Preparation of a Series of Benzothieno[3,2-*b*]pyridine-3-carbonitriles and Benzofuro[3,2-*b*]pyridine-3-carbonitriles

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New and shorter routes to the benzothieno[3,2-*b*]pyridine-3-carbonitrile and benzofuro[3,2-*b*]pyridine-3-carbonitrile ring systems are reported. These heterocycles may function as new templates for kinase inhibitors.

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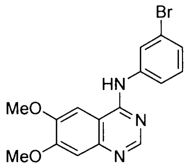
Introduction.

Protein kinases are enzymes that phosphorylate selective amino acid residues on proteins resulting in numerous and diverse cell signaling events, including aberrant cell proliferation. Therefore, small molecule kinase inhibitors can potentially be used to treat various diseases, including cancer. The first potent kinase inhibitor identified was **1**, a 4-anilinoquinazoline, which selectively inhibited the activity of the epidermal growth factor receptor tyrosine kinase (EGFr) [1]. Subsequently, it was shown that variation of the aniline group at C-4 of **1** provided selectivity for other kinases [2]. The versatility of the quinazoline ring system as a template for kinase inhibitors is illustrated by the several 4-anilinoquinazolines currently in clinical trials for the treatment of cancer, including the EGFr inhibitor **2** [3] and the vascular endothelial growth factor receptor tyrosine kinase (VEGFr) inhibitor **3** [4].



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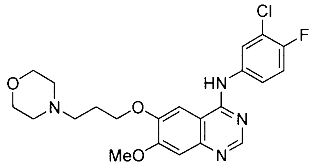

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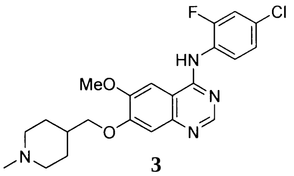

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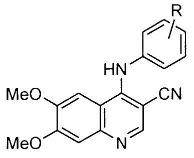
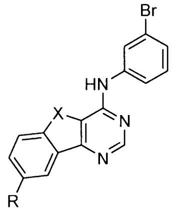
The 3-quinolinecarbonitrile ring system has also been used as a template for kinase inhibitors. As was seen with the quinazoline core, varying the aniline group at C-4 of the 3-quinolinecarbonitrile changed the kinase specificity. The 4-anilino-3-quinolinecarbonitriles **4a**, **4b** and **4c** were previously reported to be potent and selective inhibitors of EGFr [5], mitogen-activated protein kinase [6] and Src kinase [7], respectively. Additional heterocyclic systems utilized as templates for kinase inhibitors include the benzo[*b*]thieno[3,2-*d*]pyrimidines **5a**,**c,d** and the benzo[*b*]furo[3,2-*d*]pyrimidine **5b** which were reported to be inhibitors of EGFr [8]. The acrylamide derivative of **5d**, namely **5e**, was shown to form a covalent bond with the sulfur atom of a cysteine residue in the inhibitor binding pocket of EGFr thereby irreversibly inhibiting the enzyme [9]. Since both the quinazoline and 3-quinolinecarbonitrile groups could be used as templates for kinase inhibitors, the corresponding benzothieno[3,2-*b*]pyridine-3-carbonitrile and benzofuro[3,2-*b*]pyridine-3-carbonitrile analogs of **5a-e** were prepared as potential EGFr inhibitors. In addition, various substituted aniline moieties were employed at C-4 in the hope that these new heterocyclic cores could provide inhibitors of other kinases.



4a: R = 3-Br
4b: R = 4-OPh
4c: R = 2,4-diCl



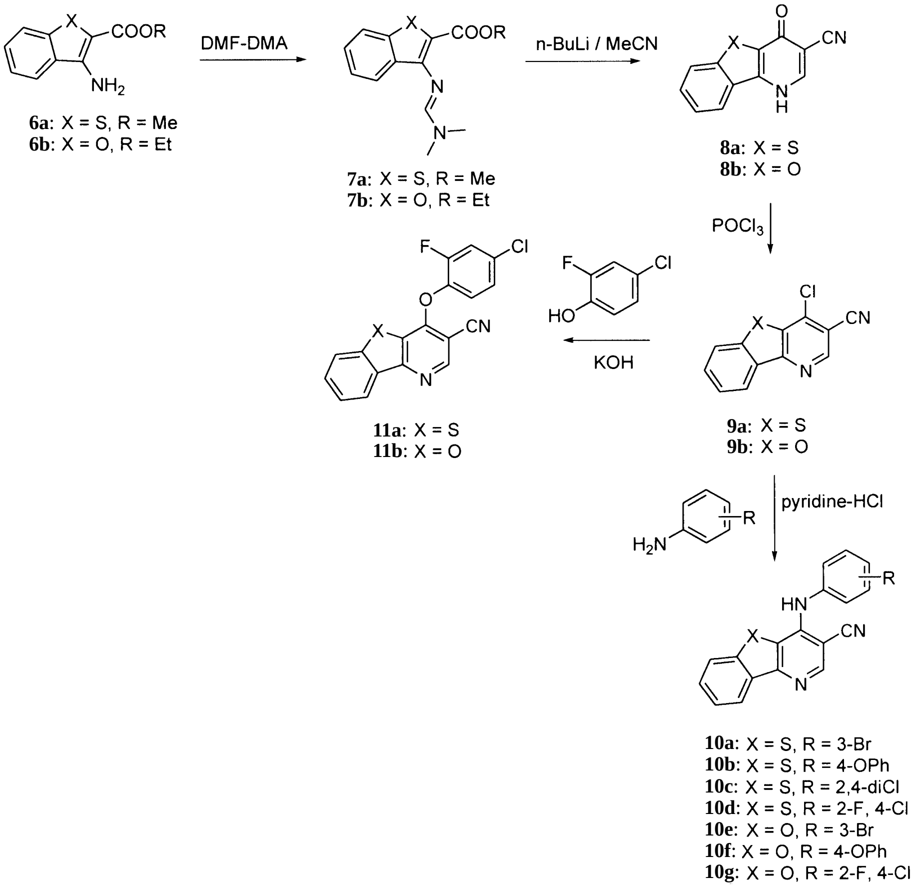
5a: X = S, R = H
5b: X = O, R = H
5c: X = S, R = NO_2
5d: X = S, R = NH_2
5e: X = S, R = $NHC(O)CH=CH_2$

Results.

Methyl 3-aminobenzo[*b*]thiophene-2-carboxylate (**6a**) [10] was converted to the amidine **7a** by treatment with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA). Reaction of **7a** with the anion of acetonitrile, generated *in situ* by the reaction of *n*-butyl lithium with acetonitrile at reduced temperature, gave the tricyclic derivative **8a**. Chlorination of **8a** with phosphorous oxychloride provided the key intermediate **9a** in an overall yield of 38% from **6a**. The synthetic route described here is more efficient than a recently reported route wherein **9a** was obtained in 7 steps from the potassium salt of the acid corresponding to **6a** in an overall yield of 5% [11]. Reaction of **9a** with 3-bromoaniline in 2-ethoxyethanol in the presence of pyridine hydrochloride resulted in **10a**. Additional substituted anilines were added under the same conditions to give the 4-anilino-[1]benzothieno[3,2-*b*]pyridine-3-carbonitriles

10b-**d** in yields of 58-66%. Treatment of **9a** with 4-chloro-2-fluorophenol with potassium hydroxide as base provided the 4-phenoxy derivative **11a** in 55% yield.

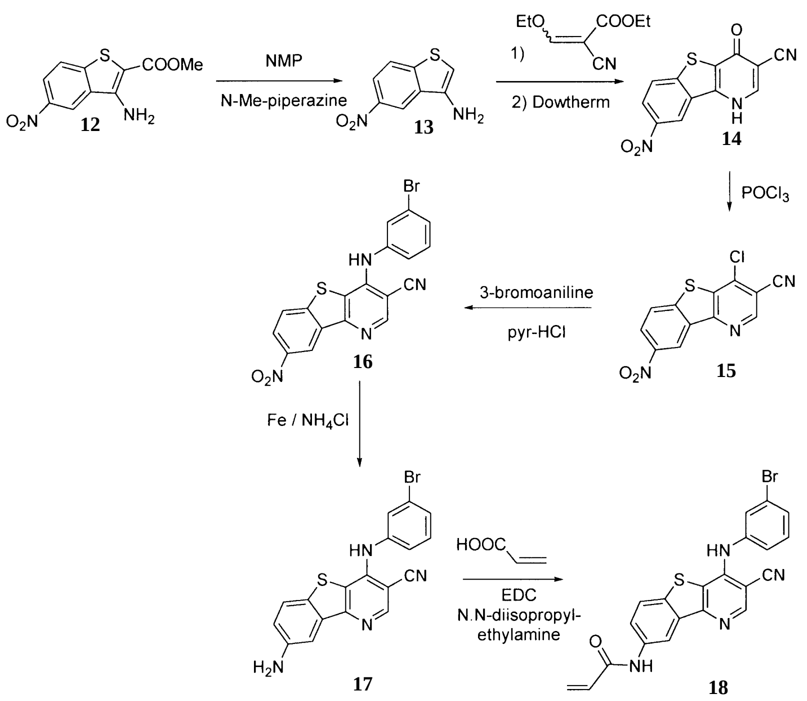
An analogous synthetic sequence was utilized for the preparation of the benzofuro[3,2-*b*]pyridine-3-carbonitriles from **6b** [12]. Surprisingly, in the formation of **8b** from the amidine **7b**, it was necessary to heat the initially formed intermediate in acetic acid at reflux in order to obtain the desired tricyclic product. Chlorination of **8b** readily provided **9b** in an overall yield of 40% from **6b**. The synthetic route described here is therefore again more efficient than a recently reported route wherein **9b** was obtained in 7 steps from the potassium salt of the acid corresponding to **6b** in an overall yield of 9% [13]. Displacement of the 4-chloro substituent of **9b** with various substituted anilines provided **10e**-**g** in yields of 35-42%. The 4-phenoxy compound **11b** was obtained in 44% yield by displacement of the 4-chloro substituent of **9b** with 4-chloro-2-fluorophenol.



Attempts to apply the route used for the synthesis of **8a** to the preparation of the corresponding 8-nitro analog was unsuccessful. While methyl 3-amino-5-nitrobenzo[*b*]thiophene-2-carboxylate (**12**) [14] was readily converted to the corresponding amidine, treatment of this amidine with the anion of acetonitrile resulted only in intractable material. Therefore, **12** was decarboxylated in refluxing *N*-methyl-2-pyrrolidinone (NMP) and *N*-methylpiperazine [15] to provide **13**. This amine was treated with ethyl (ethoxymethylene)cyanoacetate and the intermediate was subjected to high temperature to provide the desired tricyclic compound **14** in an overall yield of 23% from **12**. Chlorination of **14** gave **15**, which was treated with 3-bromoaniline under the conditions reported earlier to afford **16**. Reduction of the 8-nitro group of **16** to the amine **17** was accomplished by reaction with iron and ammonium chloride in aqueous methanol. The low yield in this reaction (35%) may be due to the poor solubility of both **16** and **17**. Treatment of **17** with acrylic acid using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) as the coupling agent in the presence of *N*,*N*-diisopropylethylamine provided **18**.

Conclusion.

In summary, we present here new and shorter routes to the benzothieno[3,2-*b*]pyridine-3-carbonitrile and benzofuro[3,2-*b*]pyridine-3-carbonitrile ring systems.



In addition, both anilines and phenols can readily replace the 4-chloro substituent of these heterocycles. The biological activity of these compounds will be reported elsewhere.

EXPERIMENTAL

General Methods.

Melting points were determined in open capillary tubes on a Meltemp melting point apparatus and are uncorrected. ^{1}H nmr spectra were recorded in deuteriodimethylsulfoxide using a NT-300 WB spectrometer. Chemical shifts (δ) are in parts per million referenced to tetramethylsilane as an internal standard. Electrospray (es) mass spectra were recorded on a Micromass Platform spectrometer. Electron impact (ei) and high resolution mass spectra were obtained on a Finnigan MAT-90 spectrometer. Flash chromatography was performed with Baker 40 µM silica gel. Reactions were carried out under an inert atmosphere of either nitrogen or argon.

3-[[(Dimethylamino)methylene]amino]-benzo[*b*]thiophene-2-carboxylic Acid Methyl Ester (**7a**).

A mixture of 3.38 g (16.32 mmol) of **6a** [10] in 8 ml of *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) was heated at reflux for 2 hours and then allowed to cool to room temperature. The solid was collected by filtration and washed with hexane and ethyl acetate to provide 3.96 g (93%) of **7a** as a white solid, mp 73-74 °C; ^{1}H nmr: δ 3.06 (s, 6H), 3.75 (s, 3H), 7.47 (t, J = 8 Hz, 1H), 7.50 (t, J = 8 Hz, 1H), 7.78 (d, J = 8 Hz, 1H), 7.82-7.89 (m, 2H); ms: m/z 262.9 $(M+H)^+$.

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.25; H, 5.32; N, 10.58.

3-[[(Dimethylamino)methylene]amino]-benzofuran-2-carboxylic Acid Ethyl Ester (**7b**).

A mixture of 4.20 g (20.5 mmol) of **6b** [12] in 10 ml of *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) was heated at reflux for 1.5 hours then cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with water, dried over sodium sulfate, filtered through Celite and reduced in volume under reduced pressure. The solid was collected by filtration to provide 3.90 g (73%) of **7b** as a white solid, mp 89-90°C; ^{1}H nmr: δ 1.30 (t, J = 7 Hz, 3H), 3.04 (s, 3H), 3.06 (s, 3H), 4.25 (t, J = 7 Hz, 2H), 7.38 (t, J = 8 Hz, 1H), 7.49 (t, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.68 (d, J = 8 Hz, 1H), 7.99 (s, 1H); ms: m/z 260.9 $(M+H)^+$.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.45; H, 6.04; N, 10.64.

1,4-Dihydro-4-oxo-[1]benzothieno[3,2-*b*]pyridine-3-carbonitrile (**8a**).

A solution of 1.6 ml (30.6 mmol) of acetonitrile in 10 ml of tetrahydrofuran was added to a cooled (-78 °C) solution of 12.5 ml of 2.5 *M* *n*-butyl lithium in hexane (31.2 mmol) in 40 ml of tetrahydrofuran. After stirring for 10 minutes, a solution of 4.0 g (15.2 mmol) of **7a** in 40 ml of tetrahydrofuran was added dropwise over 1 hour. The reaction mixture was stirred at reduced temperature for 30 minutes and then was allowed to warm to room temperature. After stirring at room temperature for 1 hour, the reaction mixture was cooled to -50 °C and 2.1 ml of acetic acid was added. The solution was concentrated under reduced pressure and poured into water. The aqueous solution was extracted with ethyl acetate and aqueous HCl was added to the aqueous layer. The product was extracted into ethyl acetate and the organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Ethyl acetate and hexane were added to the residue and the resulting tan solid was collected to provide 2.20 g (64%) of **8a**. An analytical sample was obtained by recrystallization from diethyl ether and hexane, mp > 300 °C; ^{1}H nmr: δ 7.65 (m, 2H), 8.17 (d, J = 7 Hz, 1H), 8.44 (d, J = 7 Hz, 1H), 8.84 (s, 1H); ms: m/z 224.9 $(M-H)^-$.

Anal. Calcd. for $C_{12}H_6N_2OS \times 0.25\ H_2O$: C, 62.46; H, 2.84; N, 12.14. Found: C, 62.52; H, 2.93; N, 12.00.

1,4-Dihydro-4-oxo-[1]benzofuro[3,2-*b*]pyridine-3-carbonitrile (**8b**).

A solution of 1.5 ml (28.6 mmol) of acetonitrile in 30 ml of tetrahydrofuran was added to a –78 °C solution of 11.4 ml of 2.5 *M n*-butyl lithium in hexane (29.0 mmol) in 35 ml of tetrahydrofuran. After stirring for 15 minutes, a solution of 3.7 g (14.2 mmol) of **7b** in 50 ml of tetrahydrofuran was added dropwise. The reaction mixture was stirred at -78 °C for 30 minutes then allowed to warm to 0 °C. The reaction mixture was again cooled to –78 °C and 3 ml of acetic acid was added. The solution was allowed to warm to room temperature and the resulting precipitate was collected. This solid was combined with 20 ml of acetic acid and heated at reflux for 1.5 hours. The mixture was cooled to room temperature and the solid was collected by filtration washing with saturated sodium bicarbonate, water, diethyl ether and ethyl acetate to provide 2.45 g (79%) of **8b** as a red solid, mp > 310 °C; ^{1}H nmr: δ 7.53 (t, J = 7 Hz, 1H), 7.72 (t, J = 7 Hz, 1H), 7.86 (d, J = 8 Hz, 1H), 8.13 (d, J = 8 Hz, 1H), 8.80 (s, 1H); ms: m/z 210.8 $(M+H)^+$.

Anal. Calcd. for $C_{12}H_6N_2O_2 \times 0.50\ H_2O$: C, 65.75; H, 3.22; N, 12.78. Found: C, 65.51; H, 3.19; N, 12.94.

4-Chloro-[1]benzothieno[3,2-*b*]pyridine-3-carbonitrile (**9a**).

A mixture of 1.01 g (4.38 mmol) of **8a** and 7 ml of phosphorous oxychloride was heated at reflux for 40 minutes then cooled to room temperature. Hexane was added and the solid was collected by filtration, dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to a small volume. The solids were collected by filtration to give 696 mg (65%) of **9a**, mp 305-308 °C; ^{1}H nmr: δ 7.70 (t, J = 8 Hz, 1H), 7.80 (t, J = 8 Hz, 1H), 8.26 (d, J = 8 Hz, 1H), 8.45 (d, J = 8 Hz, 1H), 9.20 (s, 1H); ms: m/z 244.6, 246.6 $(M+H)^+$.

Anal. Calcd. for $C_{12}H_5ClN_2S$: C, 58.90; H, 2.06; N, 11.45. Found: C, 58.29; H, 2.13; N, 11.27.

4-Chlorobenzofuro[3,2-*b*]pyridine-3-carbonitrile (**9b**).

A mixture of 2.10 g (9.58 mmol) of **8b** in 15 ml of phosphorous oxychloride was heated at reflux for 1.5 hours then cooled to room temperature. Hexane was added and the resulting solid was collected by filtration, dissolved in ethyl acetate and washed with cold 1 *N* aqueous sodium hydroxide. The organic layer was dried over sodium sulfate, filtered through Celite and concentrated under reduced pressure to give 1.55 g (71%) of **9b** as a red solid, mp 229-231 °C; ^{1}H nmr: δ 7.64 (t, J = 7 Hz, 1H), 7.87 (t, J = 7 Hz, 1H), 8.00 (d, J = 8 Hz, 1H), 8.28 (d, J = 8 Hz, 1H), 9.14 (s, 1H); ms: m/z 228.9, 230.6 $(M+H)^+$.

Anal. Calcd. for $C_{12}H_5ClN_2O$: C, 63.04; H, 2.20; N, 12.25. Found: C, 62.83; H, 2.26; N, 12.12.

General Procedure for the Reaction of **9a** and **9b** with Substituted Anilines to Provide **10a-g**.

A solution of 150 mg (0.61 mmol) of **9a** in 3 ml of 2-ethoxyethanol containing 0.74 mmol of a substituted aniline and 71 mg (0.61 mmol) of pyridine hydrochloride was heated at reflux for 4 – 30 hours. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate and the organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Diethyl ether was added to the residue and the resultant solid was collected by filtration to give the desired product.

4-[(3-Bromophenyl)amino]-[1]benzothieno[3,2-*b*]pyridine-3-carbonitrile (**10a**).

Compound **10a** was obtained as a white solid in 58% yield, mp 240-242 °C; ^{1}H nmr: δ 7.24 (d, J = 8 Hz, 1H), 7.31-7.43 (m, 3H), 7.52-7.68 (m, 2H), 8.06 (d, J = 8 Hz, 1H), 8.37 (d, J = 8 Hz, 1H), 8.83 (s, 1H), 9.84 (s, 1H); ms: m/z 379.9, 381.7 $(M+H)^+$.

Anal. Calcd. for $C_{18}H_{10}BrN_3S \times 0.5\ H_2O$: C, 55.54; H, 2.85; N, 10.79. Found: C, 55.84; H, 2.79; N, 10.73.

4-[(4-Phenoxyphenyl)amino]-[1]benzothieno[3,2-*b*]pyridine-3-carbonitrile (**10b**).

Compound **10b** was obtained as a light tan solid in 60% yield, mp 230-233 °C; ^{1}H nmr: δ 7.06-7.19 (m, 5H), 7.32-7.47 (m, 4H), 7.55-7.86 (m, 2H), 8.05 (d, J = 8 Hz, 1H), 8.34 (d, J = 8 Hz, 1H), 8.75 (s, 1H), 9.65 (s, 1H); ms: m/z 393.9 $(M+H)^+$.

Anal. Calcd. for $C_{24}H_{15}N_3OS \times 0.5\ H_2O$: C, 71.62; H, 4.01; N, 10.44. Found: C, 71.99; H, 3.80; N, 10.56.

4-[(2,4-Dichlorophenyl)amino]-[1]benzothieno[3,2-*b*]pyridine-3-carbonitrile (**10c**).

Compound **10c** was obtained as a yellow solid in 66% yield, mp 260-262 °C; ^{1}H nmr: δ 7.55-7.72 (m, 4H), 7.83 (s, 1H), 8.06 (d, J = 8 Hz, 1H), 8.35 (d, J = 8 Hz, 1H), 8.79 (s, 1H), 9.76 (s, 1H); ms: m/z 369.8, 371.8 $(M+H)^+$.

Anal. Calcd. for $C_{18}H_9Cl_2N_3S \times 0.25\ H_2O$: C, 57.68; H, 2.55; N, 11.21. Found: C, 57.64; H, 2.48; N, 10.94.

4-[(4-Chloro-2-fluorophenyl)amino]-[1]benzothieno[3,2-*b*]pyridine-3-carbonitrile (**10d**).

Compound **10d** was obtained as an off-white solid in 66% yield, mp 250-251 °C; ^{1}H nmr: δ 7.40 (d, J = 9 Hz, 1H), 7.50-7.69 (m, 4H), 8.08 (d, J = 8 Hz, 1H), 8.37 (d, J = 8 Hz, 1H), 8.80 (s, 1H), 9.68 (s, 1H); ms: m/z 353.8, 355.8 $(M+H)^+$.

Anal. Calcd. for $C_{18}H_9ClFN_3S$: C, 61.11; H, 2.56; N, 11.88. Found: C, 61.50; H, 2.58; N, 11.65.

4-[(3-Bromophenyl)amino]-benzofuro[3,2-*b*]pyridine-3-carbonitrile (**10e**).

Compound **10e** was obtained as a light tan solid in 42% yield, mp 242-245 °C; ^{1}H nmr: δ 7.21-7.57 (m, 5H), 7.70 (d, 2H), 8.18 (d, 1H), 8.74 (s, 1H), 9.93 (s, 1H); ms: m/z 361.8, 363.8 $(M-H)^-$.

Anal. Calcd. for $C_{18}H_{10}BrN_3O$: C, 59.36; H, 2.77; N, 11.54. Found: C, 59.01; H, 2.97; N, 11.36.

4-[(4-Phenoxyphenyl)amino]-benzofuro[3,2-*b*]pyridine-3-carbonitrile (**10f**).

Compound **10f** was obtained as a light tan solid in 35% yield, mp 175-179 °C; ^{1}H nmr: δ 7.01-7.18 (m, 5H), 7.31-7.45 (m, 4H), 7.54 (m, 1H), 7.65-7.73 (m, 2H), 8.15 (d, J = 7 Hz, 1H), 8.62 (s, 1H), 9.83 (s, 1H); ms: m/z 377.9 $(M+H)^+$.

Anal. Calcd. for $C_{24}H_{15}N_3O_2$: C, 76.38; H, 4.01; N, 11.13. Found: C, 76.13; H, 3.96; N, 11.14.

4-[(4-Chloro-2-fluorophenyl)amino]-benzofuro[3,2-*b*]pyridine-3-carbonitrile (**10g**).

Compound **10g** was obtained as a light tan solid in 40% yield, mp 259-261 °C; ^{1}H nmr: δ 7.24-7.39 (m, 2H), 7.43-7.53 (m, 2H), 7.61 (d, J = 4 Hz, 2H), 8.09 (d, J = 7 Hz, 1H), 8.49 (s, 1H), 10.07 (s, 1H); ms: m/z 337.8, 339.8 $(M+H)^+$.

Anal. Calcd. for $C_{18}H_9ClFN_3O$ x 1.0 H_2O: C, 60.77; H, 3.12; N, 11.81. Found: C, 60.41; H, 2.70; N, 11.60.

4-(4-Chloro-2-fluorophenoxy)-[1]benzothieno[3,2-*b*]pyridine-3-carbonitrile (**11a**).

A mixture of 0.59 ml (5.5 mmol) of 4-chloro-2-fluorophenol and 100 mg (1.78 mmol) of potassium hydroxide was heated to give a solution. To this solution was added 245 mg (1.00 mmol) of **9a** and the mixture was heated for 2 hours. Ethyl acetate was added and the solution was washed with 1 *N* aqueous sodium hydroxide. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The solid was collected and recrystallized from ethyl acetate to give 195 mg (55%) of **11a** as a light tan solid, mp 174-175 °C; ^{1}H nmr: δ 7.49 (m, 1H), 7.64-7.77 (m, 3H), 7.86 (m, 1H), 8.15 (d, J = 7 Hz, 1H), 8.46 (d, J = 7 Hz, 1H), 9.19 (s, 1H); ms: m/z 354.8, 356.8 $(M+H)^+$.

Anal. Calcd. for $C_{18}H_8ClFN_2OS$ x 0.3 H_2O: C, 60.02; H, 2.41; N, 7.78. Found: C, 60.32; H, 2.38; N, 7.25.

4-(4-Chloro-2-fluorophenoxy)-benzofuro[3,2-*b*]pyridine-3-carbonitrile (**11b**).

A mixture of 0.43 ml (4.1 mmol) of 4-chloro-2-fluorophenol and 70 mg (1.25 mmol) of potassium hydroxide was heated to give a solution. To this solution was added 170 mg (0.74 mmol) of **9b** and the mixture was heated for 1 hour. Ethyl acetate was added and the solution was washed with 1 *N* aqueous sodium hydroxide. The organic layer was dried over sodium sulfate, filtered through Celite and reduced in volume under reduced pressure. The solid was collected to give 115 mg (44%) of **11b** as a light tan solid, mp 138-140 °C; ^{1}H nmr: δ 7.41 (d, J = 9 Hz, 1H), 7.57-7.85 (m, 5H), 8.25 (d, J = 8 Hz, 1H), 9.10 (s, 1H); ms: m/z 338.8, 340.8 $(M+H)^+$.

Anal. Calcd. for $C_{18}H_8ClFN_2O_2$ x 0.5 H_2O: C, 62.16; H, 2.61; N, 8.06. Found: C, 62.00; H, 2.34; N, 7.71.

5-Nitrobenzo[*b*]thiophen-3-amine (**13**).

A solution of 23.0 g (91.3 mmol) of **12** [14] in 100 ml of *N*-methyl-2-pyrrolidinone (NMP) and 30 ml *N*-methylpiperazine was heated at 180 °C for 2 hours. The reaction was cooled to room temperature and poured into water. The resultant solid was collected by filtration, washing with water. The solid was dissolved in a mixture of ethyl acetate and diethyl ether and the solution was washed twice with water. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. Diethyl ether and hexane were added to the residue and the dark red solid was collected by filtration to provide 11.17 g (63%) of **13**, mp 155-158 °C; ^{1}H nmr: δ 5.67 (s, 2H), 6.39 (s, 1H), 8.05-8.14 (m, 2H), 8.88 (s, 1H); ms: m/z 194.9 $(M+H)^+$.

Anal. Calcd. for $C_8H_6N_2O_2S$: C, 49.48; H, 3.11; N, 14.42. Found: C, 49.73; H, 3.25; N, 14.13.

1,4-Dihydro-8-nitro-4-oxo-[1]benzothieno[3,2-*b*]pyridine-3-carbonitrile (**14**).

A mixture of 9.00 g (46.34 mmol) of **13** and 8.65 g (51.12 mmol) of ethyl (ethoxymethylene)cyanoacetate in 100 ml of toluene was heated at reflux for 2 hours. The reaction mixture was cooled to room temperature and the resulting precipitate was collected by filtration washing with diethyl ether to provide 11.50 g (78%) of a bright yellow solid. A portion (2.33 g) of this solid was added to 40 ml of Dowtherm-A and the mixture was heated at reflux for 4 hours. The mixture was cooled slightly to form a precipitate which was collected by filtration washing with diethyl ether and hexane to give 925 mg (46%) of **14** as a brown solid, mp > 305 °C; ^{1}H nmr: δ 8.43 (s, 2H), 8.95 (s, 1H), 9.45 (s, 1H); ms: m/z 270.2 $(M-H)^-$.

Anal. Calcd. for $C_{12}H_5N_3O_3S$: C, 53.14; H, 1.86; N, 15.49. Found: C, 52.81; H, 2.07; N, 15.31.

4-Chloro-8-nitro-[1]benzothieno[3,2-*b*]pyridine-3-carbonitrile (**15**).

A mixture of 1.22 g (4.49 mmol) of **14** in 20 ml of phosphorous oxychloride was heated at reflux for 3 hours then cooled to room temperature. The precipitated solid was collected by filtration, washed with hexane and then saturated aqueous sodium bicarbonate and water. The solid was dried to give 947 mg (68%) of **15** as a dark brown solid, mp softens at 270 °C; ^{1}H nmr: δ 8.59 (s, 2H), 9.09 (s, 1H), 9.34 (s, 1H); ms: m/z 289.0, 291.0 $(M+H)^+$.

Anal. Calcd. for $C_{12}H_4ClN_3O_2S$ x 1.0 H_2O: C, 46.83; H, 1.97; N, 13.66. Found: C, 47.10; H, 1.63; N, 13.54.

4-[(3-Bromophenyl)amino]-8-nitro[1]benzothieno[3,2-*b*]pyridine-3-carbonitrile (**16**).

A solution of 400 mg (1.30 mmol) of **15**, 160 mg (1.38 mmol) of pyridine hydrochloride and 0.18 ml (1.65 mmol) of 3-bromoaniline in 8 ml of 2-ethoxyethanol was heated at reflux for 4 hours. The reaction mixture was filtered while hot and the collected solid was stirred with methanol and ammonium hydroxide. The mixture was poured into water and the solid was collected, washing with ethyl acetate to give 363 mg (66%) of **16** as a brown solid, mp > 300 °C; ^{1}H nmr: δ 7.32 (d, J = 8 Hz, 1H), 7.40 (t, J = 8 Hz, 1H), 7.52 (m, 2H), 8.37 (d, J = 8 Hz, 1H), 8.43 (dd, J = 8, 2 Hz, 1H), 8.92 (s, 1H), 9.01 (d, J = 2 Hz, 1H), 10.03 (s, 1H); ms: m/z 425.0, 427.1 $(M+H)^+$.

Anal. Calcd. for $C_{18}H_9BrN_4O_2S$: C, 50.84; H, 2.13; N, 13.17. Found: C, 50.77; H, 2.47; N, 13.01.

8-Amino-4-[(3-bromophenyl)amino]-[1]benzothieno[3,2-*b*]pyridine-3-carbonitrile (**17**).

A mixture of 436 mg (1.03 mmol) of **16**, 291 mg (5.19 mmol) of iron powder and 416 mg (7.77 mmol) of ammonium chloride in 160 ml of methanol and 110 ml of water was heated at reflux for 5.5 hours. The reaction mixture was filtered hot and the solid residue was extracted with several portions of hot ethyl acetate followed by hot methanol. The organic layers were combined, washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Diethyl ether and hexane were added and the solid was collected by filtration to provide 87 mg (21%) of **17**. The filtrate was concentrated and purified by flash chromatography eluting with a gradient of 1:1 hexane:ethyl acetate to all ethyl acetate to give an additional 56 mg (14%) of **17** as a bright yellow solid, mp 295-300 °C dec; ^{1}H nmr: δ 5.43 (s, 2H), 6.95 (dd, J = 8, 2 Hz, 1H), 7.21 (m, 1H), 7.29-7.40 (m, 3H), 7.51 (d, J = 2 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), (8.77 (s, 1H), 9.67 (s, 1H); ms: m/z 395.2, 397.2 $(M+H)^+$.

Anal. Calcd. for $C_{18}H_{11}BrN_4S$: C, 54.69; H, 2.80; N, 14.17. Found: C, 54.37; H, 2.85; N, 13.98.

N-[4-[(3-Bromophenyl)amino]-3-cyano[1]benzothieno[3,2-*b*]pyridin-8-yl]-2-propenamide (**18**).

To a cooled (0 °C) solution of 164 mg (0.42 mmol) of **17** and 120 mg (0.63 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) in 2 ml of *N,N*-dimethylformamide and 2 ml of tetrahydrofuran was added 0.045 ml (0.66 mmol) of acrylic acid followed by 0.110 ml (0.63 mmol) of *N,N*-diisopropylethylamine. The reaction mixture was stirred at room temperature for 4 hours then partitioned between methylene choride and water. The aqueous layer was extracted with additional methylene chloride and the organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with a gradient of 5% methanol in methylene chloride to 10% methanol in methylene chloride to provide 69 mg (37%) of **18** as a light tan solid, mp >300 °C dec; ^{1}H nmr: δ 5.81 (dd, J = 10, 2 Hz, 1H), 6.32 (dd, J = 17, 2 Hz, 1H), 6.49 (dd, J = 17, 10 Hz, 1H), 7.25 (m, 1H), 7.30-7.47 (m, 2H), 7.80 (dd, J = 9, 2 Hz, 1H), 8.00 (d, J = 9 Hz, 1H), 8.84 (s, 1H), 8.90 (d, J = 2 Hz, 1H), 9.81 (s, 1H), 10.46 (s, 1H); ms: m/z 449.1, 451.2 $(M+H)^+$.

Anal. Calcd. for $C_{21}H_{13}BrN_4OS$: C, 56.13; H, 2.92; N, 12.47. Found: C, 55.91; H, 3.08; N, 12.18.

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REFERENCES AND NOTES

[1] D. W. Fry, A. J. Kraker, A. McMichael, L. A. Ambroso, J. M. Nelson, W. R. Leopold, R. W. Connors and A. J. Bridges, *Science*, **265**, 1093 (1994).

[2] Reviewed in D. H. Boschelli, *Drugs Future*, **24**, 515 (1999).

[3] A. J. Barker, K. H. Gibson, W. Grundy, A. A. Godfrey, J. J. Barlow, M. P. Healy, J. R. Woodburn, S. E. Ashton, B. J. Curry, L. Scarlett, L. Henthorn and L. Richards, *Bioorg. Med. Chem. Lett.*, **11**, 1911 (2001).

[4] L. F. Hennequin, E. S. E. Stokes, A. P. Thomas, C. Johnstone, P. A. Ple, D. J. Oglivie, M. Dukes, S. R. Wedge, J. Kendrew and J. O. Curwen, *J. Med. Chem.*, **45**, 1300 (2002).

[5] A. Wissner, D. M. Berger, D. H. Boschelli, M. B. Floyd, L. M. Greenberger, B. C. Gruber, B. D. Johnson, N. Mamuya, R. Nilakatan, M. F. Reich, R. Shen, H. R. Tsou, E. Upeslacis, Y. F. Wang, B. Wu, F. Ye and N. Zhang, *J. Med. Chem.*, **43**, 3244 (2000).

[6] N. Zhang, B. Wu, D. Powell, A. Wissner, M. B. Floyd, E. D. Kovacs, L. Toral-Barza and C. Kohler, *Bioorg. Med. Chem. Lett.*, **10**, 2825 (2000).

[7] D. H. Boschelli, D. Y. Wang, F. Ye, B. Wu, N. Zhang, M. Dutia, D. W. Powell, A. Wissner, K. Arndt, J. M. Weber and F. Boschelli, *J. Med. Chem.*, **44**, 822 (2001).

[8] H. D. H. Showalter, A. J. Bridges, H. Zhou, A. D. Sercel, A. McMichael and D. W. Fry, *J. Med. Chem*. **42**, 5464 (1999).

[9] A. J. Bridges, W. A. Denny, E. M. Dobrusin, A. M. Doherty, D. W. Fry, D. J. McNamara, H. D. H. Showalter, J. B. Smaill and H. Zhou, WO 9738983 (1997); *Chem. Abstr*., 1997: 3695; and H. Zhou, A. J. Bridges, S. Trumpp-Kallmeyer, D. Fry and J. M. Nelson, National Meeting of American Chemical Society, Boston, 1998; *Chem. Abstr*., 1998:529753.

[10] J. Beck, *J. Org. Chem*., **37**, 3224 (1972).

[11] K. Gorlitzer, C. Kramer and C. Boyle, *Pharmazie*, **55**, 595 (2000).

[12] S. S. Sangapure and Y. S. Agasimundin, *Indian J. Chem., Sect. B*, **14**, 688 (1976).

[13] K. Gorlitzer, C. Kramer and C. Boyle, *Pharmazie*, **55**, 651 (2000).

[14] A. J. Bridges and H. Zhou, *J. Heterocyclic Chem.*, **34**, 1163 (1997).

[15] M. H. Norman and F. Navas, WO 9316073 (1993); *Chem. Abstr*., 1994: 409406.