.7 mmol), and the mixture was refluxed for 20 h. After removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The brown oily residue (crude **3e**) was used without further purification. ^{1}H NMR (300 MHz, deuterochloroform): δ 2.14 and 2.16 (each s, each 3H, 2 × CMe), 3.01 and 3.35 (each br s, each 3H, NMe_2), 7.05 (br s, 1H, H5′), 7.12 (br s, 1H, H6′), 7.25 (br s, 1H, H2′), 7.44 (dd, 1H, J = 8.1, 4.5 Hz, H8), 8.60 (s, 1H, H2), 8.62 (br d, 1H, J = 8.1 Hz, H9), 8.76 (dd, 1H, J = 4.5, 1.8 Hz, H7).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-yl)-4-methoxybenzamidine (3f).** To a solution of **9** (200 mg, 0.989 mmol) in dry pyridine (30 mL) were added *N*,*N*-dimethyl-4-methoxybenzamide [14] (212.7 mg, 1.19 mmol) and phosphoryl chloride (1.40 g, 9.13 mmol), and the mixture was refluxed for 16.5 h. After removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The brown oily residue (crude **3f**) was used without further purification. ^{1}H NMR (300 MHz, deuterochloroform): δ 3.09 and 3.38 (each br s, each 3H, NMe_2), 3.75 (s, 3H, OMe), 6.89 (dd, 2H, J = 9.0, 1.2 Hz, H3′ and 5′), 7.33 (br d, 2H, J = 9.0 Hz, H2′ and 6′), 7.47 (dd, 1H, J = 7.8, 4.5 Hz, H8), 8.57 (s, 1H, H2), 8.68 (br d, 1H, J = 7.8 Hz, H9), 8.78 (dd, 1H, J = 4.5, 1.5 Hz, H7).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-yl)-4-fluorobenzamidine (3g).** To a solution of **9** (200 mg, 0.989 mmol) in dry pyridine (30 mL) were added *N*,*N*-dimethyl-4-fluorobenzamide [15] (198.4 mg, 1.19 mmol) and phosphoryl chloride (1.40 g, 9.13 mmol), and the mixture was refluxed for 28 h. After removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The brown oily residue (crude **3g**) was used without further purification. ^{1}H NMR (300 MHz, deuterochloroform): δ 2.99 and 3.36 (each br s, each 3H, NMe_2), 6.93 (t, 2H, J = 9.0 Hz, H3′ and 5′), 7.24–7.26 (m, 2H, H2′ and 6′), 7.45 (dd, 1H, J = 8.4, 4.8 Hz, H8), 8.60 (dd, 1H, J = 8.4, 1.8 Hz, H9), 8.61 (s, 1H, H2), 8.77 (dd, 1H, J = 4.8, 1.8 Hz, H7).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-yl)-4-chlorobenzamidine (3h).** To a solution of **9** (300 mg, 1.48 mmol) in dry pyridine (40 mL) were added *N*,*N*-dimethyl-4-chlorobenzamide [14] (326.9 mg, 1.78 mmol) and phosphoryl chloride (2.10 g, 13.7 mmol), and the mixture was refluxed for 14 h. After removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The brown oily residue (crude **3h**) was used without further purification. ^{1}H NMR (300 MHz, deuterochloroform): δ 2.98 and 3.36 (each br s, each 3H, NMe_2), 7.20–7.25 (m, 4H, H2′, 3′, 5′, and 6′), 7.46 (dd, 1H, J = 8.1, 4.8 Hz, H8), 8.60 (dd, 1H, J = 8.1, 1.8 Hz, H9), 8.61 (s, 1H, H2), 8.77 (dd, 1H, J = 4.8, 1.8 Hz, H7).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-yl)-4-nitrobenzamidine (3i).** To a solution of **9** (300 mg, 1.48 mmol) in dry pyridine (40 mL) were added *N*,*N*-dimethyl-4-nitrobenzamide [14] (345.7 mg, 1.78 mmol) and phosphoryl chloride (2.10 g, 13.7 mmol), and the mixture was refluxed for 18 h. After removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The brown oily residue (crude **3i**) was used without further purification. ^{1}H NMR (300 MHz, deuterochloroform): δ 2.96 and 3.41 (each br s, each 3H, NMe_2), 7.44–7.48 (m, 1H, H8), 7.58 (dd, 2H, J = 9.0, 2.1 Hz, H2′ and 6′), 8.27 (dd, 2H, J = 9.0, 2.1 Hz, H3′ and 5′), 8.56 (s, 1H, H2), 8.60 (dd, 1H, J = 7.8, 1.8 Hz, H9), 8.77 (dd, 1H, J = 4.8, 1.8 Hz, H7).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-yl)nicotinamidine (3j).** To a solution of **9** (500 mg, 2.47 mmol) in dry pyridine (60 mL) were added *N*,*N*-dimethylnicotinamide (556.9 mg, 3.71 mmol) and phosphoryl chloride (3.50 g, 22.8 mmol), and the mixture was refluxed for 6.5 h. After removal

of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The residue was recrystallized from ethanol to give **3j** (383.8 mg, 46%) as yellow granules, mp 200–201 °C; ^{1}H NMR (300 MHz, deuterochloroform): δ 3.02 and 3.42 (each br s, each 3H, NMe_2), 7.22 (ddd, 1H, *J* = 7.8, 4.8, 0.6 Hz, H5′), 7.46 (dd, 1H, *J* = 7.8, 4.5 Hz, H8), 7.63 (br d, 1H, *J* = 7.8 Hz, H4′), 8.51–8.55 (m, 2H, H2′ and 6′), 8.56 (s, 1H, H2), 8.62 (dd, 1H, *J* = 7.8, 1.8 Hz, H9), 8.78 (dd, 1H, *J* = 4.5, 1.8 Hz, H7); ESI-ms *m/z*: 335 (MH^+). *Anal*. Calcd. for $C_{17}H_{14}N_6S$: C, 61.06; H, 4.22; N, 25.13. Found: C, 61.02; H, 4.49; N, 25.29.

General procedure for the reaction of 3 with hydroxylamine hydrochloride to give 11. To a solution of amidine (**3**) in dry methanol was added hydroxylamine hydrochloride, and the reaction mixture was stirred at an appropriate temperature. Then, it was made basic with sat. sodium bicarbonate aq. The precipitate was filtered, washed with water, and then recrystallized from methanol or DMF to give **11**.

N-[2-(3-Methyl[1,2,4]oxadiazol-5-yl)thieno[2,3-b]pyridin-3-yl]formamide oxime (11a). Compound **3a** (200 mg, 0.737 mmol) was allowed to react with hydroxylamine hydrochloride (204.9 mg, 2.95 mmol) in dry methanol (20 mL) at room temperature for 1 h. Compound **11a** (148.1 mg, 73%) from methanol as colorless feathers, mp 232–233 °C; IR (potassium bromide) cm^{-1}: 3216, 3245, 3405 (NH and OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.44 (s, 3H, Me), 7.56 (dd, 1H, *J* = 8.4, 4.5 Hz, H5), 7.88 (d, 1H, *J* = 10.2 Hz, changed to singlet after addition of deuterium oxide, NC*H*NOH), 8.63 (dd, 1H, *J* = 8.4, 1.5 Hz, H4), 8.86 (dd, 1H, *J* = 4.5, 1.5 Hz, H6), 9.87 (d, 1H, *J* = 10.2 Hz, deuterium oxide exchangeable, NH), 10.60 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms *m/z*: 276 (MH^+). *Anal*. Calcd. for $C_{11}H_9N_5O_2S$: C, 47.99; H, 3.30; N, 25.44. Found: C, 47.73; H, 3.60; N, 25.60.

N-[2-(3-Ethyl[1,2,4]oxadiazol-5-yl)thieno[2,3-b]pyridin-3-yl]formamide oxime (11b). Crude intermediate **3b** was allowed to react with hydroxylamine hydrochloride (263.0 mg, 3.78 mmol) in dry methanol (20 mL) under reflux for 18 h. Compound **11b** (60.1 mg, 14% (two steps)) from methanol as yellow feathers, mp 235–236 °C; IR (potassium bromide) cm^{-1}: 3188, 3405 (NH and OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.32 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 2.82 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 7.57 (dd, 1H, *J* = 8.4, 4.8 Hz, H5), 7.93 (d, 1H, *J* = 10.2 Hz, changed to singlet after addition of deuterium oxide, NC*H*NOH), 8.68 (dd, 1H, *J* = 8.4, 1.5 Hz, H4), 8.76 (dd, 1H, *J* = 4.8, 1.5 Hz, H6), 10.08 (d, 1H, *J* = 10.2 Hz, deuterium oxide exchangeable, NH), 10.64 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms *m/z*: 290 (MH^+). *Anal*. Calcd. for $C_{12}H_{11}N_5O_2S \cdot 1/2H_2O$: C, 48.31; H, 4.05; N, 23.48. Found: C, 48.27; H, 4.05; N, 23.43.

N-[2-(3-Phenyl[1,2,4]oxadiazol-5-yl)thieno[2,3-b]pyridin-3-yl]formamide oxime (11c). Crude intermediate **3c** was allowed to react with hydroxylamine hydrochloride (355.2 mg, 5.11 mmol) in dry methanol (20 mL) under reflux for 12 h. Compound **11c** (230.2 mg, 42% (two steps)) from DMF as yellow needles, mp 240–242 °C; IR (potassium bromide) cm^{-1}: 3211, 3415 (NH and OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.57–7.66 (m, 4H, H5, 3′, 4′, and 5′), 8.06 (d, 1H, *J* = 10.2 Hz, changed to singlet after addition of deuterium oxide, NC*H*NOH), 8.15 (dd, 2H, *J* = 7.8, 1.5 Hz, H2′ and 6′), 8.74 (dd, 1H, *J* = 8.4, 1.2 Hz, H4), 8.79 (dd, 1H, *J* = 4.5, 1.2 Hz, H6), 10.49 (d, 1H, *J* = 10.2 Hz, deuterium oxide exchangeable, NH), 10.85 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms *m/z*: 338 (MH^+). *Anal*. Calcd. for $C_{16}H_{11}N_5O_2S \cdot 1/2DMF$: C, 56.21; H, 3.91; N, 20.60. Found: C, 56.58; H, 3.84; N, 20.81.

N-{2-[3-(4-Methylphenyl)[1,2,4]oxadiazol-5-yl]thieno[2,3-b]pyridin-3-yl}formamide oxime (11d). Crude intermediate **3d** was allowed to react with hydroxylamine hydrochloride (412.3 mg, 5.93 mmol) in dry methanol (30 mL) under reflux for 10 h. Compound **11d** (375.3 mg, 72% (2 steps)) from DMF as yellow feathers, mp 250–252 °C; IR (potassium bromide) cm^{-1}: 3211, 3423 (NH and OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.42 (s, 3H, Me), 7.40 (br d, 2H, *J* = 8.1 Hz, H3′ and 5′), 7.59 (dd, 1H, *J* = 8.4, 4.5 Hz, H5), 8.02 (br d, 2H, *J* = 8.1 Hz, H2′ and 6′), 8.05 (d, 1H, *J* = 10.2 Hz, changed to singlet after addition of deuterium oxide, NC*H*NOH), 8.75 (dd, 1H, *J* = 8.4, 1.5 Hz, H4), 8.79 (dd, 1H, *J* = 4.5, 1.5 Hz, H6), 10.48 (d, 1H, *J* = 10.2 Hz, deuterium oxide exchangeable, NH), 10.80 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms *m/z*: 352 (MH^+); *Anal*. Calcd. for $C_{17}H_{13}N_5O_2S$: C, 58.11; H, 3.73; N, 19.93. Found: C, 58.10; H, 4.12; N, 20.10.

N-{2-[3-(3,4-Dimethylphenyl)[1,2,4]oxadiazol-5-yl]thieno[2,3-b]pyridin-3-yl}formamide oxime (11e). Crude intermediate **3e** was allowed to react with hydroxylamine hydrochloride (412.3 mg, 5.93 mmol) in dry methanol (30 mL) under reflux for 11 h. Compound **11e** (357.7 mg, 60% (two steps)) from DMF as yellow feathers, mp 241–242 °C; IR (potassium bromide) cm^{-1}: 3210, 3406 (NH and OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.32 and 2.34 (each s, each 3H, 2 × Me), 7.34 (d, 1H, *J* = 8.1 Hz, H5′), 7.59 (dd, 1H, *J* = 8.4, 4.8 Hz, H5), 7.85 (br d, 1H, *J* = 8.1 Hz, H6′), 7.87 (br s, 1H, H2′), 8.08 (d, 1H, *J* = 10.2 Hz, changed to singlet after addition of deuterium oxide, NC*H*NOH), 8.75–8.79 (m, 2H, H4 and 6), 10.56 (d, 1H, *J* = 10.2 Hz, deuterium oxide exchangeable, NH), 10.92 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms *m/z*: 366 (MH^+). *Anal*. Calcd. for $C_{18}H_{15}N_5O_2S \cdot 1/2DMF$: C, 58.27; H, 4.64; N, 19.17. Found: C, 58.65; H, 4.73; N, 19.28.

N-{2-[3-(4-Methoxyphenyl)[1,2,4]oxadiazol-5-yl]thieno[2,3-b]pyridin-3-yl}formamide oxime (11f). Crude intermediate **3f** was allowed to react with hydroxylamine hydrochloride (274.9 mg, 3.96 mmol) in dry methanol (20 mL) under reflux for 33 h. Compound **11f** (7.2 mg, 2% (two steps)) from DMF as yellow feathers, mp 254–255 °C; IR (potassium bromide) cm^{-1}: 3217, 3423 (NH and OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.87 (s, 3H, OMe), 7.12 (br d, 2H, *J* = 8.4 Hz, H3′ and 5′), 7.58 (dd, 1H, *J* = 8.1, 4.8 Hz, H5), 8.05 (d, 1H, *J* = 10.2 Hz, changed to singlet after addition of deuterium oxide, NC*H* = NOH), 8.08 (br d, 2H, *J* = 8.4 Hz, H2′ and 6′), 8.73–8.79 (m, 2H, H4 and 6), 10.46 (d, 1H, *J* = 10.2 Hz, deuterium oxide exchangeable, NH), 10.82 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms *m/z*: 368 (MH^+). *Anal*. Calcd. for $C_{17}H_{13}N_5O_3S \cdot H_2O$: C, 52.98; H, 3.92; N, 18.17. Found: C, 52.92; H, 4.03; N, 17.90.

N-{2-[3-(4-Fluorophenyl)[1,2,4]oxadiazol-5-yl]thieno[2,3-b]pyridin-3-yl}formamide oxime (11g). Crude intermediate **3g** was allowed to react with hydroxylamine hydrochloride (219.9 mg, 3.16 mmol) in dry methanol (20 mL) under reflux for 9 h. Compound **11g** (179.2 mg, 46% (two steps)) from DMF as yellow feathers, mp 258–260 °C; IR (potassium bromide) cm^{-1}: 3212, 3415 (NH and OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.44 (t, 2H, *J* = 9.0 Hz, H3′ and 5′), 7.60 (dd, 1H, *J* = 8.4, 4.8 Hz, H5), 8.04 (d, 1H, *J* = 10.2 Hz, changed to singlet after addition of deuterium oxide, NC*H*NOH), 8.19 (dd, 2H, *J* = 9.0, 5.1 Hz, H2′ and 6′), 8.74–8.80 (m, 2H, H4 and 6), 10.43 (d, 1H, *J* = 10.2 Hz, deuterium oxide exchangeable, NH), 10.83 (s, 1H,

deuterium oxide exchangeable, OH); FAB-ms *m/z*: 356 (MH^+). *Anal*. Calcd. for $C_{16}H_{10}FN_5O_2S \cdot 1/2DMF$: C, 53.63; H, 3.47; N, 19.66. Found: C, 53.61; H, 3.28; N, 19.85.

***N*-{2-[3-(4-Chlorophenyl)[1,2,4]oxadiazol-5-yl]thieno[2,3-b]pyridin-3-yl}formamide oxime (11h).** Crude intermediate **3h** was allowed to react with hydroxylamine hydrochloride (338.1 mg, 4.87 mmol) in dry methanol (20 mL) under reflux for 8 h. Compound **11h** (275.8 mg, 46% (two steps)) from DMF as yellow feathers, mp 254–255 °C; IR (potassium bromide) cm^{-1}: 3211, 3433 (NH and OH); ^1H NMR (300 MHz, DMSO-d_6): δ 7.59 (dd, 1H, $J = 8.4$, 4.8 Hz, H5), 7.66 (br d, 2H, $J = 8.7$ Hz, H3′ and 5′), 8.04 (d, 1H, $J = 10.2$ Hz, changed to singlet after addition of deuterium oxide, NC*H*NOH), 8.13 (br d, 2H, $J = 8.7$ Hz, H2′ and 6′), 8.74–8.80 (m, 2H, H4 and 6), 10.42 (d, 1H, $J = 10.2$ Hz, deuterium oxide exchangeable, NH), 10.82 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms *m/z*: 372 (MH^+), 374 ($MH^+ + 2$). *Anal*. Calcd. for $C_{16}H_{10}ClN_5O_2S \cdot 1/2DMF$: C, 51.47; H, 3.33; N, 18.87. Found: C, 51.57; H, 3.19; N, 19.05.

***N*-{2-[3-(4-Nitrophenyl)[1,2,4]oxadiazol-5-yl]thieno[2,3-b]pyridin-3-yl}formamide oxime (11i).** Crude intermediate **3i** was allowed to react with hydroxylamine hydrochloride (362.8 mg, 5.22 mmol) in dry methanol (20 mL) under reflux for 10 h. Compound **11i** (340.3 mg, 55% (two steps)) from DMF as a yellow powder, mp > 300 °C; IR (potassium bromide) cm^{-1}: 3218, 3433 (NH and OH); ^1H NMR (300 MHz, DMSO-d_6): δ 7.58 (dd, 1H, $J = 8.4$, 4.5 Hz, H5), 8.04 (d, 1H, $J = 10.2$ Hz, changed to singlet after addition of deuterium oxide, NC*H*NOH), 8.33–8.42 (m, 4H, H2′, 3′, 5′, and 6′), 8.73–8.79 (m, 2H, H4 and 6), 10.44 (d, 1H, $J = 10.2$ Hz, deuterium oxide exchangeable, NH), 10.84 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms *m/z*: 383 (MH^+). *Anal*. Calcd. for $C_{16}H_{10}N_6O_4S \cdot 1/2DMF$: C, 50.18; H, 3.25; N, 21.73. Found: C, 49.79; H, 3.11; N, 21.87.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[2′,3′:4,5]furo[3,2-d]pyrimidin-4-yl) acetamidine (12a).** To a suspension of 4-aminopyrido[2′,3′:4,5]furo[3,2-*d*]pyrimidine (**13**, 186 mg, 0.999 mmol) [11] in dry toluene (10 mL) was added *N,N*-dimethylacetamide dimethyl acetal (160 mg, 1.20 mmol), the mixture was refluxed for 2 h. After evaporation of solvent *in vacuo*, the residue was recrystallized from *n*-hexane/ethyl acetate to give **12a** (227 mg, 89%) as pale yellow needles, mp 125–126 °C; ^1H NMR (300 MHz, deuterochloroform): δ 2.34 (s, 3H, CMe), 3.22, 3.32 (each s, each 3H, NMe_2), 7.51 (dd, 1H, $J = 8.4$, 4.8 Hz, H7), 7.94 (dd, 1H, $J = 8.4$, 1.2 Hz, H6), 8.81 (dd, 1H, $J = 4.8$, 1.2 Hz, H8), 8.89 (s, 1H, H2). FAB-ms: *m/z* 256 (MH^+); *Anal*. Calcd. for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 60.94; H, 5.19; N, 27.07.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[2′,3′:4,5]furo[3,2-d]pyrimidin-4-yl) benzamidine (12b).** To a solution of **13** (186 mg, 0.999 mmol) in dry pyridine (30 mL) were added *N,N*-dimethylbenzamide (179 mg, 1.20 mmol) and phosphorus pentoxide (1.42 g, 10.0 mmol), and the mixture was refluxed for 6 h. After removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous magnesium sulfate, and then evaporated *in vacuo*. The brown oily residue (crude **12b**) was used without further purification. ^1H NMR (300 MHz, deuterochloroform): δ 3.33, 3.59 (each s, each 3H, NMe_2), 7.19–7.29 (m, 3H, H3′, 4′, and 5′), 7.62 (dd, 1H, $J = 9.3$, 4.5 Hz, H7), 7.79–7.85 (m, 2H, H2′ and 6′), 8.01 (br d, 1H, $J = 9.3$ Hz, H6), 8.46 (s, 1H, H2), 8.89 (br d, 1H, $J = 4.5$ Hz, H8).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[2′,3′:4,5]furo[3,2-d]pyrimidin-4-yl)-4-methoxybenzamidine (12c).** To a solution of **13** (186 mg, 0.999 mmol) in dry pyridine (30 mL) were added *N,N*-dimethyl-4-methoxybenzamide [14] (215 mg, 1.20 mmol) and phosphorus pentoxide (1.42 g, 10.0 mmol), and the mixture was refluxed for 14 h. After removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate, then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous magnesium sulfate, and then evaporated *in vacuo*. The brown oily residue (crude **12c**) was used without further purification. ^1H NMR (300 MHz, deuterochloroform): δ 3.06, 3.43 (each s, each 3H, NMe_2), 3.83 (s, 3H, OMe), 6.73 (d, 2H, $J = 8.4$ Hz, H3′ and 5′), 7.31 (d, 2H, $J = 8.4$ Hz, H2′ and 6′), 7.51 (dd, 1H, $J = 8.4$, 4.5 Hz, H7), 7.91 (br d, 1H, $J = 8.4$ Hz, H6), 8.65 (s, 1H, H2), 8.82 (br d, 1H, $J = 4.5$ Hz, H8).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[2′,3′:4,5]furo[3,2-d]pyrimidin-4-yl)-4-fluorobenzamidine (12d).** To a solution of **13** (186 mg, 0.999 mmol) in dry pyridine (30 mL) were added *N,N*-dimethyl-4-fluorobenzamide [15] (201 mg, 1.20 mmol) and phosphorus pentoxide (1.42 g, 10.0 mmol), and the mixture was refluxed for 8 h. After removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous magnesium sulfate, and then evaporated *in vacuo*. The brown oily residue (crude **12d**) was used without further purification. ^1H NMR (300 MHz, deuterochloroform): δ 3.14, 3.48 (each s, each 3H, NMe_2), 7.01 (br t, 2H, $J = 8.7$ Hz, H3′ and 5′), 7.40 (br d, 2H, $J = 8.7$ Hz, H2′ and 6′), 7.56 (dd, 1H, $J = 8.4$, 4.5 Hz, H7), 7.95 (dd, 1H, $J = 8.4$, 1.2 Hz, H6), 8.57 (s, 1H, H2), 8.83 (dd, 1H, $J = 4.5$, 1.2 Hz, H8).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[2′,3′:4,5]furo[3,2-d]pyrimidin-4-yl)-4-chlorobenzamidine (12e).** To a solution of **13** (186 mg, 0.999 mmol) in dry pyridine (30 mL) were added *N,N*-dimethyl-4-chlorobenzamide [14] (220 mg, 1.20 mmol) and phosphorus pentoxide (1.42 g, 10.0 mmol), and the mixture was refluxed for 10 h. After removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate, then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous magnesium sulfate, and then evaporated *in vacuo*. The brown oily residue (crude **12e**) was used without further purification. ^1H NMR (300 MHz, deuterochloroform): δ 3.03, 3.54 (each s, each 3H, NMe_2), 7.22 (br d, 2H, $J = 9.0$ Hz, H3′ and 5′), 7.31 (br d, 2H, $J = 9.0$ Hz, H2′ and 6′), 7.52 (dd, 1H, $J = 8.4$, 4.5 Hz, H7), 7.92 (dd, 1H, $J = 8.4$, 1.2 Hz, H6), 8.64 (s, 1H, H2), 8.79 (dd, 1H, $J = 4.5$, 1.2 Hz, H8).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyrido[2′,3′:4,5]furo[3,2-d]pyrimidin-4-yl)-4-nitrobenzamidine (12f).** To a solution of **13** (186 mg, 0.999 mmol) in dry pyridine (30 mL) were added *N,N*-dimethyl-4-nitrobenzamide [14] (233 mg, 1.20 mmol) and phosphorus pentoxide (1.42 g, 10.0 mmol), and the mixture was refluxed for 9 h. After removal of solvent *in vacuo*, ice water was added to the residue. The mixture was made basic with sodium carbonate then extracted with ethyl acetate. The organic phase was washed with sat. brine, dried over anhydrous magnesium sulfate, and then evaporated *in vacuo*. The brown oily residue (crude **12f**) was used without further purification. ^1H NMR (300 MHz, deuterochloroform): δ 3.07, 3.38 (each s, each 3H, NMe_2), 7.41–7.44 (m, 3H, H7, 2′, and 6′), 7.87 (br d, 1H, $J = 7.9$ Hz, H6), 8.05 (br d, 2H, $J = 7.0$ Hz, H3′ and 5′), 8.54 (s, 1H, H2), 8.72 (dd, 1H, $J = 4.8$, 1.5 Hz, H8).

General procedure for the reaction of 12 with hydroxylamine hydrochloride to give 14. To a solution of amidine (**12**) in dry methanol was added hydroxylamine hydrochloride, and the reaction mixture was stirred at room temperature for an appropriate time. After evaporation of solvent *in vacuo*, the residue was made basic with sat. sodium bicarbonate aq. The precipitate was collected on a filter, washed with water, and then recrystallized from dioxane/methanol to give **14**.

N-[2-(3-Methyl[1,2,4]oxadiazol-5-yl)furo[3,2-b]pyridin-3-yl] formamide oxime (14a). Compound **12a** (255 mg, 0.999 mmol) was allowed to react with hydroxylamine hydrochloride (278 mg, 4.00 mmol) in dry methanol (20 mL) at room temperature for 3 h. Compound **14a** (210 mg, 79%) as colorless feathers, mp 225–226 °C; IR (potassium bromide) cm^{-1}: 3300, 3363, 3450 (NH and OH); ^1H NMR (300 MHz, DMSO-d_6): δ 2.32 (s, 3H, Me), 7.65 (dd, 1H, J = 8.4, 4.8 Hz, H6), 8.23 (dd, 1H, J = 8.4, 1.2 Hz, H7), 8.70 (d, 1H, J = 10.2 Hz, changed to singlet with addition of deuterium oxide, NC*H*NOH), 8.71 (dd, 1H, J = 4.8, 1.2 Hz, H5), 8.97 (d, 1H, J = 10.2 Hz, deuterium oxide exchangeable, NH), 10.65 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 260 (MH^+). *Anal*. Calcd. for $C_{11}H_9N_5O_3 \cdot 1/4CH_3OH$: C, 50.56; H, 3.77; N, 26.21. Found: C, 50.87; H, 3.67; N, 26.45.

N-[2-(3-Phenyl[1,2,4]oxadiazol-5-yl)furo[3,2-b]pyridin-3-yl] formamide oxime (14b). Crude intermediate **12b** was allowed to react with hydroxylamine hydrochloride (278.0 mg, 4.00 mmol) in dry methanol (20 mL) at room temperature for 6 h. Compound **14b** (202 mg, 55% (two steps)) as colorless feathers; mp 246–247 °C. IR (potassium bromide) cm^{-1}: 3073, 3270, 3339 (NH and OH); ^1H NMR (300 MHz, DMSO-d_6): δ 7.57–7.63 (m, 3H, H3′, 4′, and 5′), 7.67 (dd, 1H, J = 8.7, 4.8 Hz, H6), 8.09 (dd, 2H, J = 7.5, 2.4 Hz, H2′ and 6′), 8.27 (dd, 1H, J = 8.7, 1.2 Hz, H7), 8.72 (dd, 1H, J = 4.8, 1.2 Hz, H5), 8.74 (d, 1H, J = 9.0 Hz, changed to singlet with addition of deuterium oxide, NC*H*NOH), 9.31, 10.75 (each br, each 1H, deuterium oxide exchangeable, NH, OH); FAB-ms: *m/z* 322 (MH^+). *Anal*. Calcd. for $C_{16}H_{11}N_5O_3 \cdot 1/2$dioxane: C, 59.18; H, 4.14; N, 19.17. Found: C, 58.81; H, 4.18; N, 19.05.

N-{2-[3-(4-Methoxyphenyl)[1,2,4]oxadiazol-5-yl]furo[3,2-b] pyridin-3-yl}formamide oxime (14c). Crude intermediate **12c** was allowed to react with hydroxylamine hydrochloride (278.0 mg, 4.00 mmol) in dry methanol (20 mL) at room temperature for 5 h. Compound **14c** (207 mg, 55% (two steps)) as colorless feathers, mp 243–244 °C; IR (potassium bromide) cm^{-1}: 3230, 3350, 3448 (sh.) (NH and OH); ^1H NMR (300 MHz, DMSO-d_6): δ 3.90 (s, 3H, OMe), 7.19 (d, 2H, J = 9.0 Hz, H3′ and 5′), 7.71 (dd, 1H, J = 8.7, 4.8 Hz, H6), 8.06 (d, 2H, J = 9.0 Hz, H2′ and 6′), 8.31 (br d, 1H, J = 8.7 Hz, H7), 8.76 (d, 1H, J = 4.8, H5), 8.76 (d, 1H, J = 4.2 Hz, changed to singlet with addition of deuterium oxide, NC*H*NOH), 9.32, 10.81 (each br, each 1H, deuterium oxide exchangeable, NH and OH); FAB-ms: *m/z* 352 (MH^+). *Anal*. Calcd. for $C_{17}H_{13}N_5O_4 \cdot 1/2H_2O \cdot 1/2CH_3OH$: C, 55.85; H, 4.29; N, 18.61. Found: C, 56.20; H, 4.00; N, 18.35.

N-{2-[3-(4-Fluorophenyl)[1,2,4]oxadiazol-5-yl]furo[3,2-b] pyridin-3-yl}formamide oxime (14d). Crude intermediate **12d** was allowed to react with hydroxylamine hydrochloride (278.0 mg, 4.00 mmol) in dry methanol (20 mL) at room temperature for 7 h. Compound **14d** (153 mg, 42% (two steps)) as pale green feathers, mp 237–238 °C; IR (potassium bromide) cm^{-1}: 3110, 3280, 3480 (sh.) (NH and OH); ^1H NMR (300 MHz, DMSO-d_6): δ 7.40–7.50 (m, 2H, H3′ and 5′), 7.67 (dd, 1H, J = 8.4, 4.5 Hz, H6), 8.06–8.15 (m, 2H, H2′ and 6′), 8.27 (br d, 1H, J = 8.4 Hz, H7), 8.71 (br d, 1H, J = 4.5 Hz, H5), 8.74 (d, 1H, J = 10.5 Hz, changed to singlet with addition of deuterium oxide, NC*H*=NOH), 9.24 (d, 1H, J = 10.5 Hz, deuterium oxide exchangeable, NH), 10.76 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 340 (MH^+). *Anal*. Calcd. for $C_{16}H_{10}FN_5O_3$•1/3dioxane: C, 56.47; H, 3.46; N, 19.00. Found: C, 56.60; H, 3.69; N, 19.04.

N-{2-[3-(4-Chlorophenyl)[1,2,4]oxadiazol-5-yl]furo[3,2-b] pyridin-3-yl}formamide oxime (14e). Crude intermediate **12e** was allowed to react with hydroxylamine hydrochloride (278.0 mg, 4.00 mmol) in dry methanol (20 mL) at room temperature for 4 h. Compound **14e** (231 mg, 64% (two steps)) as pale green feathers, mp 248–249 °C; IR (potassium bromide) cm^{-1}: 3187, 3339, 3490 (NH and OH); ^1H NMR (300 MHz, DMSO-d_6): δ 7.64–7.72 (m, 3H, H6, 3′, and 5′), 8.06 (d, 2H, J = 8.4 Hz, H2′ and 6′), 8.26 (dd, 1H, J = 8.7, 1.2 Hz, H7), 8.71 (d, 1H, J = 4.5 Hz, changed to singlet with addition of deuterium oxide, NC*H*NOH), 8.72 (dd, 1H, J = 4.5, 1.2 Hz, H5), 9.21, 10.78 (each br, each 1H, deuterium oxide exchangeable, NH and OH); FAB-ms: *m/z* 356 (MH^+), 358 ($MH^+ + 2$). *Anal*. Calcd. for $C_{16}H_{10}ClN_5O_3$•1/4H_2O: C, 53.35; H, 2.94; N, 19.44. Found: C, 53.64; H, 3.00; N, 19.28.

N-{2-[3-(4-Nitrophenyl)[1,2,4]oxadiazol-5-yl]furo[3,2-b]pyridin-3-yl}formamide oxime (14f). Crude intermediate **12f** was allowed to react with hydroxylamine hydrochloride (278.0 mg, 4.00 mmol) in dry methanol (20 mL) at room temperature for 5 h. Compound **14f** (256 mg, 66% (two steps)) as pale yellow feathers, mp 229–230 °C; IR (potassium bromide) cm^{-1}: 3110, 3229, 3490 (NH and OH); ^1H NMR (300 MHz, DMSO-d_6): δ 7.68 (dd, 1H, J = 8.7, 4.8 Hz, H6), 8.27 (br d, 1H, J = 8.7 Hz, H7), 8.30 (d, 2H, J = 9.0 Hz, H3′ and 5′), 8.44 (d, 2H, J = 9.0 Hz, H2′ and 6′), 8.74 (d, 1H, J = 10.2 Hz, changed to singlet with addition of deuterium oxide, NC*H*NOH), 8.76 (br d, 1H, J = 4.8 Hz, H5), 9.21 (d, 1H, J = 10.2 Hz, deuterium oxide exchangeable, NH), 10.81 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: *m/z* 367 (MH^+). *Anal*. Calcd. for $C_{16}H_{10}N_6O_5$•1/4dioxane: C, 52.58; H, 3.11; N, 21.64. Found: C, 52.73; H, 3.24; N, 21.74.

Determination of pentosidine formation *in vitro*. Test compound stock solutions were prepared at 100 mM concentration in DMSO. The reaction mixture (total volume 200 μL) consisting of 24 mg/mL bovine serum albumin, 10 mM D-glucose, and 2.0 mM test compounds was incubated at 37 °C for 4 weeks in 100 mM phosphate buffer (pH 7.4). Then, 10% trichloroacetic acid was added to precipitate proteins. After collecting the precipitate by centrifugation, 2% protease (Sigma) was added and incubated for 18 h at 37 °C followed by 2% aminopeptidase (Sigma) for 18 h at 37 °C. After digestion, samples were filtered through a 0.22 mm filter (Millipore, USA) for ESI/LC/MS analysis. The quantitative ESI/LC/MS analysis was performed on the basis of a method described previously [16].

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