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Multicomponent synthesis and molecular structure of 3-amino-2-aroyl(alkoxycarbonyl, arylcarbamoyl)-4-aryl(hetaryl)-5-arylcarbamoyl-6-methylthieno[2,3-*b*]pyridines

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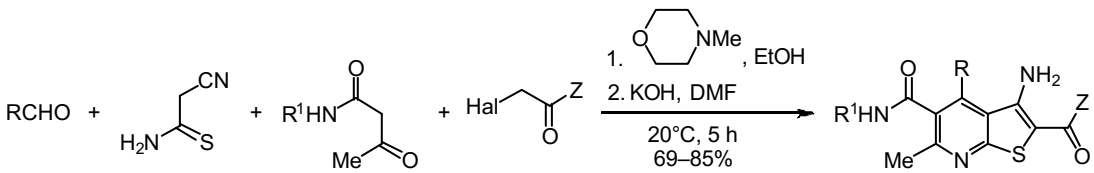


R, R^1 = Ar; Hal = Br, Cl; Z = Ar, NHAr, *n*-BuO, *i*-PrO

A new, effective method has been developed for the synthesis of functionalized thieno[2,3-*b*]pyridines by multicomponent condensation reactions of aromatic and heteroaromatic aldehydes, cyanothioacetamide, acetoacetanilides, and alkylating agents containing activated methylene groups. The structures of 3-amino-2-benzoyl-4-(furan-2-yl)-6-methyl-*N*-phenylthieno[2,3-*b*]pyridine-5-carboxamide, 3-amino-N^2-(4-bromophenyl)-N^5-(4-chlorophenyl)-6-methyl-4-(3-methylthiophen-2-yl)thieno[2,3-*b*]pyridine-2,5-dicarboxamide, and 3-amino-4-(2-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-(4-methylbenzoyl)thieno[2,3-*b*]pyridine-5-carboxamide were studied by X-ray structural analysis.

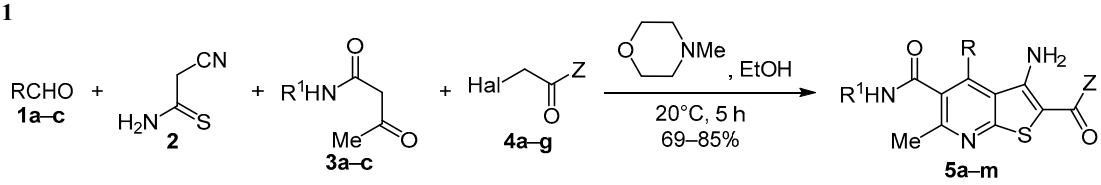
Keywords: acetoacetanilides, alkylating reagents, aromatic aldehydes, cyanothioacetamide, thieno[2,3-*b*]pyridines, X-ray structural analysis.

Functionalized thieno[2,3-*b*]pyridines have shown antitumor[1,2] and antiviral[3,4] activity, some of them have been identified as kinase inhibitors[5,6] and antidermatophytic agents.[7] The main methods for the synthesis of thieno[2,3-*b*]pyridine derivatives include the thiophene ring formation in a molecule of pyridine derivative or pyridine ring formation in a thiophene derivative.[8]

While continuing the investigation focused on the reactivity of 3-amino-5-arylcarbamoyl-6-methylthieno[2,3-*b*]-pyridines that were obtained by the formation of thiophene ring fused with a pyridine ring,[9–13] we developed a new method for their synthesis on the basis of a multicomponent condensation between aromatic and heteroaromatic aldehydes **1a**–**c**, cyanothioacetamide **2**,[14,15] acetoacetanilides **3a**–**c**, and alkylating reagents **4a**–**g** containing activated methylene groups. The reaction proceeded in EtOH medium at 20°C in the presence of an equimolar amount of *N*-methylmorpholine, with subsequent addition of DMF and an equimolar amount of aqueous 10% KOH solution, and resulted in the formation of 3-amino-2-aroyl-(alkoxycarbonyl, arylcarbamoyl)-4-aryl(hetaryl)-5-arylcarbamoyl-6-methylthieno[2,3-*b*]pyridines **5a**–**m** in up to 85% yields (Scheme 1).

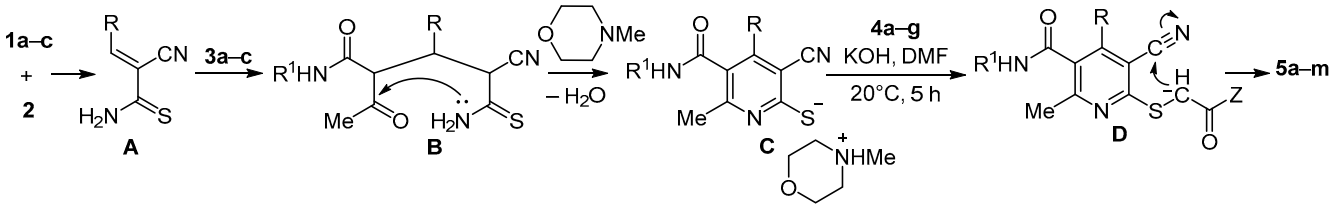
The mechanism of this synthesis included the formation of alkene **A** by Knoevenagel reaction and its Michael addition to CH acid **3**, leading to the adduct **B**. The next

Scheme 1



1 a R = 3-Me-thiophen-2-yl, **b** R = 2-ClC$_6$H$_4$, **c** R = 2-furyl; **3 a** R^1 = 4-ClC$_6$H$_4$, **b** R^1 = 2-MeOC$_6$H$_4$, **c** R^1 = Ph
4 a Hal = Br, Z = 4-MeC$_6$H$_4$; **b** Hal = Cl, Z = 4-BrC$_6$H$_4$NH; **c** Hal = Cl, Z = NH$_2$; **d** Hal = Br, Z = Ph;
e Hal = Cl, Z = *n*-BuO; **f** Hal = Br, Z = 4-MeOC$_6$H$_4$; **g** Hal = Cl, Z = *i*-PrO
5 a R = 2-furyl, R^1 = Z = Ph; **b** R = 2-furyl, R^1 = 4-ClC$_6$H$_4$, Z = 4-BrC$_6$H$_4$NH; **c** R = 2-furyl, R^1 = 4-ClC$_6$H$_4$, Z = BuO;
d R = 2-furyl, R^1 = Ph, Z = 4-MeC$_6$H$_4$; **e** R = 2-furyl, R^1 = Ph, Z = BuO; **f** R = 2-furyl, R^1 = 2-MeOC$_6$H$_4$, Z = 4-MeOC$_6$H$_4$;
g R = 2-furyl, R^1 = Ph, Z = *i*-PrO; **h** R = 2-furyl, R^1 = Ph, Z = 4-MeOC$_6$H$_4$; **i** R = 3-Me-thiophen-2-yl, R^1 = 4-ClC$_6$H$_4$, Z = 4-BrC$_6$H$_4$NH;
j R = 3-Me-thiophen-2-yl, R^1 = 4-ClC$_6$H$_4$, Z = NH$_2$; **k** R = 2-ClC$_6$H$_4$, R^1 = 4-ClC$_6$H$_4$, Z = 4-MeC$_6$H$_4$;
l R = 2-ClC$_6$H$_4$, R^1 = 4-ClC$_6$H$_4$, Z = 4-BrC$_6$H$_4$NH; **m** R = 2-ClC$_6$H$_4$, R^1 = 2-MeOC$_6$H$_4$, Z = 4-BrC$_6$H$_4$NH

Scheme 2



steps were intramolecular cyclization of adduct **B** to the salt **C**, which was regioselectively alkylated with compound **4** to the thioether **D**. The latter intermediate underwent thiophene ring closure under the reaction conditions, forming the final product **5**. Despite the complex sequence of mechanistic steps, the target heterocycles can be obtained by a one-pot procedure (Scheme 2).

A characteristic feature in ^{1}H NMR spectra of compounds **5a**–**m** was the presence of singlet signals at 2.52–2.77 ppm due to the methyl group protons, broadened singlet signals of amino group at 5.87–7.18 ppm, signals of NH group as broadened singlets in the range of 7.63–10.60 ppm, as well as proton signals of aromatic substituents in the appropriate region of the spectrum. IR spectra contained absorption bands assigned to the stretching and deformational vibrations of amino group in the ranges of 3288–3445 and 1614–1648 cm^{-1}, respectively.

We used the method of X-ray structural analysis to unequivocally confirm the molecular structures of compounds **5a**,**i**,**k** and to study their structural features (Figs. 1–3).

The overall molecular conformation of compounds **5a**,**i**,**k** was largely determined by the presence of relatively strong intramolecular N–H···O and N–H···π(C=C) hydrogen bonds, as well as intermolecular N–H···O and O–H···O hydrogen bonds. For this reason, the NH$_2$ group in all compounds assumed a slightly pyramidal configuration (355 and 358, 357, 359°, respectively), while the carbonyl group at the second position was nearly coplanar with the central thieno[2,3-*b*]pyridine ring system. The two crystallographically independent molecules of compound **5a** differed by the type of intramolecular hydrogen bond involving the NH$_2$ group: there were two N–H···O hydrogen bonds in one of them, while the other molecule formed N–H···O and N–H···π(C=C) hydrogen bonds (Fig. 1). Besides that, the dihedral angle between the planes of furanyl substituent and the central bicyclic system deviated from the sterically preferred perpendicular orientation (45.76(6) and 54.67(7)°, respectively). The dihedral angles

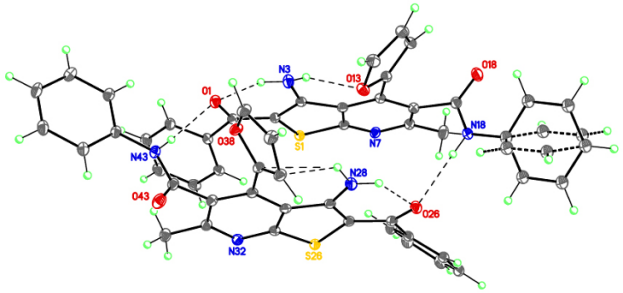


Figure 1. The molecular structure of compound **5a** (two crystallographically independent molecules forming a hydrogen-bonded dimer) with atoms represented by thermal vibration ellipsoids of 50% probability. The thick dotted lines show the alternative less populated position of the disordered phenyl substituent. The thin dotted lines show the N–H···O and N–H···π(C=C) hydrogen bonds.

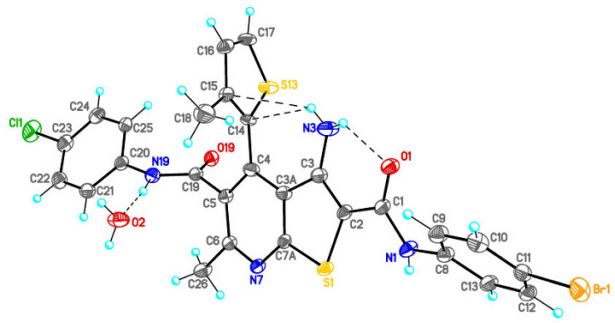


Figure 2. The molecular structure of compound **5i** with atoms represented by thermal vibration ellipsoids of 40% probability. The alternative position of the disordered 3-methylthiophene substituent is not shown. The thin dotted lines show the N–H···O and N–H···π(C=C) hydrogen bonds.

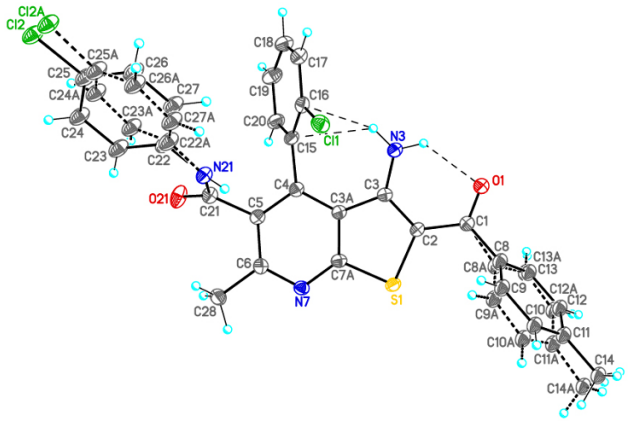


Figure 3. The molecular structure of compound **5k** with atoms represented by thermal vibration ellipsoids of 40% probability. Thick dotted lines show the alternative positions of disordered 4-methylphenyl and 4-chlorophenyl substituents. Thin dotted lines show the N–H···O and N–H···π(C=C) hydrogen bonds.

between the planes of thiophene (compound **5i**) and 2-chlorophenyl (compound **5k**) substituents and the central bicyclic fragment were equal to 75.4(2) and 79.41(8)°, respectively.

The conformation of (halo)phenylamino substituents was directly affected by intermolecular hydrogen bonds. Thus, the crystal of compound **5a** contained two crystallographically independent molecules that formed dimers strongly linked by two N–H···O hydrogen bonds. The dimers were further arranged in alternating chains along the crystallographic axis *b*, linked by C–H···O hydrogen bonds (Fig. S1 in the Supplementary information file). The molecules in crystals of compounds **5i**,**k** formed layers that were parallel to the (0 0 1) and (0 1 0) planes, respectively. Furthermore, in the case of compound **5i**, the layers were linked *via* N–H···O, O–H···N, and O–H···O hydrogen bonds through solvated water molecules (Figs. S2 and S3 in the Supplementary information file).

Thus, a multicomponent condensation of aromatic and heteroaromatic aldehydes, cyanothioacetamide, acetoacetanilides, and alkylating reagents was shown to be a convenient method for the synthesis of functionalized thieno[2,3-*b*]pyridines – potential synthetic intermediates providing access to promising biologically active molecules.

Experimental

IR spectra were recorded on an IKS-40 instrument for samples in Nujol mulls. ^{1}H and ^{13}C NMR spectra were acquired on a Varian VXR-400 spectrometer (400 and 100 MHz, respectively) for samples in $CDCl_3$ solutions (compounds **5d**–**f**,**h**) and DMSO-d_6 solutions (the rest of the compounds), using TMS as internal standard. ^{1}H and ^{13}C NMR spectra of compound **5g** were acquired on a Varian VXR-500 spectrometer (500 and 125 MHz, respectively) in DMSO-d_6. Mass spectra of compounds **5a**,**b**,**i**,**k** were recorded on a Thermo Scientific Orbitrap Elite high-resolution mass spectrometer. Mass spectral samples were prepared by dissolving in DMSO (1 ml) and diluting 100-fold with 1% HCOOH solution in MeCN. The samples were injected into the electrospray ionization source by syringe pump at 40 μl/min flow rate. The source gas flow was turned off, capillary voltage 3.5 kV, capillary temperature 275°C. Orbitrap mass spectra were recorded in positive and negative ion modes with the resolution of 480000. Internal standards: 2DMSO+H$^+$ ion (*m*/*z* 157.03515) in positive ion mode and dodecyl sulfate anion (*m*/*z* 265.14789) in negative ion mode. Mass spectra for the rest of the compounds were recorded on an Agilent 1100 Series liquid chromatograph equipped with an Agilent LS/MSDLS mass selective detector (introduction of samples in AcOH matrix, EI ionization, 70 eV). Elemental analysis was performed on a PerkinElmer CHN-analyzer. Melting points were determined on a Kofler bench. The reaction progress and purity of the obtained compounds were controlled by TLC on Silufol UV-254 plates with 3:5 Me_2CO–hexane mobile phase, visualization in iodine vapor and under UV light.

Synthesis of substituted thieno[2,3-*b*]pyridines 5a–m (General method). A mixture of aldehyde **1a**–**c** (10 mmol), cyanothioacetamide **2** (1.0 g, 10 mmol), and DMF (30 ml) was stirred at 20°C and treated by adding 3 drops of *N*-methylmorpholine, followed by stirring for 15 min until the crystallization of alkene **A** started. Then acetoacetanilide **3a**–**c** (10 mmol) and *N*-methylmorpholine (1.1 ml, 10 mmol) were added to the mixture, stirring was continued for 30 min until the solution became homogeneous, and the reaction mixture was maintained for 1 day. The stirred mixture was then diluted with DMF (30 ml) and treated with alkylating reagent **4a**–**g** (10 mmol), stirred for 1 h, treated with 10% aqueous KOH solution (5.6 ml, 10 mmol), stirred for 2 h, and maintained for 1 day. The mixture was then diluted with an equal amount of water and the obtained precipitate was filtered off, washed with H_2O, EtOH, and hexane.

3-Amino-2-benzoyl-4-(furan-2-yl)-6-methyl-*N*-phenylthieno-[2,3-*b*]pyridine-5-carboxamide (5a). Yield 3.9 g (85%), yellow log-like crystals, mp 232–234°C (BuOH). IR spectrum, ν, cm^{-1}: 1644 (δNH$_2$), 1667 (CONH), 1703 (C=O), 3310–3404 (NH, NH$_2$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.60 (3H, s, CH$_3$); 6.69 (1H, br. s, H-4 Fur); 6.86 (1H, d, *J* = 3.4, H-3 Fur); 7.07 (1H, t, *J* = 7.4, H Ph); 7.17 (2H, br. s, NH$_2$); 7.29 (2H, t, *J* = 7.7, H Ph); 7.49–7.64 (5H, m, H Ph); 7.75 (2H, d, *J* = 6.8, H Ph); 7.95 (1H, d, *J* = 2.5, H-5 Fur); 10.48 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 23.2; 104.1; 112.8; 114.3; 119.3 (2C); 120.1; 124.5; 127.8 (2C); 129.0 (2C); 129.3 (2C); 130.8; 131.8; 133.2; 138.8; 141.0; 145.3; 146.2; 150.5; 157.8; 161.7; 165.2; 189.7. Found, *m*/*z*: 454.1223 [M+H]$^+$. $C_{26}H_{20}N_3O_3S$. Calculated, *m*/*z*: 454.1220.

3-Amino-N^2-(4-bromophenyl)-N^5-(4-chlorophenyl)-4-(furan-2-yl)-6-methylthieno[2,3-*b*]pyridine-2,5-dicarboxamide (5b). Yield 4.4 g (76%), yellow powder, mp 147–149°C (AcOH). IR spectrum, ν, cm^{-1}: 1648 (δNH$_2$), 1665 (CONH), 3296–3387 (NH, NH$_2$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.60 (3H, s, CH$_3$); 6.24 (2H, br. s, NH$_2$); 6.64 (1H, d, *J* = 3.4, H-4 Fur); 6.77 (1H, d, *J* = 4.1, H-3 Fur); 7.35 (2H, d, *J* = 8.9, H Ar); 7.47 (2H, d, *J* = 9.0, H Ar); 7.52 (2H, d, *J* = 9.0, H Ar); 7.63 (2H, d, *J* = 8.9,

H Ar); 7.91 (1H, s, H-5 Fur); 9.73 (1H, br. s, NH); 10.60 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 23.0; 112.6 (2C); 114.0 (2C); 115.9; 126.4 (4C); 126.6 (4C); 129.2 (4C); 131.7 (4C); 137.8; 145.9 (2C); 165.6. Found, *m*/*z*: 580.9880 $[M–H]^-$. $C_{26}H_{17}BrClN_4O_3S$. Calculated, *m*/*z*: 580.9906.

Butyl 3-amino-5-(4-chlorophenyl)-4-(furan-2-yl)-6-methylcarbamoylthieno[2,3-*b*]pyridine-2-carboxylate (5c). Yield 3.6 g (75%), yellow powder, mp 168–170°C (AcOH). IR spectrum, ν, cm^{-1}: 1641 (δNH$_2$), 1666 (CONH), 1712 (COO), 3292–3407 (NH, NH$_2$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.94 (3H, t, *J* = 7.1, C<u>H</u>$_3$(CH$_2$)$_3$); 1.25–1.46 (2H, m, CH$_2$); 1.54–1.76 (2H, m, CH$_2$); 2.63 (3H, s, CH$_3$); 4.25 (2H, t, *J* = 6.6, OCH$_2$); 6.08 (2H, br. s, NH$_2$); 6.69 (1H, br. s, H-4 Fur); 6.83 (1H, d, *J* = 3.0, H-3 Fur); 7.36 (2H, d, *J* = 8.7, H Ar); 7.55 (2H, d, *J* = 8.7, H Ar); 7.93 (1H, s, H-5 Fur); 10.63 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 14.1; 19.2; 23.0; 30.8; 64.5; 95.9; 112.7; 114.2; 119.9; 121.6 (2C); 128.2; 129.3 (2C); 130.5; 132.6; 137.8; 145.4; 146.2; 148.0; 156.6; 160.6; 164.9; 165.6. Mass spectrum, *m*/*z* (I_{rel}, %): 484 $[M+H]^+$ (100). Found, %: C 59.41; H 4.39; N 8.55. $C_{24}H_{22}ClN_3O_4S$. Calculated, %: C 59.56; H 4.58; N 8.68.

3-Amino-4-(furan-2-yl)-6-methyl-2-(4-methylbenzoyl)-*N*-phenylthieno[2,3-*b*]pyridine-5-carboxamide (5d). Yield 3.7 g (80%), light-yellow powder, mp 246–248°C (dioxane). IR spectrum, ν, cm^{-1}: 1638 (δNH$_2$), 1666 (CONH), 1714 (C=O), 3311–3405 (NH, NH$_2$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.43 (3H, s, CH$_3$); 2.59 (3H, s, CH$_3$); 6.59 (1H, t, *J* = 3.4, H-4 Fur); 6.83 (1H, d, *J* = 3.0, H-3 Fur); 7.18 (2H, br. s, NH$_2$); 7.25 (1H, t, *J* = 7.4, H Ph); 7.30 (2H, d, *J* = 7.9, H Ar); 7.34 (2H, t, *J* = 8.0, H Ar); 7.47 (2H, d, *J* = 7.9, H Ar); 7.62 (1H, s, H-5 Fur); 7.74 (2H, d, *J* = 8.0, H Ar); 7.88 (1H, br. s, CONH). Mass spectrum, *m*/*z* (I_{rel}, %): 468 $[M+H]^+$ (100). Found, %: C 69.18; H 4.33; N 8.78. $C_{27}H_{21}N_3O_3S$. Calculated, %: C 69.36; H 4.53; N 8.99.

Butyl 3-amino-4-(furan-2-yl)-6-methyl-5-phenylcarbamoylthieno[2,3-*b*]pyridine-2-carboxylate (5e). Yield 3.3 g (74%), yellow powder, fluorescence observed under UV light, mp 80–82°C (BuOH). IR spectrum, ν, cm^{-1}: 1640 (δNH$_2$), 1668 (CONH), 1718 (COO), 3310–3422 (NH, NH$_2$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.97 (3H, t, *J* = 7.4, C<u>H</u>$_3$(CH$_2$)$_3$); 1.38–1.51 (2H, m, CH$_2$); 1.66–1.73 (2H, m, CH$_2$); 2.77 (3H, s, CH$_3$); 4.28 (2H, t, *J* = 6.6, OCH$_2$); 5.87 (2H, br. s, NH$_2$); 6.57 (1H, s, H-4 Fur); 6.80 (1H, d, *J* = 3.1, H-3 Fur); 7.21 (1H, t, *J* = 8.0, H Ph); 7.26–7.31 (3H, m, H-5 Fur, H Ph); 7.39 (2H, d, *J* = 7.7, H Ph); 7.63 (1H, br. s, CONH). Mass spectrum, *m*/*z* (I_{rel}, %): 450 $[M+H]^+$ (100). Found, %: C 63.98; H 5.03; N 9.14. $C_{24}H_{23}N_3O_4S$. Calculated, %: C 64.13; H 5.16; N 9.35.

3-Amino-4-(furan-2-yl)-2-(4-methoxybenzoyl)-*N*-(2-methoxyphenyl)-6-methylthieno[2,3-*b*]pyridine-5-carboxamide (5f). Yield 4.0 g (78%), light-yellow fibrous solid, fluorescence observed under UV light, mp 217–219°C (AcOH). IR spectrum, ν, cm^{-1}: 1635 (δNH$_2$), 1669 (CONH), 1713 (C=O), 3296–3417 (NH, NH$_2$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.77 (3H, s, CH$_3$); 3.80 (3H, s, CH$_3$O); 3.89 (3H, s, CH$_3$O); 6.55 (1H, s, H-4 Fur); 6.80 (1H, d, *J* = 3.0, H-3 Fur); 6.85 (2H, d, *J* = 7.9, H Ar); 6.88–7.02 (3H, m, H Ar, NH$_2$); 7.07 (2H, t, *J* = 7.3, H Ar); 7.62 (1H, s, H-5 Fur); 7.77 (1H, br. s, CONH); 7.88 (2H, d, *J* = 8.7, H Ar); 8.31 (1H, d, *J* = 7.2, H Ar). Mass spectrum, *m*/*z* (I_{rel}, %): 514 $[M+H]^+$ (100). Found, %: C 65.42; H 4.37; N 8.03. $C_{28}H_{23}N_3O_5S$. Calculated, %: C 65.51; H 4.52; N 8.19.

Isopropyl 3-amino-4-(furan-2-yl)-6-methyl-5-phenylcarbamoylthieno[2,3-*b*]pyridine-2-carboxylate (5g). Yield 3.1 g (71%), yellow powder, mp 103–105°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 1639 (δNH$_2$), 1665 (CONH), 1714 (COO), 3300–3422 (NH, NH$_2$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32 (6H, d, *J* = 6.3, 2CH$_3$); 2.54 (3H, s, CH$_3$); 5.16–5.24 (1H, q, *J* = 6.3, OCH); 6.04 (2H, br. s, NH$_2$); 6.69 (1H, dd, *J* = 3.3, *J* = 1.8, H-4 Fur); 6.83 (1H, d, *J* = 3.3, H-3 Fur); 7.10 (1H, t, *J* = 7.4, H Ph); 7.32 (2H, d, *J* = 7.9, H Ph); 7.51 (2H, d, *J* = 8.1, H Ph); 7.95 (1H, d, *J* = 0.8, H-5 Fur); 10.49 (1H, br. s, CONH). ^{13}C NMR spectrum, δ, ppm: 22.3 (2C); 23.0; 68.5; 97.2; 112.7; 114.0; 120.0; 120.2 (2C); 124.5; 129.3 (2C); 130.8; 132.5; 138.9; 145.5; 145.9; 147.9; 156.6; 160.4; 164.5; 165.4. Mass spectrum, *m*/*z* (I_{rel}, %): 436 $[M+H]^+$ (100). Found, %: C 63.38; H 4.72; N 9.55. $C_{23}H_{21}N_3O_4S$. Calculated, %: C 63.43; H 4.86; N 9.65.

3-Amino-4-(furan-2-yl)-2-(4-methoxybenzoyl)-6-methyl-*N*-phenylthieno[2,3-*b*]pyridine-5-carboxamide (5h). Yield 3.4 g (70%), bright-yellow powder, mp 120–122°C (BuOH). IR spectrum, ν, cm^{-1}: 1645 (δNH$_2$), 1667 (CONH), 1711 (C=O), 3295–3415 (NH, NH$_2$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.52 (3H, s, CH$_3$); 3.86 (3H, s, CH$_3$O); 6.58 (1H, br. s, H-4 Fur); 6.97 (1H, br. s, H-3 Fur); 6.98 (2H, d, *J* = 8.4, H Ar); 7.15 (2H, br. s, NH$_2$); 7.25 (1H, t, *J* = 7.2, H Ph); 7.34 (2H, t, *J* = 7.2, H Ph); 7.52 (2H, d, *J* = 7.5, H Ph); 7.60 (1H, br. s, H-5 Fur); 7.84 (2H, d, *J* = 8.4, H Ar); 8.17 (1H, br. s, CONH). Mass spectrum, *m*/*z* (I_{rel}, %): 484 $[M+H]^+$ (100). Found, %: C 66.87; H 4.22; N 8.58. $C_{27}H_{21}N_3O_4S$. Calculated, %: C 67.07; H 4.38; N 8.69.

3-Amino-N^2-(4-bromophenyl)-N^5-(4-chlorophenyl)-6-methyl-4-(3-methylthiophen-2-yl)thieno[2,3-*b*]-pyridine-2,5-dicarboxamide (5i). Yield 5.0 g (81%), yellow crystals, fluorescence observed under UV light, mp 274–276°C (BuOH). IR spectrum, ν, cm^{-1}: 1647 (δNH$_2$), 1671 (CONH), 3280–3422 (NH, NH$_2$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.97 (3H, s, CH$_3$); 2.61 (3H, s, CH$_3$); 5.92 (2H, br. s, NH$_2$); 6.99 (1H, d, *J* = 5.1, H-4 Th); 7.31 (2H, d, *J* = 6.8, H Ar); 7.44 (2H, d, *J* = 7.4, H Ar); 7.46 (2H, d, *J* = 7.4, H Ar); 7.62 (2H, d, *J* = 6.8, H Ar); 7.65 (1H, d, *J* = 5.1, H-5 Th); 9.66 (1H, br. s, CONH); 10.58 (1H, br. s, CONH). ^{13}C NMR spectrum, δ, ppm: 14.6; 22.9; 97.9; 115.8; 118.3; 121.5 (2C); 123.5 (2C); 126.8; 128.0; 128.4 (2C); 129.2; 130.1; 131.7 (2C); 132.4; 136.6; 137.7; 138.5; 138.6; 147.3; 155.7; 159.1; 164.1; 165.0. Found, *m*/*z*: 610.9809 $[M–H]^-$. $C_{27}H_{19}BrClN_4O_2S_2$. Calculated, *m*/*z*: 610.9785.

3-Amino-N^5-(4-chlorophenyl)-6-methyl-4-(3-methylthiophen-2-yl)thieno[2,3-*b*]pyridine-2,5-dicarboxamide (5j). Yield 3.6 g (79%), bright-yellow powder, fluorescence observed under UV light, mp 293–295°C (BuOH). IR spectrum, ν, cm^{-1}: 1638 (δNH$_2$), 1672 (CONH), 3311–3418 (NH, NH$_2$). ^{1}H NMR spectrum, δ, ppm

(*J*, Hz): 2.49 (3H, s, CH_3); 2.62 (3H, s, CH_3); 5.78 (2H, br. s, NH_2); 6.99 (1H, d, *J* = 4.8, H-4 Th); 7.27 (2H, br. s, $CONH_2$); 7.33 (2H, d, *J* = 8.6, H Ar); 7.47 (2H, d, *J* = 8.6, H Ar); 7.64 (1H, d, *J* = 4.8, H-5 Th); 10.58 (1H, br. s, CONH). Mass spectrum, *m*/*z* (I_{rel}, %): 457 $[M+H]^+$ (100). Found, %: C 55.08; H 3.66; N 12.07. $C_{21}H_{17}ClN_4O_2S_2$. Calculated, %: C 55.20; H 3.75; N 12.26.

3-Amino-4-(2-chlorophenyl)-*N*-(4-chlorophenyl)-6-methyl-2-(4-methylbenzoyl)thieno[2,3-*b*]pyridine-5-carboxamide (5k). Yield 3.8 g (69%), yellow crystals, mp 262–264°C (dioxane). IR spectrum, ν, cm^{-1}: 1647 (δNH_2), 1668 (CONH), 1709 (C=O), 3315–3445 (NH, NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.37 (3H, s, CH_3); 2.63 (3H, s, CH_3); 6.52 (2H, br. s, NH_2); 7.28 (2H, d, *J* = 8.9, H Ar); 7.32 (2H, d, *J* = 8.1, H Ar); 7.38 (2H, d, *J* = 8.9, H Ar); 7.47 (1H, t, *J* = 8.9, H Ar); 7.51 (1H, t, *J* = 8.1, H Ar); 7.61 (1H, t, *J* = 6.2, H Ar); 7.63 (1H, d, *J* = 6.2, H Ar); 7.66 (2H, d, *J* = 8.1, H Ar); 10.53 (1H, br. s, CONH). ^{13}C NMR spectrum, δ, ppm: 21.5; 23.2; 104.0; 119.6; 121.5 (4C); 127.9 (4C); 129.2 (4C); 129.5; 132.1 (2C); 133.2; 137.5; 138.3; 141.9 (2C); 150.1; 157.4; 161.1; 164.6; 189.4. Found, *m*/*z*: 546.0806 $[M-H]^-$. $C_{29}H_{20}Cl_2N_3O_2S$. Calculated, *m*/*z*: 546.0729.

3-Amino-N^2-(4-bromophenyl)-4-(2-chlorophenyl)-N^5-(4-chlorophenyl)-6-methylthieno[2,3-*b*]pyridine-2,5-dicarboxamide (5l). Yield 4.6 g (73%), dark-red crystals, fluorescence observed under UV light, mp 312–314°C (BuOH). IR spectrum, ν, cm^{-1}: 1640 (δNH_2), 1665 (CONH), 3288–3430 (NH, NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.67 (3H, s, CH_3); 5.70 (2H, br. s, NH_2); 7.32 (2H, d, *J* = 8.7, H Ar); 7.38–7.52 (6H, m, H Ar); 7.57–7.68 (4H, m, H Ar); 10.63 (2H, br. s, 2CONH). Mass spectrum, *m*/*z* (I_{rel}, %): 627 $[M+H]^+$ (100). Found, %: C 53.55; H 2.94; N 8.81. $C_{28}H_{19}BrCl_2N_4O_2S$. Calculated, %: C 53.69; H 3.06; N 8.95.

3-Amino-N^2-(4-bromophenyl)-4-(2-chlorophenyl)-N^5-(2-methoxyphenyl)-6-methylthieno[2,3-*b*]pyridine-2,5-dicarboxamide (5m). Yield 5.3 g (85%), yellow powder, mp 277–279°C (BuOH). IR spectrum, ν, cm^{-1}: 1614 (δNH_2), 1655 (CONH), 3318, 3396, 3476 (NH, NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.72 (3H, s, CH_3); 3.78 (3H, s, CH_3O); 5.73 (2H, br. s, NH_2); 6.83 (1H, t, *J* = 7.5, H Ar); 7.00 (1H, d, *J* = 8.1, H Ar); 7.10 (1H, t, *J* = 7.6, H Ar); 7.32 (1H, d, *J* = 7.6, H Ar); 7.44–7.58 (4H, m, H Ar); 7.64 (4H, t, *J* = 8.7, H Ar); 9.65 (1H, br. s, CONH); 9.68 (1H, br. s, CONH). ^{13}C NMR spectrum, δ, ppm: 23.1; 56.2; 98.0; 112.0; 115.8; 120.5; 120.6; 123.6; 123.9 (4C); 126.5; 129.9; 131.4; 131.7 (4C); 131.8; 133.1; 138.7; 140.6; 147.5; 151.6; 156.4; 158.8; 164.2; 165.0. Mass spectrum, *m*/*z* (I_{rel}, %): 622 $[M+H]^+$ (100). Found, %: C 55.88; H 3.44; N 8.95. $C_{29}H_{22}BrClN_4O_3S$. Calculated, %: C 56.01; H 3.57; N 9.01.

X-ray structural analysis of compounds 5a,i,k was performed at the "Belok" synchrotron beamline at the National Research Center "Kurchatov Institute", using a Rayonix SX165 CCD two-dimensional detector (100.0(2) K, λ 0.96990 Å, φ-scanning with a step of 1.0°). Processing of experimental data was performed with the iMOSFLM program, obtained as a part of the CCP4 software suite.[16] Absorption of X-ray radiation was taken into account by processing the obtained data with the Scala program.[17]

Compound 5a. Yellow prismatic crystals, $C_{26}H_{19}N_3O_3S$ (M_r 453.50), monoclinic, space group $P2_1/c$; *a* 10.184(2), *b* 30.374(6), *c* 14.527(3) Å; β 104.00(3)°; *V* 4360.1(16) $Å^3$; *Z* 8; d_{calc} 1.382 g/cm^3; *F*(000) 1888; μ 0.416 mm^{-1}. A total of 56256 reflections were collected (8957 independent reflections, R_{int} 0.084, 2θ 76.96°). The structure was solved by direct method and refined by full-matrix method of least squares F^2 in anisotropic approximation for non-hydrogen atoms. The (amino)phenyl substituent in one of the two crystallographically independent molecules was disordered across two positions with population ratio of 0.9:0.1. The hydrogen atoms of amino groups were localized objectively from Fourier difference syntheses of electron density and refined isotropically with fixed shift parameters (U_{iso}(H) = 1.2U_{eq}(N)). The rest of the hydrogen atoms, the positions of which were calculated geometrically, were included in the refinement with fixed positional parameters according to the riding model and isotropic shift parameters (U_{iso}(H) = 1.5U_{eq}(C) for CH_3 groups and U_{iso}(H) = 1.2U_{eq} (C) for the rest of the groups). The final probability factors were R_1 0.050 for 7552 independent reflections with $I \geq 2\sigma(I)$ and wR_2 0.136 for all independent reflections. The maximum and minimum values of residual electron density peaks were 0.66 and –0.90 e/$Å^3$. The complete X-ray structural dataset for compound **5a** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1896354).

Compound 5i. Yellow platelets, $C_{27}H_{20}N_4O_2S_2ClBr \cdot H_2O$ (M_r 629.96), triclinic, space group *P*-1; *a* 9.5200(19), *b* 9.766(2), *c* 17.160(3) Å; α 74.91(3)°; β 83.54(3)°; γ 64.03(3)°; *V* 1384.9(6) $Å^3$; *Z* 2; d_{calc} 1.511 g/cm^3; *F*(000) 640; μ 1.230 mm^{-1}. A total of 18895 reflections were collected (5547 independent reflections, R_{int} 0.053, 2θ 76.82°). The structure was solved by direct method and refined by full matrix method of least squares F^2 in anisotropic approximation for non-hydrogen atoms. The 3-methylthiophene substituent was disordered across two positions with equal populations. The hydrogen atoms of amino groups and solvated water molecule were objectively localized from Fourier difference syntheses of electron density and refined isotropically with fixed shift parameters (U_{iso}(H) = 1.2U_{eq}(N) and 1.5U_{eq}(O)). The rest of the hydrogen atoms, the positions of which were calculated geometrically, were included in the refinement with fixed positional parameters according to the riding model and isotropic shift parameters (U_{iso}(H) = 1.5U_{eq}(C) for the CH_3 group and U_{iso}(H) = 1.2U_{eq}(C) for the rest of the groups). The final probability factors were R_1 0.050 for 4916 independent reflections with $I \geq 2\sigma(I)$ and wR_2 0.123 for all independent reflections. The maximum and minimum values of residual electron density peaks were 0.48 and –0.62 e/$Å^3$. The complete X-ray structural dataset for compound **5i** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1896355).

Compound 5k. Yellow platelets, $C_{29}H_{21}N_3O_2SCl_2$ (M_r 546.45), monoclinic, space group $P2_1/n$; *a* 8.9393(18), *b* 31.024(6), *c* 9.901(2) Å; β 108.76(3)°; *V* 2600.0(10) $Å^3$; *Z* 4; d_{calc} 1.396 g/cm^3; *F*(000) 1128; μ 0.854 mm^{-1}. A total of 36328 reflections were collected (5519 independent

reflections, R_{int} 0.086, 2θ 76.95°). The structure was solved by direct method and refined by full-matrix method of least squares F^2 in anisotropic approximation for non-hydrogen atoms. The 4-methylphenyl and 4-chlorophenyl substituents were disordered each across two positions with equal populations. The hydrogen atoms of amino groups were objectively localized from Fourier difference syntheses of electron density and included in the refinement with fixed positional parameters according to the riding model and isotropic shift parameters (U_{iso}(H) = 1.2U_{eq}(N)). The rest of the hydrogen atoms, the positions of which were calculated geometrically, were included in the refinement with fixed positional parameters according to the riding model and isotropic shift parameters (U_{iso}(H) = 1.5U_{eq}(C) for CH_3 groups and U_{iso}(H) = 1.2U_{eq}(C) for the rest of the groups). The final probability parameters were R_1 0.088 for 3927 independent reflections with $I \geq 2\sigma(I)$ and wR_2 0.229 for all independent reflections. The maximal and minimal values of residual electron density peak values were 1.09 and −0.77 e/Å^3. The complete X-ray structural dataset for compound **5k** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1896356).

All calculations were performed using the SHELXTL software suite.[18]

Supplementary information file containing X-ray structural analysis results for compound **5a** is available at the journal website at http://link.springer.com/journal/10593.

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