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# POLYCYCLIC *N*-HETEROCYCLIC COMPOUNDS. PART 70: SYNTHESIS OF 5-AMINO-1,2-DIHYDROFURO[2,3-*b*]PYRIDO[3',2':4,5]-THIENO[3,2-*d*]PYRIDINES AND RELATED COMPOUNDS. EVALUATION OF EFFECTS ON LIPOPROTEIN LIPASE mRNA EXPRESSION

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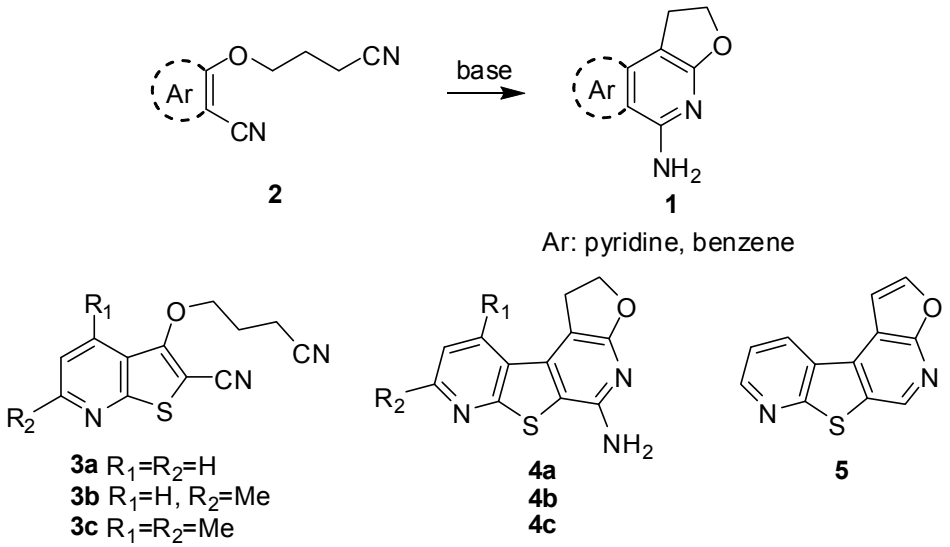
**Abstract** – Reaction of 3-(3-cyanopropoxy)thieno[2,3-*b*]pyridine-2-carbonitriles with potassium *tert*-butoxide gave 5-amino-1,2-dihydrofuro[2,3-*b*]pyrido-[3',2':4,5]thieno[3,2-*d*]pyridines *via* a Truce-Smiles rearrangement. The 5-amino group was transformed to the chloro derivatives which were allowed to react with various nucleophiles. Effects of the newly synthesized compounds on lipoprotein lipase mRNA expression were also evaluated. The previously unreported parent compound, furo[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine, was also synthesized.

## INTRODUCTION

Formation of carbon–carbon (C–C) bonds is a central issue in synthetic organic chemistry. In this regard, the Truce-Smiles rearrangement is among those useful rearrangement reactions that provide access to complex structures from simple precursors through formation of new C-C bonds.[1-5]

We have previously reported the application of the Truce-Smiles rearrangement for the synthesis of many aromatic fused dihydrofuro[2,3-*b*]pyridines (**1**) in one step from cyano aromatic ring having a 3-cyanopopoxy group adjacent to cyano group (**2**). Thus, base-mediated Truce-Smiles rearrangement of **2** followed by intramolecular cyclization (Scheme 1) produces **1** in moderate to good yields.[6-8] 5-Substituted derivatives of **1** were also accessible by usual $S_NAr$ reactions. An *in vitro* screening

evaluation of these compounds and derivatives to measures their effects on lipoprotein lipase (LPL) mRNA expression in 3T3-L1 preadipocytes was performed as part of our continuing program to develop agents for hyperlipemia.[9]



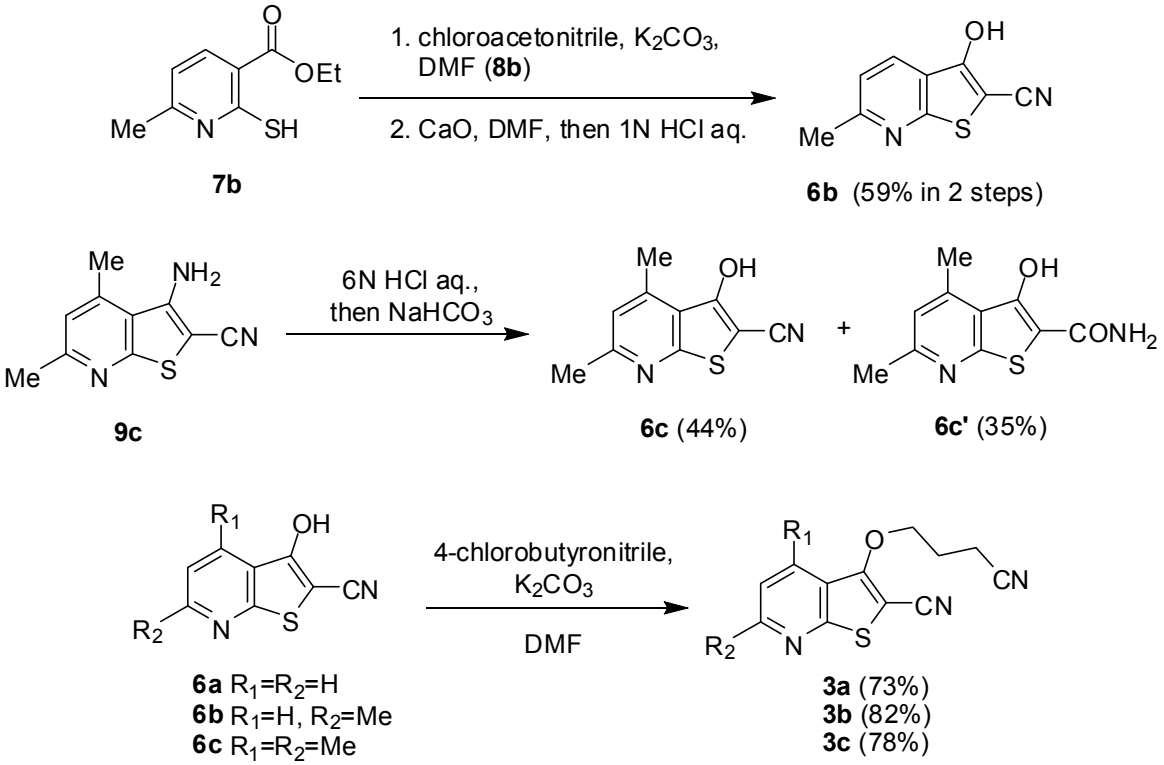

Scheme 1. Substrates (**2** and **3**) and their rearranged products (**1** and **4**), as well as furo[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (**5**)

With a goal to develop more potent compounds, we have pursued the preparation of other fused dihydrofuropyridines derivatives using our rearrangement methodology. Thus, we sought to expand this rearrangement reaction system to 3-(3-cyanopropoxy)thieno[2,3-*b*]pyridine-2-carbonitriles (**3**) as a route to 5-amino-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridines (**4**). This is a fairly challenging substrate because the electron rich thiophene is a less reactive candidate for the Truce-Smiles rearrangement. Herein we report the details of the Truce-Smiles type rearrangement reaction for a series of **3**. We also report preparation of 5-substituted derivatives as well as a dihydrofuran ring cleaved derivative.[9] The effect of these fused dihydrofuropyridines on LPL mRNA expression, one of key targets for development of diabetes drug, was evaluated. Finally, the parent skeleton, furo[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (**5**) was also synthesized.

## RESULTS AND DISCUSSION

The starting compounds were readily obtained as follows. Reaction of 3-hydroxythieno[2,3-*b*]pyridine-2-carbonitrile[10] (**6a**) with 4-chlorobutyronitrile in the presence of potassium carbonate in DMF gave the desired **3a** (73%) (Scheme 2). In the IR spectrum of **3a**, the hydroxy band present in **6a** had disappeared, strongly indicating that **3a** is an O-alkyl derivative, not a

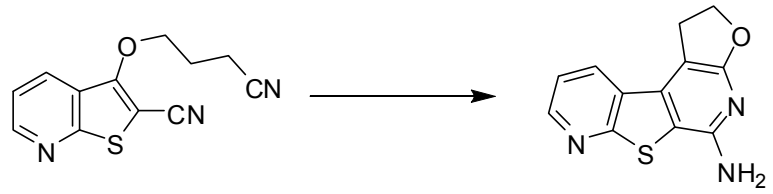
C-alkyl derivative. Compound **6b** was prepared from ethyl 6-methyl-2-sulfanylnicotinate[11] (**7b**) by two steps and **6c** was prepared from 3-amino-4,6-dimethylthieno[2,3-*b*]pyridine-2-carbonitrile[12] (**9c**) directly. A similar reaction of **6b** and **6c** with 4-chlorobutyronitrile afforded the desired **3b** (82%) and **3c** (78%), respectively.




Scheme 2. Preparation of **3a**–**c**

The initial reaction of **3a** with potassium *tert*-butoxide in 1,4-dioxane at room temperature produced **4a** in 59% yield (Table 1, Run 1). In the IR spectrum of **4a**, the cyano band was absent and amino bands were observed at 3400, 3325, and 3200 $cm^{-1}$. In the $^1H$ NMR spectrum of **4a**, two dihydrofuran methylene resonances appeared at 3.54 and 4.65 ppm, respectively. The two deuterium oxide exchangeable protons of the amino group appeared at 6.47 ppm. These data are consistent with the structure of **4a** and assignment was further supported by FAB-MS and elemental analysis. If the solvent were changed from 1,4-dioxane to THF, the reaction did not proceed at room temperature, but reflux conditions gave **4a** in 53% yield (Run 2). The best yield was obtained when DMF was used as solvent at room temperature (72%, Run 3). Sodium hydride did not improve the product yield (Run 4). Compounds **3b** and **3c** were also treated with potassium *tert*-butoxide in DMF to give **4b** (68%) and **4c** (61%), respectively.

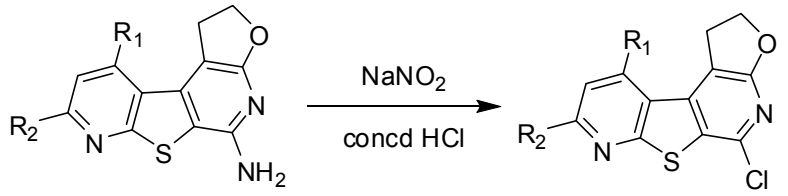
Table 1. Reaction of dinitrile **3a** with bases to give **4a**



**3a** **4a**

| Run | Base (2 eq) | Solvent | Temperature | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | *t*-BuOK | 1,4-dioxane | rt | 2 | 59 |
| 2 | *t*-BuOK | THF | reflux | 1 | 53 |
| 3 | *t*-BuOK | DMF | rt | 0.1 | 72 |
| 4 | NaH | DMF | 80 °C | 1 | 62 |

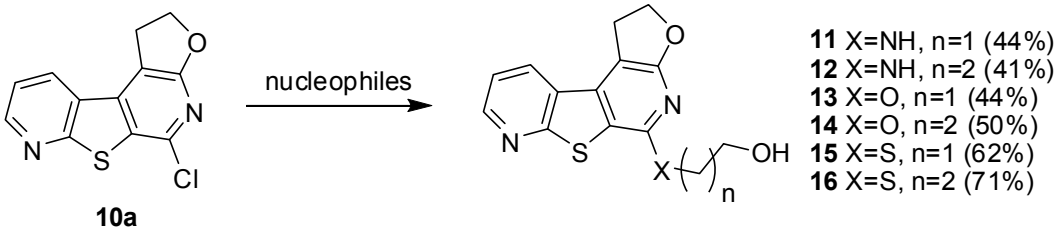
With the goal of synthesizing additional derivatives for biological evaluation, the 5-amino groups of **4a–c** were transformed to 5-chloro derivatives (**10a–c**) as potential intermediates for coupling with nucleophiles. Thus the 5-amino derivatives **4a–c** were treated with sodium nitrite and concd hydrochloric acid to give **10a–c** in 66–70% yield (Scheme 3). Next, **10a** was subjected to reactions with various nucleophiles (2-aminoethanol, 3-amino-1-propanol, ethylene glycol, 1,3-propanediol, 2-sulfanylethanol, 3-sulfanyl-1-propanol, pyrrolidine, piperidine, and morpholine) to give derivatives **11–19** in 41–79% yield (Scheme 4 and 5).



**4a** $R_1$=$R_2$=H
**4b** $R_1$=H, $R_2$=Me
**4c** $R_1$=$R_2$=Me

**10a** (70%)
**10b** (67%)
**10c** (66%)

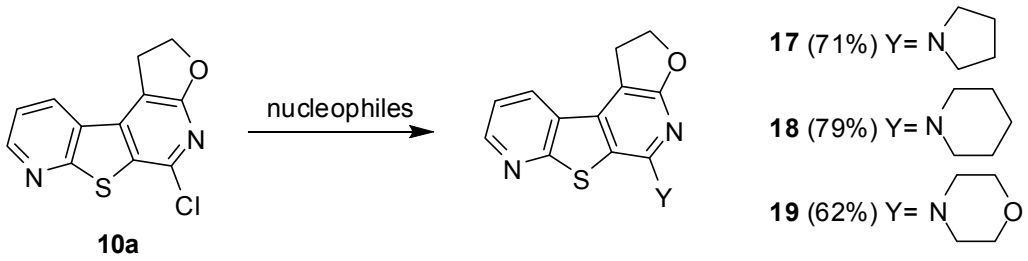
Scheme 3. Preparation of **10a–c**



**10a**

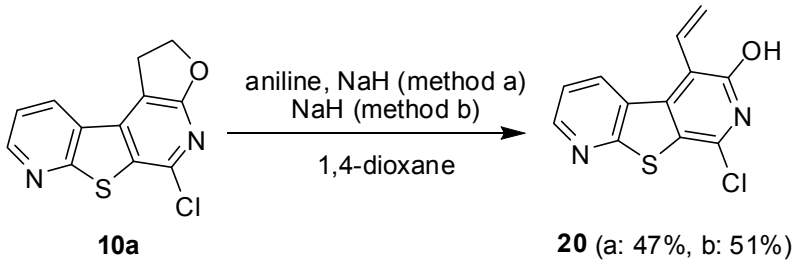
**11** X=NH, n=1 (44%)
**12** X=NH, n=2 (41%)
**13** X=O, n=1 (44%)
**14** X=O, n=2 (50%)
**15** X=S, n=1 (62%)
**16** X=S, n=2 (71%)

Scheme 4. Reaction of **10a** with linear nucleophiles




Scheme 5. Reaction of **10a** with cyclic nucleophiles

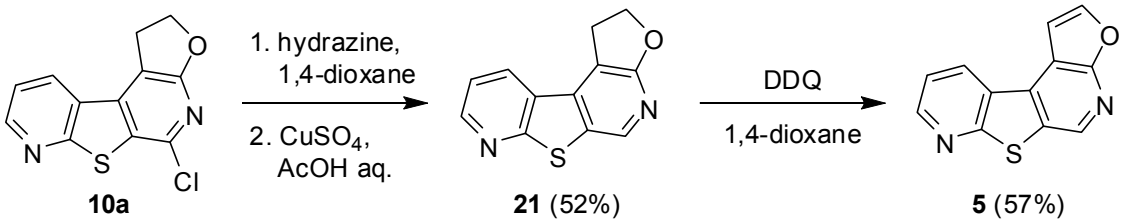
In contrast to the above results, a similar reaction of **10a** with the anilide anion (3 eq.), prepared by reaction of aniline with sodium hydride in dry 1,4-dioxane, produced a 47% yield of the furan ring opened vinyl derivative **20** that retains the chloro atom (Scheme 6). Typical vinyl protons were observed at 5.85–7.14 ppm in the $^1$H NMR spectrum. The strong basicity of the anilide anion (aniline p$K_a$ 30.6)[13] causes the anilide anion to function as a base rather than a nucleophile in this experiment. When **10a** was treated with sodium hydride (6 eq.) alone in dry 1,4-dioxane under reflux, the yield of **20** was slightly increased to 51% yield.




Scheme 6. Reaction of **10a** with bases

With these derivatives in hand, effects on LPL mRNA expression in 3T3-L1 preadipocytes were examined using an *in vitro* screening test for hyperlipemia. Troglitazone[14] was employed as a reference compound and GAPDH was chosen for the house keeping gene. The LPL/GAPDH mRNA ratio was evaluated as the relative values of LPL/GAPDH ratio from vehicle control group and tests were done in triplicate. None of the compounds showed significant activity (data not shown).

Finally, we pursued routes to the parent ring skeleton, unsubstituted furo[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (**5**), since the parent ring system itself had not been reported. We first attempted dechlorination of **10a** by catalytic hydrogenolysis using $H_2$/10% Pd-C but only unreacted starting material was recovered. Next we investigated a two step dechlorination strategy (Scheme 7). The 5-chlorine atom of compound **10a** was substituted by hydrazine and the resulting hydrazine derivative was treated with $CuSO_4$ to give 5-unsubsituted **21** in 52% yield (2 steps).[15] Oxidation of **21** with DDQ gave the desired parent compound **5** in 57% yield.




Scheme 7. Synthesis of furo[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (**5**)

## CONCLUSION

In summary, we have developed a method for the synthesis of 5-amino-1,2-dihydrofuro[2,3-*b*]-pyrido[3',2':4,5]thieno[3,2-*d*]pyridines (**4**) *via* a Truce-Smiles rearrangement. The 5-amino group was transformed to the chloro derivative (**10a**), which was allowed to react with various nucleophiles to give 5-substituted derivatives. None of the new compounds showed significant effects on LPL mRNA expression. In addition, the synthesis of the previously unreported parent compound, furo[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (**5**), was achieved.

## 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 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 JASCO FT/IR-200 spectrophotometer and frequencies are expressed in $cm^{-1}$. The $^1H$ NMR spectra were recorded on a Varian VXR-200 instrument operating at 200 MHz or Hitachi R-1500 instrument operating at 60 MHz with TMS as an internal standard. Column chromatography was performed on silica gel (IR-60-63-210-W, Daiso). TLC was carried out on Kieselgel 60F254 (Merck) or silica gel 70FM (Wako).

**3-(3-Cyanopropoxy)thieno[2,3-*b*]pyridine-2-carbonitrile (3a).** To a solution of 3-hydroxythieno-[2,3-*b*]pyridine-2-carbonitrile[10] (**6a**, 10.0 g, 56.8 mmol) in DMF (150 mL) were added $K_2CO_3$ (15.7 g, 114 mmol) and 4-chlorobutyronitrile (11.8 g, 114 mmol) and the mixture was stirred at 80 °C for 3.5 h. Solid was removed by filtration and the mother liquid was evaporated in vacuo. Ice water (500 mL) was poured into the residue and the resulting precipitate was collected by filtration. Recrystallization from cyclohexane-benzene gave **3a** (10.1 g, 73%) as colorless needles, mp 99–101 °C; IR (Nujol) 2240, 2210 (CN) $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 2.31 (quin, $J$ = 6.5 Hz, 2H, 2'-H), 2.66 (t, $J$ = 6.5 Hz, 2H, 3'-H), 4.84 (t, $J$ = 6.5 Hz, 2H, 1'-H), 7.41 (dd, $J$ = 8.1, 4.6 Hz, 1H, 5-H), 8.20 (dd, $J$ = 8.1, 1.7 Hz, 1H, 4-H), 8.76 (dd, $J$ = 4.6, 1.7 Hz, 1H, 6-H); MS *m/z* 244 ($MH^+$). Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27. Found: C, 59.16; H, 3.88; N, 17.11.

**Ethyl 2-(cyanomethylsulfanyl)-6-methylnicotinate (8b).** To a solution of ethyl 6-methyl-2-sulfanylnicotinate[11] (**7b**, 4.50 g, 22.8 mmol) in DMF (50 mL) were added $K_2CO_3$ (6.30 g, 45.6 mmol) and chloroacetonitrile (3.40 g, 45.0 mmol) and the mixture was stirred at 80 °C for 2 h. Solid was removed by filtration and the mother liquid was evaporated in vacuo. Ice water (300 mL) was poured into the residue and the resulting precipitate was collected by filtration. Recrystallization from cyclohexane gave **8b** (3.90 g, 72%) as colorless needles, mp 76–78 °C; IR (Nujol) 2245 (CN), 1705 (CO) $cm^{-1}$; $^1H$ NMR (60 MHz, $CDCl_3$) δ 1.41 (t, $J$ = 7.0 Hz, 3H, $CH_2CH_3$), 2.62 (s, 3H, $CH_3$), 3.93 (s, 2H, -$CH_2CN$), 4.40 (q, $J$ = 7.0 Hz, 2H, -$CH_2CH_3$), 7.02 (d, $J$ = 8.0 Hz, 1H, 5-H), 8.19 (d, $J$ = 8.0 Hz, 1H, 4-H); MS *m/z* 237 ($MH^+$). Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86. Found: C, 56.08; H, 5.22; N, 11.58.

**3-Hydroxy-6-methylthieno[2,3-*b*]pyridine-2-carbonitrile (6b).** To a solution of **8b** (5.00 g, 21.2 mmol) in DMF (100 mL) was added CaO (3.50 g, 62.4 mmol) and the reaction was then stirred at 100 °C for 3 h. Solid was removed by filtration and the mother liquid was evaporated in vacuo. Ice water (300 mL) was poured into the residue and the mixture was neutralized with 1N HCl aq. The resulting precipitate was collected by filtration. The mother liquid was extracted with EtOAc (200 mL x 3). The combined organic layer was washed with saturated brine, dried over anhydrous $Na_2SO_4$, and evaporated in vacuo. The residue and the precipitate described above were combined and recrystallized from EtOAc to give **6b** (3.30 g, 82%) as colorless needles, mp 188–192 °C (dec.); IR (Nujol) 3400 (OH), 2210 (CN) $cm^{-1}$; $^1H$ NMR (60 MHz, DMSO-$d_6$) δ 2.61 (s, 3H, $CH_3$), 7.41 (d, $J$ = 8.4 Hz, 1H, 5-H), 8.30 (d, $J$ = 8.4 Hz, 1H, 4-H), 12.44 (br, $D_2O$ exchangeable, 1H, OH); MS *m/z* 191 ($MH^+$); Anal. Calcd for $C_9H_6N_2OS \cdot H_2O$: C, 51.91; H, 3.87; N, 13.45. Found: C, 51.96; H, 3.95; N, 13.36.

**3-(3-Cyanopropoxy)-6-methylthieno[2,3-*b*]pyridine-2-carbonitrile (3b).** To a solution of **6b** (1.40 g, 7.36 mmol) in DMF (20 mL) were added $K_2CO_3$ (2.00 g, 14.5 mmol) and 4-chlorobutyronitrile (1.50 g, 14.5 mmol) and the reaction mixture was stirred at 100 °C for 2 h. Solid was removed by filtration and the mother liquid was evaporated in vacuo. Ice water (150 mL) was poured into the residue and the resulting precipitate was collected by filtration. Recrystallization from cyclohexane-benzene gave **3b** (1.55 g, 82%) as colorless needles, mp 113–115 °C; IR (Nujol) 2250, 2210 (CN) $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 2.29 (quin, $J$ = 6.0 Hz, 2H, 2'-H), 2.65 (t, $J$ = 6.0 Hz, 2H, 3'-H), 2.70 (s, 3H, $CH_3$), 4.81 (t, $J$ = 6.0 Hz, 2H, 1'-H), 7.25 (d, $J$ = 8.3 Hz, 1H, 5-H), 8.05 (d, $J$ = 8.3 Hz, 1H, 4-H); MS *m/z* 258 ($MH^+$). Anal. Calcd for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33. Found: C, 60.84; H, 4.46; N, 16.30.

**3-Hydroxy-4,6-dimethylthieno[2,3-*b*]pyridine-2-carbonitrile (6c) and 3-Hydroxy-4,6-dimethylthieno[2,3-*b*]pyridine-2-carboxamide (6c').** A solution of 3-amino-4,6-dimethylthieno-[2,3-*b*]pyridine-2-carbonitrile[12] (**9c**, 5.00 g, 24.6 mmol) in 6N HCl aq. (100 mL) was refluxed for 3 h. After cooling, the solution was neutralized with $NaHCO_3$ and the resulting precipitate was collected by

filtration. The mother liquid was extracted with EtOAc (200 mL x 3). The combined organic layer was washed with saturated brine, dried over anhydrous $Na_2SO_4$, and evaporated in vacuo. The residue and the precipitate described above were combined and chromatographed on silica gel. The eluate of cyclohexane-EtOAc (2:1) was evaporated in vacuo and the residue was recrystallized from EtOAc to give **6c** (2.20 g, 44%) as colorless needles. The further eluate of EtOAc was evaporated in vacuo and the residue was recrystallized from MeOH to give **6c'** (1.90 g, 35%) as colorless needles. **6c**: mp 241–245 °C (dec.); IR (Nujol) 3450 (OH), 2210 (CN) $cm^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$) δ 2.53 (s, 3H, $CH_3$), 2.65 (s, 3H, $CH_3$), 7.17 (s, 1H, 5-H), 12.53 (br, $D_2O$ exchangeable, 1H, OH); MS *m/z* 205 ($MH^+$). Anal. Calcd for $C_{10}H_8N_2OS \cdot H_2O$: C, 54.04; H, 4.53; N, 12.60. Found: C, 54.26; H, 4.80; N, 12.56. **6c'**: mp 252–254 °C; IR (Nujol) 3340, 3280, 3150 (NH and OH), 1685 (CO) $cm^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$) δ 2.53 (s, 3H, $CH_3$), 2.66 (s, 3H, $CH_3$), 7.13 (s, 1H, 5-H), 7.96 (br, $D_2O$ exchangeable, 2H, $NH_2$), 13.33 (br, $D_2O$ exchangeable, 1H, OH); MS *m/z* 223 ($MH^+$). Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 54.16; H, 4.77; N, 12.86.

**3-(3-Cyanopropoxy)-4,6-dimethylthieno[2,3-*b*]pyridine-2-carbonitrile (3c).** To a solution of **6c** (2.00 g, 9.79 mmol) in DMF (25 mL) were added $K_2CO_3$ (2.70 g, 19.5 mmol) and 4-chlorobutyronitrile (2.00 g, 19.3 mmol) and the mixture was stirred at 80 °C for 4 h. Solid was removed by filtration and the mother liquid was evaporated in vacuo. Ice water (150 mL) was poured into the residue and the resulting precipitate was collected by filtration. Recrystallization from cyclohexane-benzene gave **3c** (2.08 g, 78%) as colorless needles, mp 148–150 °C; IR (Nujol) 2240, 2200 (CN) $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 2.30 (quin, *J* = 6.2 Hz, 2H, 2'-H), 2.61 (s, 3H, $CH_3$), 2.64 (t, *J* = 6.2 Hz, 2H, 3'-H), 2.65 (s, 3H, $CH_3$), 4.80 (t, *J* = 6.2 Hz, 2H, 1'-H), 7.00 (s, 1H, 5-H); MS *m/z* 272 ($MH^+$). Anal. Calcd for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49. Found: C, 61.90; H, 4.97; N, 15.41.

**5-Amino-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (4a).** To a solution of **3a** (2.00 g, 8.22 mmol) in dry DMF (20 mL) was added *t*-BuOK (1.80 g, 16.0 mmol) and the mixture was stirred for 6 min at room temperature. Ice water (100 mL) was poured into the reaction mixture and the resulting precipitate was collected by filtration. Recrystallization from DMF gave **4a** (1.44 g, 72%) as yellow micro crystals, mp > 300 °C; IR (Nujol) 3400, 3325, 3200 (NH) $cm^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$) δ 3.54 (t, *J* = 8.5 Hz, 2H, 1-H), 4.65 (t, *J* = 8.5 Hz, 2H, 2-H), 6.47 (br, $D_2O$ exchangeable, 2H, $NH_2$), 7.54 (dd, *J* = 7.9, 4.7 Hz, 1H, 9-H), 8.42 (dd, *J* = 7.9, 1.7 Hz, 1H, 10-H), 8.71 (dd, *J* = 4.7, 1.7 Hz, 1H, 8-H); MS *m/z* 244 ($MH^+$). Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27. Found: C, 59.34; H, 4.09; N, 16.97.

**5-Amino-8-methyl-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (4b).** To a solution of **3b** (1.00 g, 3.89 mmol) in dry DMF (10 mL) was added *t*-BuOK (870 mg, 7.75 mmol) and the mixture

was stirred for 6 min at room temperature. Ice water (50 mL) was poured into the reaction mixture and the resulting precipitate was collected by filtration. Recrystallization from DMF gave **4b** (680 mg, 68%) as yellow micro crystals, mp > 300 °C; IR (Nujol) 3450, 3275, 3150 (NH) $cm^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$) δ 2.63 (s, 3H, $CH_3$), 3.50 (t, $J$ = 8.5 Hz, 2H, 1-H), 4.64 (t, $J$ = 8.5 Hz, 2H, 2-H), 6.41 (br, $D_2O$ exchangeable, 2H, $NH_2$), 7.39 (d, $J$ = 8.1 Hz, 1H, 9-H), 8.28 (d, $J$ = 8.1 Hz, 1H, 10-H); MS *m/z* 258 ($MH^+$). Anal. Calcd for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33. Found: C, 60.55; H, 4.50; N, 16.21.

**5-Amino-8,10-dimethyl-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (4c).** To a solution of **3c** (1.00 g, 3.69 mmol) in dry DMF (10 mL) was added *t*-BuOK (820 mg, 7.31 mmol) and the mixture was stirred for 6 min at room temperature. Ice water (50 mL) was poured into the reaction mixture and the resulting precipitate was collected by filtration. Recrystallization from DMF gave **4c** (610 mg, 61%) as yellow micro crystals, mp > 300 °C; IR (Nujol) 3435, 3275, 3160 (NH) $cm^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$) δ 2.55 (s, 3H, $CH_3$), 2.82 (s, 3H, $CH_3$), 3.68 (t, $J$ = 8.6 Hz, 2H, 1-H), 4.50 (t, $J$ = 8.6 Hz, 2H, 2-H), 6.33 (br, $D_2O$ exchangeable, 2H, $NH_2$), 7.16 (s, 1H, 9-H); MS *m/z* 272 ($MH^+$). Anal. Calcd for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49. Found: C, 61.97; H, 5.20; N, 15.38.

**5-Chloro-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (10a).** To a stirred suspension of **4a** (2.00 g, 8.22 mmol) in concd HCl (50 mL) cooled in an ice water bath (0–5 °C) was added dropwise $NaNO_2$ (1.70 g, 24.6 mmol) in water (4.0 mL) and the mixture was then stirred for 1h. After the end point of the reaction was confirmed with KI-starch paper, the mixture was basified with $NaHCO_3$. The resulting precipitate was collected by filtration. The mother liquid was extracted with EtOAc (100 mL x 3). The combined organic layer was washed with saturated brine, dried over anhydrous $Na_2SO_4$, and evaporated in vacuo. The residue and the precipitate described above were combined and recrystallized from 1,4-dioxane to give **10a** (1.52 g, 70%) as colorless needles, mp 278–280 °C; $^1H$ NMR (200 MHz, DMSO-$d_6$) δ 3.73 (t, $J$ = 8.7 Hz, 2H, 1-H), 4.84 (t, $J$ = 8.7 Hz, 2H, 2-H), 7.65 (dd, $J$ = 8.0, 4.7 Hz, 1H, 9-H), 8.54 (dd, $J$ = 8.0, 1.7 Hz, 1H, 10-H), 8.81 (dd, $J$ = 4.7, 1.7 Hz, 1H, 8-H); MS *m/z* 263 ($MH^+$), 265 ($MH^+$ + 2). Anal. Calcd for $C_{12}H_7ClN_2OS$: C, 54.86; H, 2.69; N, 10.66. Found: C, 54.79; H, 2.87; N, 10.49.

**5-Chloro-8-methyl-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (10b).** To a stirred suspension of **4b** (2.00 g, 7.77 mmol) in concd HCl (50 mL) cooled in an ice water bath (0–5 °C) was added dropwise $NaNO_2$ (1.60 g, 23.2 mmol) in water (4.0 mL) and the reaction was then stirred for 1h. After the end point of the reaction was confirmed with KI-starch paper, the mixture was basified with $NaHCO_3$. The resulting precipitate was collected by filtration. The mother liquid was extracted with EtOAc (100 mL x 3). The combined organic layer was washed with saturated brine, dried over anhydrous $Na_2SO_4$, and evaporated in vacuo. The residue and the precipitate described above was combined and

recrystallized from 1,4-dioxane to give **10b** (1.44 g, 67%) as colorless needles, mp > 300 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 2.66 (s, 3H, $CH_3$), 3.70 (t, $J$ = 8.7 Hz, 2H, 1-H), 4.83 (t, $J$ = 8.7 Hz, 2H, 2-H), 7.50 (d, $J$ = 8.2 Hz, 1H, 9-H), 8.39 (d, $J$ = 8.2 Hz, 1H, 10-H); MS *m/z* 277 ($MH^+$), 279 ($MH^+$ + 2). Anal. Calcd for $C_{13}H_9ClN_2OS$: C, 56.42; H, 3.28; N, 10.12. Found: C, 56.54; H, 3.26; N, 9.96.

**5-Chloro-8,10-dimethyl-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (10c).** To a stirred suspension of **4c** (1.00 g, 3.69 mmol) in concd HCl (20 mL) cooled in an ice water bath (0–5 °C) was added dropwise $NaNO_2$ (760 mg, 11.0 mmol) in water (2.0 mL) and the reaction was stirred for 1h. After the end point of the reaction was confirmed with KI-starch paper, the mixture was basified with $NaHCO_3$. The resulting precipitate was collected by filtration. The mother liquid was extracted with EtOAc (100 mL x 3). The combined organic layer was washed with saturated brine, dried over anhydrous $Na_2SO_4$, and evaporated in vacuo. The residue and the precipitate described above were combined and recrystallized from 1,4-dioxane to give **10c** (710 mg, 66%) as colorless needles, mp 283–285 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 2.57 (s, 3H, $CH_3$), 2.88 (s, 3H, $CH_3$), 3.93 (t, $J$ = 8.7 Hz, 2H, 1-H), 4.67 (t, $J$ = 8.7 Hz, 2H, 2-H), 7.28 (s, 1H, 9-H); MS *m/z* 291 ($MH^+$), 293 ($MH^+$ + 2). Anal. Calcd for $C_{14}H_{11}ClN_2OS$: C, 57.83; H, 3.81; N, 9.63. Found: C, 57.84; H, 4.18; N, 9.50.

**5-(2-Hydroxyethylamino)-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (11).** To a suspension of **10a** (300 mg, 1.14 mmol) in 1,4-dioxane (5.0 mL) was added 2-aminoethanol (2.10 g, 34.4 mmol) and the mixture was heated at 100 °C for 22 h with stirring. Ice water (50 mL) was poured into the reaction mixture which was then extracted with EtOAc (100 mL x 3). The combined organic layer was washed with saturated brine, dried over anhydrous $Na_2SO_4$, and then evaporated in vacuo. The residue was recrystallized from DMF to give **11** (143 mg, 44%) as yellow needles, mp 290–292 °C; IR (Nujol) 3440, 3175 (NH and OH) $cm^{-1}$; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 3.44–3.68 (m, 6H, 1, 1', and 2'-H), 4.66 (t, $J$ = 8.7 Hz, 2H, 2-H), 7.54 (dd, $J$ = 7.8, 4.7 Hz, 1H, 9-H), 8.42 (dd, $J$ = 7.8, 1.6 Hz, 1H, 10-H), 8.71 (dd, $J$ = 4.7, 1.6 Hz, 1H, 8-H); MS *m/z* 288 ($MH^+$). Anal. Calcd for $C_{14}H_{13}N_3O_2S$: C, 58.52; H, 4.56; N, 14.62. Found: C, 58.36; H, 4.39; N, 14.46.

**5-(3-Hydroxypropylamino)-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (12).** To a suspension of **10a** (300 mg, 1.14 mmol) in 1,4-dioxane (5.0 mL) was added 3-amino-1-propanol (2.50 g, 33.3 mmol) and the reaction was heated at 80 °C for 18 h while stirring. Ice water (50 mL) was poured into the reaction mixture which was then extracted with EtOAc (100 mL x 3). The combined organic layer was washed with saturated brine, dried over anhydrous $Na_2SO_4$, and then evaporated in vacuo. The residue was recrystallized from MeOH to give **12** (141 mg, 41%) as yellow needles, mp 171–173 °C; IR (Nujol) 3340, 3180 (NH and OH) $cm^{-1}$; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 1.75 (quin, $J$ = 6.3 Hz, 2H, 2'-H), 3.41–3.58 (m, 6H, 1, 1', and 3'-H), 4.66 (t, $J$ = 8.6 Hz, 2H, 2-H), 6.78 (br, $D_2O$ exchangeable, 1H,

NH or OH), 7.55 (dd, *J* = 8.0, 4.7 Hz, 1H, 9-H), 8.43 (dd, *J* = 8.0, 1.7 Hz, 1H, 10-H), 8.71 (dd, *J* = 4.7, 1.7 Hz, 1H, 8-H); MS *m/z* 302 ($MH^+$). Anal. Calcd for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02; N, 13.94. Found: C, 59.70; H, 4.72; N, 13.72.

**5-(2-Hydroxyethoxy)-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (13).** To a mixture of **10a** (300 mg, 1.14 mmol) and ethylene glycol (5.0 mL) was added $K_2CO_3$ (470 mg, 3.40 mmol) and the reaction was heated at 100 °C for 9 h with stirring. Ice water (50 mL) was poured into the reaction mixture and the resulting precipitate was collected by filtration. Recrystallization from DMF gave **13** (144 mg, 44%) as colorless needles, mp 269–271 °C; IR (Nujol) 3180 (OH) $cm^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$) δ 3.63 (t, *J* = 8.6 Hz, 2H, 1-H), 3.77 (t, *J* = 5.0 Hz, 2H, 2'-H), 4.42 (t, *J* = 5.0 Hz, 2H, 1'-H), 4.77 (t, *J* = 8.6 Hz, 2H, 2-H), 7.60 (dd, *J* = 8.0, 4.6 Hz, 1H, 9-H), 8.50 (dd, *J* = 8.0, 1.5 Hz, 1H, 10-H), 8.76 (dd, *J* = 4.6, 1.5 Hz, 1H, 8-H); MS *m/z* 289 ($MH^+$). Anal. Calcd for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.20; N, 9.72. Found: C, 58.42; H, 4.13; N, 9.67.

**5-(3-Hydroxypropoxy)-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (14).** To a mixture of **10a** (300 mg, 1.14 mmol) and 1,3-propanediol (5.0 mL) was added $K_2CO_3$ (470 mg, 3.40 mmol) and the stirred mixture was heated at 100 °C for 10 h. Ice water (50 mL) was poured into the reaction mixture and the resulting precipitate was collected by filtration. Recrystallization from DMF gave **14** (174 mg, 50%) as colorless granules, mp 210–212 °C; IR (Nujol) 3300 (OH) $cm^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$) δ 1.92 (quin, *J* = 6.3 Hz, 2H, 2'-H), 3.55–3.67 (m, 4H, 1 and 3'-H), 4.47 (t, *J* = 6.3 Hz, 2H, 1'-H), 4.77 (t, *J* = 8.8 Hz, 2H, 2-H), 7.59 (dd, *J* = 8.1, 4.7 Hz, 1H, 9-H), 8.49 (dd, *J* = 8.1, 1.7 Hz, 1H, 10-H), 8.76 (dd, *J* = 4.7, 1.7 Hz, 1H, 8-H); MS *m/z* 303 ($MH^+$). Anal. Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27. Found: C, 59.53; H, 4.47; N, 9.18.

**5-(2-Hydroxyethylsulfanyl)-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (15).** To a solution of **10a** (300 mg, 1.14 mmol) in DMF (5.0 mL) were added 2-sulfanylethanol (890 mg, 11.4 mmol) and $K_2CO_3$ (630 mg, 4.56 mmol) and the mixture was then heated at 80 °C for 5 h with stirring. Ice water (50 mL) was poured into the reaction mixture and the resulting precipitate was collected by filtration. Recrystallization from DMF gave **15** (217 mg, 62%) as yellow needles, mp > 300 °C; IR (Nujol) 3200 (OH) $cm^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$) δ 3.30 (t, *J* = 6.3 Hz, 2H, 1'-H), 3.63–3.72 (m, 4H, 1 and 2'-H), 4.75 (t, *J* = 8.6 Hz, 2H, 2-H), 7.58 (dd, *J* = 8.1, 4.6 Hz, 1H, 9-H), 8.49 (dd, *J* = 8.1, 1.6 Hz, 1H, 10-H), 8.76 (dd, *J* = 4.6, 1.6 Hz, 1H, 8-H); MS *m/z* 305 ($MH^+$). Anal. Calcd for $C_{14}H_{12}N_2O_2S_2$: C, 55.24; H, 3.97; N, 9.20. Found: C, 55.37; H, 3.90; N, 9.24.

**5-(3-Hydroxypropylsulfanyl)-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (16).** To a solution of **10a** (300 mg, 1.14 mmol) in DMF (5.0 mL) were added 3-sulfanyl-1-propanol (1.05 g, 11.4 mmol) and $K_2CO_3$ (630 mg, 4.56 mmol) and the reaction was then heated at 80 °C for 3.5 h. Ice water (50

mL) was poured into the mixture and the resulting precipitate was collected by filtration. Recrystallization from 1,4-dioxane gave **16** (257 mg, 71%) as yellow needles, mp 189–191 °C; IR (Nujol) 3280 (OH) $cm^{-1}$; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 1.83 (quin, $J$ = 6.5 Hz, 2H, 2'-H), 3.33 (t, $J$ = 6.5 Hz, 2H, 1'-H), 3.52 (t, $J$ = 6.5 Hz, 2H, 3'-H), 3.69 (t, $J$ = 8.7 Hz, 2H, 1-H), 4.78 (t, $J$ = 8.7 Hz, 2H, 2-H), 7.61 (dd, $J$ = 8.0, 4.7 Hz, 1H, 9-H), 8.50 (dd, $J$ = 8.0, 1.5 Hz, 1H, 10-H), 8.60 (dd, $J$ = 4.7, 1.5 Hz, 1H, 8-H); MS *m/z* 319 ($MH^+$). Anal. Calcd for $C_{15}H_{14}N_2O_2S_2$: C, 56.58; H, 4.43; N, 8.80. Found: C, 56.41; H, 4.21; N, 8.72.

**5-(Pyrrolidin-1-yl)-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (17).** A mixture of **10a** (300 mg, 1.14 mmol) and pyrrolidine (5.0 mL) was heated at 80 °C for 7 h with stirring. Ice water (50 mL) was poured into the reaction mixture and the resulting precipitate was collected by filtration. Recrystallization from EtOAc gave **17** (240 mg, 71%) as yellow needles, mp 171–173 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 1.93–2.03 (m, 4H, 3' and 4'-H), 3.51 (t, $J$ = 8.6 Hz, 2H, 1-H), 3.66–3.75 (m, 4H, 2' and 5'-H), 4.64 (t, $J$ = 8.6 Hz, 2H, 2-H), 7.52 (dd, $J$ = 8.0, 4.6 Hz, 1H, 9-H), 8.40 (dd, $J$ = 8.0, 1.5 Hz, 1H, 10-H), 8.69 (dd, $J$ = 4.6, 1.5 Hz, 1H, 8-H); MS *m/z* 298 ($MH^+$). Anal. Calcd for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.65; H, 4.87; N, 14.05.

**5-(Piperidin-1-yl)-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (18).** A mixture of **10a** (300 mg, 1.14 mmol) and piperidine (5.0 mL) was heated at 100 °C for 14 h while being stirred. Ice water (50 mL) was poured into the reaction mixture and the resulting precipitate was collected by filtration. Recrystallization from *n*-hexane-benzene gave **18** (281 mg, 79%) as yellow needles, mp 146–148 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 1.65 (br, 6H, 3', 4', and 5'-H), 3.38–3.45 (m, 4H, 2' and 6'-H), 3.61 (t, $J$ = 8.6 Hz, 2H, 1-H), 4.71 (t, $J$ = 8.6 Hz, 2H, 2-H), 7.57 (dd, $J$ = 8.2, 4.6 Hz, 1H, 9-H), 8.46 (dd, $J$ = 8.2, 1.5 Hz, 1H, 10-H), 8.74 (dd, $J$ = 4.6, 1.5 Hz, 1H, 8-H); MS *m/z* 312 ($MH^+$). Anal. Calcd for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49. Found: C, 65.72; H, 5.28; N, 13.28.

**5-(Morpholin-4-yl)-1,2-dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (19).** A mixture of **10a** (300 mg, 1.14 mmol) and morpholine (5.0 mL) was heated at 100 °C for 29 h with stirring. Ice water (50 mL) was poured into the reaction mixture and the resulting precipitate was collected by filtration. Recrystallization from MeOH gave **19** (221 mg, 62%) as yellow needles, mp 220–222 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 3.39 (t, $J$ = 4.6 Hz, 4H, 4H, 3' and 5'-H), 3.63 (t, $J$ = 8.8 Hz, 2H, 1-H), 3.79 (t, $J$ = 4.6 Hz, 4H, 2' and 6'-H), 4.73 (t, $J$ = 8.8 Hz, 2H, 2-H), 7.57 (dd, $J$ = 7.9, 4.7 Hz, 1H, 9-H), 8.46 (dd, $J$ = 7.9, 1.5 Hz, 1H, 10-H), 8.74 (dd, $J$ = 4.7, 1.5 Hz, 1H, 8-H); MS *m/z* 314 ($MH^+$). Anal. Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41. Found: C, 61.16; H, 4.63; N, 13.26.

**4-Chloro-2-hydroxy-1-vinylpyrido[3',2':4,5]thieno[2,3-*c*]pyridine (20).** (method a): To a suspension of **10a** (200 mg, 0.761 mmol) in dry 1,4-dioxane (20 mL) was added aniline (210 mg, 2.25 mmol) and NaH (55 mg, 2.29 mmol) and the mixture was refluxed for 1 h. After removal of solvent in vacuo, ice

water (30 mL) was poured into the residue and the mixture was neutralized with 1N HCl aq. The resulting precipitate was collected by filtration. Recrystallization from EtOAc gave **20** (94.0 mg, 47%) as colorless needles, mp 265–270 °C (dec.); IR (Nujol) 3100 (OH) $cm^{-1}$; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 5.85 (dd, $J$ = 11.1, 1.9 Hz, 1H, 2'-H), 5.97 (dd, $J$ = 17.6, 1.9 Hz, 1H, 2'-H), 7.14 (dd, $J$ = 17.6, 11.1 Hz, 1H, 1'-H), 7.59 (dd, $J$ = 8.3, 5.3 Hz, 1H, 8-H), 8.76–8.84 (m, 2H, 7- and 9-H), 11.90 (br, $D_2O$ exchangeable, 1H, OH); MS *m/z* 263 ($MH^+$), 265 ($MH^+$ + 2). Anal. Calcd for $C_{12}H_7ClN_2OS$: C, 54.86; H, 2.69; N, 10.66. Found: C, 54.98; H, 2.90; N, 10.66. (method b): To a suspension of **10a** (200 mg, 0.761 mmol) in dry 1,4-dioxane (20 mL) was added NaH (110 mg, 4.58 mmol) and the mixture was refluxed for 48 h. After removal of solvent in vacuo, ice water (30 mL) was poured into the residue and the mixture was neutralized with 1N HCl aq. The resulting precipitate was collected by filtration. Recrystallization from EtOAc gave **20** (103 mg, 51%) as colorless needles. All analytical data were in good agreement with values obtained from the compound synthesized by method a.

**1,2-Dihydrofuro[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (21).** To a suspension of **10a** (1.00 g, 3.81 mmol) in 1,4-dioxane (50 mL) was added anhydrous hydrazine (2.44 g, 76.3 mmol) and the reaction was refluxed for 4 d. The resulting precipitate was collected by filtration to give the hydrazine intermediate (770 mg, mp >300 °C) as yellow micro needles, which was used without further purification. To a mixture of this intermediate in water (12 mL) and acetic acid (12 mL) under reflux was added dropwise 10% $CuSO_4$ aq. (10 mL) and the reaction mixture was further refluxed for 2 h. After cooling to room temperature, the mixture was basified with 10% NaOH aq. and then extracted with EtOAc (100 mL x 3). The combined organic layer was washed with saturated brine, dried over anhydrous $Na_2SO_4$, and evaporated in vacuo. The residue was recrystallized from 1,4-dioxane to give **21** (452 mg, 52%) as colorless micro prisms, mp 231–233 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 3.73 (t, $J$ = 8.7 Hz, 2H, 1-H), 4.77 (t, $J$ = 8.7 Hz, 2H, 2-H), 7.60 (dd, $J$ = 8.0, 4.7 Hz, 1H, 9-H), 8.52 (dd, $J$ = 8.0, 1.6 Hz, 1H, 10-H), 8.65 (s, 1H, 5-H), 8.76 (dd, $J$ = 4.7, 1.6 Hz, 1H, 8-H); MS *m/z* 229 ($MH^+$). HRMS *m/z* 229.0475 (Calcd for $C_{12}H_9N_2OS$: 229.0436).

**Furo[2,3-*b*]pyrido[3',2':4,5]thieno[3,2-*d*]pyridine (5).** To a mixture of **21** (400 mg, 1.75 mmol) and 1,4-dioxane (50 mL) was added DDQ (1.60 g, 7.14 mmol) and the reaction was refluxed for 5 d. After removal of solvent in vacuo, $Et_2O$ (100 mL) was poured into the residue and the solution was washed with 10% NaOH aq. (50 mL x 3), saturated brine, dried over anhydrous $Na_2SO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel. The eluate of *n*-hexane-EtOAc (1:1) was evaporated and the residue was recrystallized from cyclohexane to give **5** (227 mg, 57%) as colorless needles, mp 243–245 °C; $^1$H NMR (200 MHz, DMSO-$d_6$) δ 7.32 (d, $J$ = 2.4 Hz, 1H, 1-H), 7.54 (dd, $J$ = 8.0, 4.7 Hz, 1H, 9-H), 7.95 (d, $J$ = 2.4 Hz, 1H, 2-H), 8.61 (dd, $J$ = 8.0, 1.7 Hz, 1H, 10-H), 8.82 (dd, $J$ = 4.7, 1.7 Hz,

1H, 8-H), 8.87 (s, 1H, 5-H); MS *m/z* 227 ($MH^+$). Anal. Calcd for $C_{12}H_6N_2OS$: C, 63.70; H, 2.67; N, 12.38. Found: C, 63.48; H, 2.97; N, 12.28.

**Effects on LPL mRNA expression in 3T3-L1 preadipocytes** The effects were assayed according to the literature procedure.[9]

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## REFERENCES

1. T. J. Snape, *Chem. Soc. Rev.*, 2008, **37**, 2452.
2. W. R. Erickson and M. J. McKennon, *Tetrahedron Lett.*, 2000, **41**, 4541.
3. A. Kimbaris, J. Cobb, G. Tsakonas, and G. Varvounis, *Tetrahedron*, 2004, **60**, 8807.
4. L. H. Mitchell and N. C. Barvian, *Tetrahedron Lett.*, 2004, **45**, 5669.
5. T. J. Snape, *Synlett*, 2008, 2689.
6. T. Hirota, T. Matsushita, K. Sasaki, and S. Kashino, *Heterocycles*, 1995, **41**, 2565.
7. K. Sasaki, A. S. S. Rouf, and T. Hirota, *J. Heterocycl. Chem.*, 1996, **33**, 49.
8. K. Okuda, M. Yoshida, T. Hirota, and K. Sasaki, *Chem. Pharm. Bull.*, 2010, **58**, 363.
9. K. Okuda, H. Deguchi, S. Kashino, T. Hirota, and K. Sasaki, *Chem. Pharm. Bull.*, 2010, **58**, 685.
10. H. Sugiyama, M. Yoshida, K. Mori, T. Kawamoto, S. Sogabe, T. Takagi, H. Oki, T. Tanaka, H. Kimura, and Y. Ikeura, *Chem. Pharm. Bull.*, 2007, **55**, 613.
11. M. Masaki and S. Matsunami, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3274.
12. Y. W. Ho and I. J. Wang, *J. Heterocycl. Chem.*, 1995, **32**, 819.
13. F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456.
14. R. B. Goldberg, *Curr. Atheroscler. Rep.*, 2006, **8**, 397.
15. E. V. Brown, *J. Am. Chem. Soc.*, 1954, **76**, 3167.