Synthesis of 5-aminopyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline derivatives from 3-cyanopyridine-2(1*H*)-thiones and 2-(chloromethyl)benzamide

V. E. Kalugin★ *and A. M. Shestopalov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (495) 952 5308. E-mail: vek@ioc.ac.ru

Substituted 5-aminopyrido[3′,2′:4,5]thieno[3,2-c]isoquinolines were synthesized by condensation of substituted 3-cyanopyridine-2(1*H*)-thiones with 2-(chloromethyl)benzamide and subsequent treatment of the condensation products with potassium *tert*-butoxide. Oxidation of the condensation products to sulfoxides and sulfones followed by treatment of these compounds with potassium *tert*-butoxide gives substituted 5-aminopyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline 11-oxides and substituted 5-aminopyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline 11,11-dioxides in good yields.

Key words: 3-cyanopyridine-2(1*H*)-thiones, 2-(chloromethyl)benzamides, potassium *tert*-butoxide, domino reactions, 5-aminopyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinolines, 5-aminopyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline 11-oxides, 5-aminopyrido[3′,2′:4,5]thieno[3,2-*c*]-isoquinoline 11,11-dioxides.

Derivatives of fused isoquinolines are of practical interest since they show different types of pharmacological activities. Thus, indeno[1,2-*c*]isoquinolines are cytotoxic and can be used for treating some types of cancer.[1—3] Fused isoquinolines may inhibit poly(ADP-ribose) synthetase playing an essential role in the development of a number of inflammatory diseases.[4] For instance, derivatives of indeno[1,2-*c*]isoquinolines, indolo[3,2-*c*]isoquinolines, benzofuro[3,2-*c*]isoquinolines, and benzothieno[3,2-*c*]-isoquinolines are capable of inhibiting this enzyme and can be used for prophylaxis and treatment of arthritis, diabetes, asthma, colitis, and cardiovascular diseases.[5] Thieno[3,2-*c*]isoquinoline derivatives are found to inhibit estrogen receptors and can be applied to treat inflammation in atherosclerosis, myocardial infarction, heart failure, inflammatory bowel diseases, and arthritis.[6]

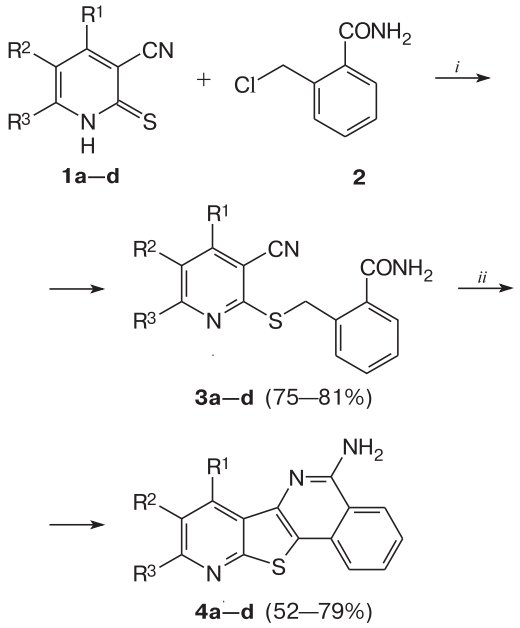
Our studies on the synthesis of fused isoquinolines result in the development of a general synthetic approach to this type of heterocycles. This approach involves alkylation of the derivatives of benzoyl nitrile and nicotinoyl nitrile bearing either the hydroxy or thiol group adjacent to the nitrile moiety with 2-(chloromethyl)benzoic acid derivatives followed by treatment of the resulting alkylation products with potassium *tert*-butoxide. The structure of the obtained fused isoquinolines depends on the nature of 2-(chloromethyl)benzoic acid derivatives used in the alkylation step. Thus, when the products obtained by alkylation of salicylic acid nitrile, thiosalicylic acid nitrile, 3-cyanopyridine-2(1*H*)-ones, and 3-cyanopyridine-2(1*H*)-thiones with 2-(chloromethyl)benzoate are treated with potassium *tert*-butoxide, derivatives of benzofuro[3,2-*c*]-isoquinoline-5(6*H*)-one,[7] benzothieno[3,2-*c*]isoquinoline-5(6*H*)-one,[8] pyrido[3′,2′:4,5]furo[3,2-*c*]isoquinoline-5(6*H*)-one,[9] and pyrido[3′,2′:4,5]thieno[3,2-*c*]-isoquinoline-5(6*H*)-one[10] were synthesized *via* the Thorpe—Ziegler → Thorpe—Guareschi domino reaction. At the same time, when the products of alkylation of salicylic acid nitriles, thiosalicylic acid nitriles, 3-cyanopyridine-2(1*H*)-ones, and 3-cyanopyridine-2(1*H*)-thiones with 2-(chloromethyl)benzoyl nitrile are treated with Bu^tOK, derivatives of 5-aminobenzofuro[3,2-*c*]isoquinolines,[7] 5-aminobenzothieno[3,2-*c*]isoquinolines,[11] and 5-aminopyrido[3′,2′:4,5]furo[3,2-*c*]isoquinoline[9] were prepared *via* the Thorpe—Ziegler → hetero-Thorpe—Ziegler domino reaction. Similar types of the domino reactions are well known.[12] However, synthesis of fused isoquinolines *via* the reaction sequence involving alkylation of benzoic acid nitriles and nicotinic acid nitriles bearing either hydroxy or thiol group adjacent to the nitrile moiety with 2-(chloromethyl)benzamide or its substituted derivatives and subsequent treatment of the alkylation products with Bu^tOK has not been studied to date. The present study is focused on the synthesis of pyrido-[3′,2′:4,5]thieno[3,2-*c*]isoquinoline derivatives from substituted 3-cyanopyridine-2(1*H*)-thiones and 2-(chloromethyl)benzamide.

Substituted 3-cyanopyridine-2(1*H*)-thiones **1a—d** react with 2-(chloromethyl)benzamide **2** in the presence of Et_3N in refluxing $CHCl_3$ to give substituted 2-[(2-aminocarbonylbenzyl)thio]-3-cyanopyridines **3a—d** in good

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1492—1499, August, 2018.

yields. Treatment of sulfides **3a**—**d** with Bu^{t}OK (1.5 equiv.) in DMF results in substituted 5-aminopyrido[3′,2′:4,5]-thieno[3,2-*c*]isoquinolines **4a**—**d** in good yields (Scheme 1).

Scheme 1



1, 3, 4: $R^1 = R^3 = Me$, $R^2 = H$ (**a**); $R^1 = H$, $R^2 + R^3 = (CH_2)_4$ (**b**); $R^1 = R^3 = Ph$, $R^2 = H$ (**c**); $R^1 = CF_3$, $R^2 = H$, $R^3 = Ph$ (**d**)

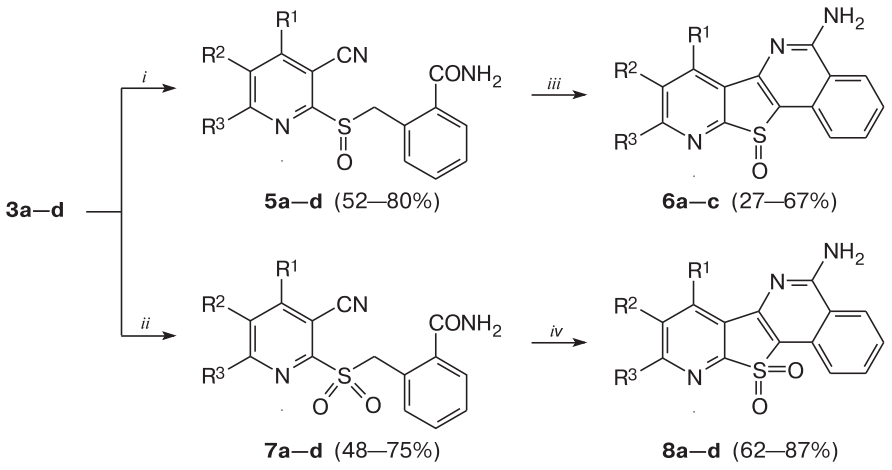
Reagents and conditions: *i.* Et_3N (1.5 equiv.), DMF, 60—65 °C, 40 min; *ii.* Bu^{t}OK (1.5 equiv.), DMF, 70—75 °C, 40 min.

It was interesting to study the possibility of synthesizing the derivatives of 5-aminopyrido[3′,2′:4,5]thieno-[3,2-*c*]isoquinolines bearing the oxidized sulfur atom by oxidation of sulfides **3a**—**d** to the corresponding sulfoxides and sulfones and subsequent treatment of the obtained derivatives with potassium *tert*-butoxide according to the procedure described earlier for the derivatives of benzothieno[3,2-*c*]isoquinolines[8,11] and pyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinolines.[10] Oxidation of sulfides **3a**—**d** with 30% aqueous H_2O_2 in AcOH at 50—55 °C for 3—4 h gives sulfoxides **5a**—**d**. Oxidation of sulfides **3a**—**d** with $KMnO_4$ in AcOH at room temperature leads to sulfones **7a**—**d** (Scheme 2).

Treatment of sulfoxides **5a**—**d** with Bu^{t}OK under the same conditions used for the reactions involving sulfides **3a**—**d** gives the corresponding substituted 5-aminopyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline 11-oxides **6**. It should be noted that the yields of the target products strongly depend on the substitution pattern of the starting sulfoxides **5**. Thus, alkyl-substituted sulfoxides **5a**,**b** give compounds **6a**,**b** in good yields; while treatment of sulfoxide **5c** bearing the phenyl group with Bu^{t}OK produces a large number of the side-products, therefore, target product **6c** was isolated in 27% yield only. The reaction of sulfoxide **5d** with potassium *tert*-butoxide leads only to a mixture of the side products with heterocycle **4d** being one of the components of this mixture. In contrast, treatment of sulfones **7a**—**d** with Bu^{t}OK in all cases gives substituted 5-aminopyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline 11,11-dioxides **8a**—**d** in good yields (see Scheme 2).

The structures of compounds **3a**—**d**, **5a**—**d**, and **7a**—**d** were established by IR spectroscopy, ^1H and ^{13}C NMR spectroscopy, and confirmed by elemental analysis. Characteristic features of the IR spectra of these compounds are the absorptions of the CN group at the 2212—2237 cm^{-1} and the amide group at 1650—1674 cm^{-1}

Scheme 2



3, 5—8: $R^1 = R^3 = Me$, $R^2 = H$ (**a**); $R^1 = H$, $R^2 + R^3 = (CH_2)_4$ (**b**); $R^1 = R^3 = Ph$, $R^2 = H$ (**c**); $R^1 = CF_3$, $R^2 = H$, $R^3 = Ph$ (**d**)

Reagents and conditions: *i.* AcOH, 30% H_2O_2 (1.1 equiv.), 50—55 °C, 3—4 h; *ii.* AcOH, $KMnO_4$ (1.6 equiv.), 20—25 °C, 40 min; *iii.* Bu^{t}OK (1.5 equiv.), DMF, 55—60 °C, 1 h; *iv.* Bu^{t}OK, DMF (1.5 equiv.), 55—60 °C, 40 min.

(C=O) and 3178—3478 cm^{-1} (NH_2). The S=O groups of sulfoxides **5a**—**d** absorb at the 1037—1067 cm^{-1} range. In the IR spectra of sulfones **7a**—**d**, the SO_2 group gives two absorption bands at the ranges of 1310—1326 and 1132—1149 cm^{-1}. In the ^1H NMR spectra of compounds **3a**—**d**, **5a**—**d**, and **7a**—**d**, the $CONH_2$ amide group protons resonate as two broadened singlets at δ_H 7.27—7.42 and 7.67—7.96. ^1H NMR spectra of sulfides **3a**—**d** exhibit the singlet signal of the CH_2S protons at δ_H 4.73—4.99. The protons of the $CH_2S(O)$ moiety of sulfoxides **5a**—**d** resonate as two doublets at δ_H 4.70—4.87 and 4.80—4.94 with the spin-spin coupling constants of J = 11.7 Hz for **5b** and 12.5 Hz for **5a** and **5d**. The protons of the $CH_2S(O)$ group of sulfoxide **5c** appear as a singlet at δ_H 4.96. The singlets of the CH_2SO_2 group protons of sulfones **7a**—**d** were found at δ_H 5.37—5.65. In the ^{13}C NMR spectra of compounds **3a**—**d**, **5a**—**d**, and **7a**—**d**, the CN group carbon atoms resonate at the δ_C 110.83—115.57 range. ^{13}C NMR spectra of sulfides **3a**—**d** show characteristic signals of the CH_2S group carbon atoms at δ_C 31.00—32.12; the signals of the $CH_2S(O)$ group carbon atoms of sulfoxides **5a**—**d** are observed at δ_C 56.87—57.84, and the CH_2SO_2 group carbon atoms of sulfones **7a**—**d** resonate at δ_C 53.77—55.38. The carbon atoms of the $CONH_2$ amide moieties appear at the δ_C 169.51—170.51 range. The ^{13}C NMR signals of the carbon atoms bonded to the amide groups are of special interest. Thus, the signals of these carbons are observed at δ_C 135.60—136.29 for sulfides **3a**—**d**, at δ_C 128.00—128.55 for sulfoxides **5a**—**d**, and at δ_C 125.77—126.19 for sulfones **7a**—**d**.

IR spectra of the target products **4a**—**d**, **6a**—**c**, and **8a**—**d** characterize by the presence of two or more absorption bands of the NH_2 group at the 3227—3484 cm^{-1} range. The S=O groups of sulfoxides **6a**—**c** absorb at the 1000—1015 cm^{-1} range. The sulfonyl groups of heterocycles **8a**—**d** give rise to two absorption bands at 1269—1292 and 1132—1152 cm^{-1}. ^1H NMR spectra of compounds **4a**—**d**, **6a**—**c**, and **8a**—**d** exhibit the broadened singlet signal of the NH_2 group protons at δ_H 6.98—7.09 (**4a**—**d**), 7.36—7.96 (**6a**—**c**), and 6.89—8.25 (**8a**—**d**). ^{13}C NMR spectra of these compounds show signals of the CNH_2 group carbon atoms at δ_C 155.35—156.68 (**4a**—**d**), 158.58—159.82 (**6a**—**c**), and 160.03—160.70 (**8a**—**c**).

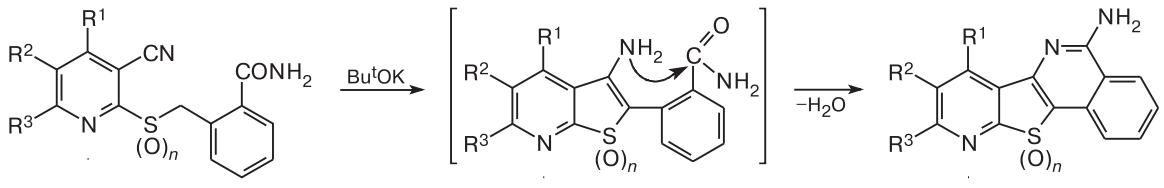
We believe that the reactions of sulfides **3**, sulfoxides **5**, and sulfones **7** with potassium *tert*-butoxide follow the same mechanism, namely, the domino reaction. On the first step, the Thorpe—Ziegler reaction of compounds **3**, **5**, and **7** produces the corresponding benzothiophenic intermediates **9**, **10**, and **11**. Then these intermediates undergo heterocyclization accompanied by the elimination of the water molecule to give the target compounds **4**, **6**, and **8** (Scheme 3).

Such a mechanism of the reaction of amides **3**, **5**, and **7** with Bu^tOK allowed us to hope that the reaction of the corresponding *N*-substituted amides with potassium *tert*-butoxide would yield the derivatives of pyrido[3′,2′:4,5]-thieno[3,2-*c*]isoquinolines bearing the 5-positioned *N*-substituted amino group.

To verify this assumption, we synthesized 4-[2-(chloromethyl)benzoyl]morpholine (**12**) by the reaction of 2-(chloromethyl)benzoyl chloride (**13**) with morpholine. Alkylation of 3-cyanopyridine-2(1*H*)-thione **1a** with chloride **12** gives amide **14** in high yield. The reaction of compound **14** with Bu^tOK is accompanied by the side-product formation; therefore, it was carried out under milder conditions than the analogous reactions of compound **3**. Despite this precaution, the reaction produces pyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline derivative **15** bearing the 5-positioned morpholine moiety in 43% isolated yield (Scheme 4).

In summary, we succeeded in the high-yield synthesis of new 5-aminopyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinolines by alkylation of substituted 3-cyanopyridine-2(1*H*)-thiones with 2-(chloromethyl)benzamide followed by treatment of the alkylation products with potassium *tert*-butoxide. Oxidation of the alkylation products to the corresponding sulfoxides and sulfones and the subsequent reaction of these compounds with Bu^tOK give rise to 5-aminopyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline derivatives bearing the oxidized sulfur atom. Besides, we were able to demonstrate that treatment of the product of alkylation of 3-cyanopyridine-2(1*H*)-thione with *N*-substituted 2-(chloromethyl)benzamide with potassium *tert*-butoxide gives the derivative of pyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinolines bearing the 5-positioned *N*-substituted amino group.

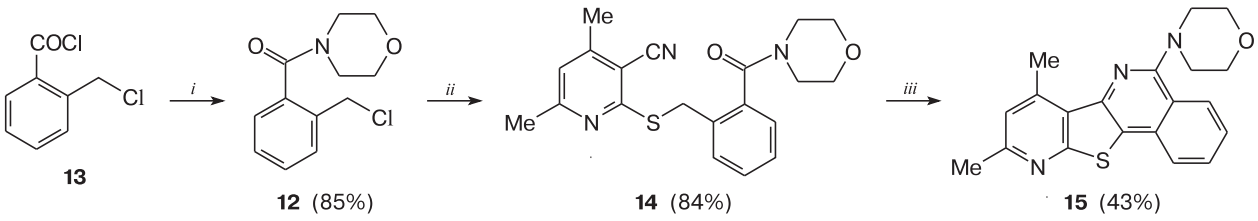
Scheme 3



3, **5**, **7** **9—11** **4**, **6**, **8**

n = 0 (**3**, **4**, **9**), 1 (**5**, **6**, **10**), 2 (**7**, **8**, **11**)

Scheme 4



Reagents and conditions: *i.* morpholine (1.1 equiv.), $CHCl_3$, 0—25 °C; *ii.* **1a**, Et_3N (1.5 equiv.), $CHCl_3$, reflux, 1 ч; *iii.* Bu^tOK (1.5 equiv.), DMF, 20—25 °C, 40 min.

Experimental

Melting points were measured with a Kofler apparatus. IR spectra were recorded on a Specord M82 spectrometer in the KBr pellets. ^1H and ^{13}C NMR spectra were run with a Bruker Avance-300 instrument (working frequencies of 300 (^1H) and 75 MHz (^{13}C)) in DMSO-d_6. The chemical shifts are given in the δ scale relative to $SiMe_4$ as an internal standard. Notations used in the description of the NMR spectra are as follows: Bza is the benzamide moiety; py is the pyridine moiety, THQ is 5,6,7,8-tetrahydroquinoline; PTI is pyrido[3′,2′:4,5]thieno-[3,2-*c*]isoquinoline; THTIQTQ is tetrahydroisoquinolino-[3′,4′:4,5]thieno[2,3-*b*]quinoline. Elemental analysis was carried out with a Perkin-Elmer 2400 CHN analyzer.

3-Cyanopyridine-2(*1H*)-thiones **1a**,[13] **1b**,[14] **1c**,[15] and **1d**[16] were synthesized by known procedures.

2-(Chloromethyl)benzamide (2). To H_2SO_4 (70 mL) heated to 80—85 °C, finely ground 2-(chloromethyl)benzonitrile (15.1 g, 0.1 mol) was added by portions. The reaction mixture was stirred at 90 °C for 1 h, cooled to room temperature and poured into cold water (300 mL). The precipitated product was collected by filtration, washed with cold water, and dried in air. Yield 13.2 g (78%), colorless crystals, m.p.194—196 °C (EtOH). Found (%): C, 56.88; H, 4.62; N, 8.14; Cl, 20.74. C_8H_8ClNO. Calculated (%): C, 56.65; H, 4.75; N, 8.26; Cl, 20.90. IR, ν/cm^{-1}: 3381, 3189, 3037, 2924, 1680, 1647, 1618, 1577, 1446, 1392, 1082, 740. ^1H NMR, δ: 4.90 (s, 2 H, CH_2Cl); 7.27 (br.s, 1 H, NH); 7.39 (t, 1 H, H $(5)_{Bza}$, J = 6.6 Hz); 7.42—7.50 (m, 2 H, H $(3,4)_{Bza}$); 7.51 (br.s, 1 H, NH); 7.58 (d, 1 H, H $(6)_{Bza}$, J = 7.3 Hz).

Synthesis of substituted 2-{[2-(aminocarbonyl)benzyl]thio}-3-cyanopyridines 3a—d (general procedure). To a solution of 3-cyanopyridine-2(1*H*)-thione **1a—d** (3 mmol) and 2-(chloromethyl)benzamide **2** (0.51 g, 3 mmol) in DMF (5 mL), Et_3N (0.6 mL, 4.2 mmol) was added. The reaction mixture was stirred at 60—65 °C for 40 min and poured into water (30 mL). The precipitated solid was collected by filtration, washed with water, dried in air, and crystallized from the appropriate solvent.

2-{[2-(Aminocarbonyl)benzyl]thio}-3-cyano-4,6-dimethylpyridine (3a). Yield 0.72 g (81%), colorless crystals, m.p. 194—196 °C (DMF—MeOH). Found (%): C, 64.73; H, 5.16; N, 14.22; S, 10.66. $C_{16}H_{15}N_3OS$. Calculated (%): C, 64.62; H, 5.08; N, 14.13; S, 10.78. IR, ν/cm^{-1}: 3368, 3200 (NH_2), 3068, 2212 (CN), 1652 (C=O), 1620, 1584, 1544, 1392, 1272. ^1H NMR, δ: 2.37 (s, 3 H, C(4)Me); 2.54 (s, 3 H, C(6)Me); 4.74 (s, 2 H, CH_2S); 7.08 (s, 1 H, $H(5)_{py}$); 7.30—7.43 (m, 3 H, NH and $H(3,5)_{Bza}$); 7.46—7.56 (m, 2 H, $H(4,6)_{Bza}$); 7.87 (br.s, 1 H, NH). ^{13}C NMR, δ: 19.57 (C(4)Me); 24.28 (C(6)Me); 31.09 (CH_2S); 103.45 $(C(3)_{py})$; 114.97 (CN_{py}); 120.25 $(C(5)_{py})$; 127.14 $(C(5)_{Bza})$; 127.84 $(C(6)_{Bza})$; 129.70 $(C(3)_{Bza})$; 130.76 $(C(4)_{Bza})$; 135.77 $(C(2)_{Bza})$; 136.28 $(C(1)_{Bza})$; 152.44 $(C(4)_{py})$; 160.94 $(C(2)_{py})$; 161.32 $(C(6)_{py})$; 170.32 (C=O).

2-{[(2-Aminocarbonyl)benzyl]thio}-3-cyano-5,6,7,8-tetrahydroquinoline (3b). Yield 0.72 g (84%), colorless crystals, m.p. 208—210 °C (DMF—MeOH). Found (%): C, 66.71; H, 5.37; N, 12.92; S, 10.04. $C_{18}H_{17}N_3OS$. Calculated (%): C, 66.85; H, 5.30; N, 12.99; S, 9.91. IR, ν/cm^{-1}: 3447, 3358, 3179 (NH_2), 2938, 2223 (CN), 1650 (C=O), 1621, 1413, 1390. ^1H NMR, δ: 1.68—1.80 (m, 2 H, $C(6)H_{2(THQ)}$); 1.82—1.90 (m, 2 H, $C(7)H_{2(THQ)}$); 2.69 (t, 2 H, $C(5)H_{2(THQ)}$, J = 5.9 Hz); 2.92 (t, 2 H, $C(8)H_{2(THQ)}$, J = 5.9 Hz); 4.73 (s, 2 H, CH_2S); 7.25—7.32 (m, 3 H, NH and $H(3,5)_{Bza}$); 7.47—7.60 (m, 2 H, $H(4,6)_{Bza}$); 7.81 (br.s, 1 H, NH); 7.85 (s, 1 H, $H(5)_{py}$). ^{13}C NMR, δ: 21.63 $(C(6)_{THQ})$, 21.91 $(C(7)_{THQ})$, 26.87 $(C(5)_{THQ})$, 31.00 (CH_2S), 32.29 $(C(8)_{THQ})$, 102.90 $(C(3)_{THQ})$, 115.81 (CN_{THQ}), 127.10 $(C(5)_{Bza})$, 127.83 $(C(6)_{Bza})$, 128.33 $(C(4a)_{THQ})$, 129.67 $(C(3)_{Bza})$, 130.78 $(C(4)_{Bza})$, 135.73 $(C(2)_{Bza})$, 136.39 $(C(1)_{Bza})$, 141.74 $(C(4)_{THQ})$, 157.23 $(C(2)_{THQ})$, 161.47 $(C(8a)_{THQ})$, 170.32 (C=O).

2-{[2-(Aminocarbonyl)benzyl]thio}-3-cyano-4,6-diphenylpyridine (3c). Yield 0.97 g (78%), colorless crystals, m.p. 240—242 °C (DMF—MeOH). Found (%): C, 74.17; H, 4.45; N, 9.88; S, 7.45. $C_{26}H_{19}N_3OS$. Calculated (%): C, 74.09; H, 4.54; N, 9.97; S, 7.61. IR, ν/cm^{-1}: 3368, 3184 (NH_2), 2216 (CN), 1652 (C=O), 1620, 1568, 1528, 1368, 776. ^1H NMR, δ: 4.98 (s, 2 H, CH_2S); 7.30—7.40 (m, 2 H, $H(3,5)_{Bza}$); 7.42 (br.s, 1 H, NH); 7.52—7.67 (m, 8 H, $H(3,4,5)_{6\text{-}Ph}$, $H(3,4,5)_{4\text{-}Ph}$ and $H(4,6)_{Bza}$); 7.70—7.78 (m, 2 H, $H(2,6)_{4\text{-}Ph}$); 7.86—7.96 (m, 2 H, $H(5)_{py}$ and NH); 8.32 (d, 2 H, $H(2,6)_{6\text{-}Ph}$, J = 7.3 Hz). ^{13}C NMR, δ: 31.67 (CH_2S), 102.51 $(C(3)_{py})$, 115.58 (CN_{py}), 116.23 $(C(5)_{py})$, 127.34 $(C(5)_{Bza})$, 127.58 $(C(3,5)_{6\text{-}Ph})$, 127.98 $(C(6)_{Bza})$, 128.65 $(C(3,5)_{4\text{-}Ph})$, 128.81 $(C(2,6)_{4\text{-}Ph})$, 129.02 $(C(2,6)_{6\text{-}Ph})$, 129.90 $(C(3)_{Bza})$, 130.06 $(C(4)_{4\text{-}Ph})$, 130.40 $(C(4)_{6\text{-}Ph})$, 130.79 $(C(4)_{Bza})$, 135.68 $(C(2)_{Bza})$, 135.75 $(C(1)_{Bza})$, 135.91 $(C(1)_{4\text{-}Ph})$, 136.68 $(C(1)_{6\text{-}Ph})$, 154.34 $(C(4)_{py})$, 157.94 $(C(6)_{py})$, 162.80 $(C(2)_{py})$, 170.32 (C=O).

2-{[2-(Aminocarbonyl)benzyl]thio-3-cyano-4-(trifluoromethyl)-6-phenylpyridine (3d). Yield 0.92 g (75%), colorless crystals, m.p. 210—212 °C (MeOH). Found (%): C, 60.88; H, 3.51; N, 9.96; S, 7.86. $C_{21}H_{14}F_3N_3OS$. Calculated (%): C, 61.01; H, 3.41; N, 10.16; S, 7.75. IR, ν/cm^{-1}: 3378, 3187 (NH_2), 3090, 2230 (CN), 1654 (C=O), 1624, 1583, 1553, 1375, 1313, 1174, 1144. ^1H NMR, δ: 4.99 (s, 2 H, CH_2S); 7.28—7.42 (m, 3 H, NH and $H(3,5)_{Bza}$); 7.50—7.72 (m, 5 H, $H(3,4,5)_{6\text{-}Ph}$ and $H(4,6)_{Bza}$); 7.96 (br.s, 1 H, NH); 8.23 (s, 1 H, $H(5)_{py}$); 8.35 (d, 2 H, $H(2,6)_{6\text{-}Ph}$,

J = 8.1 Hz). ^{13}C NMR, δ: 32.12 (CH_2S), 99.28 ($C(3)_{py}$), 112.48 (q, $C(5)_{py}$, J = 4.4 Hz); 112.84 (CN_{py}), 121.10 (q, CF_3, J_{CF} = = 275.3 Hz); 127.54 ($C(5)_{Bza}$), 127.97 ($C(3,5)_{6\text{-}Ph}$), 128.06 ($C(6)_{Bza}$), 129.19 ($C(2,6)_{6\text{-}Ph}$), 129.99 ($C(3)_{Bza}$), 130.42 ($C(4)_{6\text{-}Ph}$), 131.75 ($C(4)_{Bza}$), 135.18 ($C(2)_{Bza}$), 135.60 ($C(1)_{Bza}$), 135.77 ($C(1)_{6\text{-}Ph}$), 140.84 (q, $C(4)_{py}$, J = 34.2 Hz); 159.70 ($C(6)_{py}$), 164.52 ($C(2)_{py}$), 170.23 (C=O).

Reaction of benzamides 3a—d with potassium *tert*-butoxide (general procedure). To a solution of benzamide **3a—d** (2 mmol) in anhydrous DMF (5 mL), potassium *tert*-butoxide (0.34 g, 3 mmol) was added. The reaction mixture was stirred at 70—75 °C for 40 mim and poured into water (40 mL). The precipitate formed was collected by filtration, dried in air, and crystallized from the appropriate solvent.

5-Amino-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline (4a). Yield 0.44 g (79%), orange-yellow crystals, m.p. 278—280 °C (DMF—MeOH). Found (%): C, 68.97; H, 4.88; N, 15.17; S, 11.61. $C_{16}H_{13}N_3S$. Calculated (%): C, 68.79; H, 4.69; N, 15.04; S, 11.48. IR, ν/cm^{-1}: 3472, 3436, 3328, 3224 (NH_2), 1616, 1568, 1544, 1420, 1324, 756. ^{1}H NMR, δ: 2.57 (s, 3 H, C(7)Me); 3.02 (s, 3 H, C(9)Me); 6.98 (s, 2 H, NH_2); 7.14 (s, 1 H, $H(8)_{PTI}$); 7.61 (t, 1 H, $H(3)_{PTI}$, J = 7.3 Hz); 7.79 (t, 1 H, $H(2)_{PTI}$, J = 7.3 Hz); 7.90 (d, 1 H, $H(1)_{PTI}$, J = 8.1 Hz); 8.39 (d, 1 H, $H(4)_{PTI}$, J = 7.3 Hz). ^{13}C NMR, δ: 18.96 (C(7)Me); 23.81 (C(9)Me); 116.12 ($C(11a)_{PTI}$), 116.91 ($C(4a)_{PTI}$), 122.10 ($C(8)_{PTI}$), 123.53 ($C(4)_{PTI}$), 125.20 ($C(6b)_{PTI}$), 125.38 ($C(3)_{PTI}$), 126.49 ($C(1)_{PTI}$), 131.16 ($C(2)_{PTI}$), 132.07 ($C(11b)_{PTI}$), 144.08 ($C(7)_{PTI}$), 144.90 ($C(6a)_{PTI}$), 156.03 ($C(9)_{PTI}$), 156.50 ($C(5)_{PTI}$), 159.85 ($C(10a)_{PTI}$).

5-Amino-8,9,10,11-tetrahydroisoquinolino[3′,4′:4,5]thieno[2,3-*b*]quinoline (4b). Yield 0.45 g (74%), yellow crystals, m.p. 287—290 °C (DMF—MeOH). Found (%): C, 70.63; H, 5.05; N, 13.67; S, 10.61. $C_{18}H_{15}N_3S$. Calculated (%): C, 70.79; H, 4.95; N, 13.76; S, 10.50. IR, ν/cm^{-1}: 3360, 3256 (NH_2), 3144, 2928, 1644, 1616, 1568, 1528, 1424, 1320, 760. ^{1}H NMR, δ: 1.70—1.90 (m, 4 H, $C(9,10)H_{2(THIQTQ)}$); 2.85—3.02 (m, 4 H, $C(8,11)H_{2(THIQTQ)}$); 7.09 (s, 2 H, NH_2); 7.60 (t, 1 H, $H(3)_{THIQTQ}$, J = 7.3 Hz); 7.77 (t, 1 H, $H(2)_{THIQTQ}$, J = 8.1 Hz); 7.86 (d, 1 H, $H(1)_{THIQTQ}$, J = 8.1 Hz); 8.06 (s, 1 H, $H(7)_{THIQTQ}$); 8.39 (d, 1 H, $H(4)_{THIQTQ}$, J = 8.1 Hz). ^{13}C NMR, δ: 22.38 ($C(9)_{THIQTQ}$), 22.62 ($C(10)_{THIQTQ}$), 28.39 ($C(8)_{THIQTQ}$), 32.45 ($C(11)_{THIQTQ}$), 116.72 ($C(13a)_{THIQTQ}$), 117.80 ($C(4a)_{THIQTQ}$), 123.59 ($C(4)_{THIQTQ}$), 125.50 ($C(3)_{THIQTQ}$), 126.48 ($C(1)_{THIQTQ}$), 127.67 ($C(6b)_{THIQTQ}$), 128.88 ($C(7a)_{THIQTQ}$), 129.66 ($C(7)_{THIQTQ}$), 131.26 ($C(2)_{THIQTQ}$), 132.29 ($C(13b)_{THIQTQ}$), 141.99 ($C(6a)_{THIQTQ}$), 156.68 ($C(5)_{THIQTQ}$), 156.99 ($C(11a)_{THIQTQ}$), 157.18 ($C(12a)_{THIQTQ}$).

5-Amino-7,9-diphenylpyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline (4c). Yield 0.58 g (72%), yellow crystals, m.p. 232—234 °C (DMF—MeOH). Found (%): C, 77.22; H, 4.28; N, 10.28; S, 7.70. $C_{26}H_{17}N_3S$. Calculated (%): C, 77.39; H, 4.25; N, 10.41; S, 7.95. IR, ν/cm^{-1}: 3408, 3376, 3240, 3216 (NH_2), 3048, 1632, 1624, 1616, 1568, 1536, 1448, 1416, 1324, 752. ^{1}H NMR, δ: 6.38 (s, 2 H, NH_2); 7.45—7.60 (m, 6 H, $H(3,4,5)_{9\text{-}Ph}$ and $H(3,4,5)_{7\text{-}Ph}$); 7.63 (t, 1 H, $H(3)_{PTI}$, J = 8.1 Hz); 7.72—7.82 (m, 2 H, $H(2,6)_{7\text{-}Ph}$); 7.83 (t, 1 H, $H(2)_{PTI}$, J = 7.3 Hz); 7.88 (s, 1 H, $H(8)_{PTI}$); 7.97 (d, 1 H, $H(1)_{PTI}$, J = 8.1 Hz); 8.25 (d, 2 H, $H(2,6)_{9\text{-}Ph}$, J = 8.1 Hz); 8.37 (d, 1 H, $H(4)_{PTI}$, J = 8.1 Hz). ^{13}C NMR, δ: 117.64 ($C(4a)_{PTI}$), 117.87 ($C(11a)_{PTI}$), 119.21 ($C(8)_{PTI}$), 124.04 ($C(4)_{PTI}$), 124.59 ($C(6b)_{PTI}$), 125.50 ($C(3)_{PTI}$), 127.12 ($C(1)_{PTI}$), 127.19 ($C(3,5)_{9\text{-}Ph}$), 127.58 ($C(3,5)_{7\text{-}Ph}$), 128.64 ($C(4)_{7\text{-}Ph}$), 129.14 ($C(2,6)_{7\text{-}Ph}$), 129.70 ($C(4)_{9\text{-}Ph}$), 130.37 ($C(2,6)_{9\text{-}Ph}$), 131.45 ($C(2)_{PTI}$), 132.01 ($C(11b)_{PTI}$), 137.47 ($C(1)_{7\text{-}Ph}$), 138.05 ($C(1)_{9\text{-}Ph}$), 142.66 ($C(7)_{PTI}$), 147.67 ($C(6a)_{PTI}$), 154.43 ($C(9)_{PTI}$), 155.35 ($C(5)_{PTI}$), 161.73 ($C(12a)_{PTI}$).

5-Amino-9-phenyl-7-(trifluoromethyl)pyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline (4d). Yield 0.41 g (52%), yellow crystals, m.p. 227—230 °C (CH_2Cl_2). Found (%): C, 63.58; H, 3.14; N, 10.51; S, 8.03. $C_{21}H_{12}F_3N_3S$. Calculated (%): C, 63.79; H, 3.06; N, 10.63; S, 8.11. IR, ν/cm^{-1}: 3409, 3301, 3221, 1632, 1617, 1572, 1418, 1367, 1242, 1150, 1106, 769, 758, 706, 669. ^{1}H NMR, δ: 7.06 (s, 2 H, NH_2); 7.53—7.63 (m, 3 H, $H(3,4,5)_{9\text{-}Ph}$); 7.73 (t, 1 H, $H(3)_{PTI}$, J = 8.1 Hz); 7.88 (t, 1 H, $H(2)_{PTI}$, J = 8.1 Hz); 8.04 (d, 1 H, $H(1)_{PTI}$, J = 8.1 Hz); 8.31 (d, 2 H, $H(2,6)_{9\text{-}Ph}$, J = 8.1 Hz); 8.33 (s, 1 H, $H(8)_{PTI}$); 8.48 (d, 1 H, $H(4)_{PTI}$, J = 8.1 Hz). ^{13}C NMR, δ: 106.83 ($C(11a)_{PTI}$), 113.62 (q, $C(8)_{PTI}$, J = 5.5 Hz); 117.68 ($C(4a)_{PTI}$), 121.06 ($C(6b)_{PTI}$), 121.80 (q, CF_3, J_{CF} = 275.3 Hz); 124.13 ($C(4)_{PTI}$), 125.41 ($C(3)_{PTI}$), 127.11 ($C(3,5)_{9\text{-}Ph}$), 127.42 ($C(1)_{PTI}$), 129.03 ($C(2,6)_{9\text{-}Ph}$), 130.08 ($C(4)_{9\text{-}Ph}$), 131.34 ($C(2)_{PTI}$), 131.47 ($C(11b)_{PTI}$), 132.20 (q, $C(7)_{PTI}$, J = 34.2 Hz); 136.92 ($C(1)_{9\text{-}Ph}$), 140.78 ($C(6a)_{PTI}$), 154.79 ($C(9)_{PTI}$), 156.16 ($C(5)_{PTI}$), 161.94 ($C(10a)_{PTI}$).

Synthesis of substituted 2-{[2-(aminocarbonyl)benzyl]sulfinyl}-3-cyanopyridines 5a—d (general procedure). To a stirred suspension of compound **3a—d** (3 mmol) in a mixture of AcOH (10 mL) and $CHCl_3$ (2 mL), 30% aqueous H_2O_2 (0.33 mL, 3.3 mmol) was added. The reaction mixture was stirred at 50—55 °C for 3—4 h (TLC monitoring) and cooled to room temperature. Acetic acid was neutralized with a solution of Na_2CO_3. The target product was extracted with $CHCl_3$ (3×20 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (gradient elution with hexane—$CHCl_3$ (1 : 3), then $CHCl_3$) and subsequent crystallization from the appropriate solvent.

2-{[2-(Aminocarbonyl)benzyl]sulfinyl}-3-cyano-4,6-dimethylpyridine (5a). Yield 0.67 g (72%), colorless crystals, m.p. 196—198 °C (acetone). Found (%): C, 61.53; H, 4.96; N, 13.27; S, 10.38. $C_{16}H_{15}N_3O_2S$. Calculated (%): C, 61.32; H, 4.82; N, 13.41; S, 10.23. IR, ν/cm^{-1}: 3400, 3347, 3285, 3190 (NH_2), 2927, 2219 (CN), 1673 (C=O), 1614, 1591, 1391, 1081, 1060 (S=O), 774. ^{1}H NMR, δ: 2.46 (s, 3 H, C(4)Me); 2.57 (s, 3 H, C(6)Me); 4.70 (d, 1 H, $CH_2S(O)$, J = 12.5 Hz); 4.80 (d, 1 H, $CH_2S(O)$, J = 12.5 Hz); 7.14 (d, 1 H, $H(3)_{Bza}$, J = 7.3 Hz); 7.30—7.40 (m, 3 H, $H(4,5)_{Bza}$ and NH); 7.50—7.58 (m, 2 H, $H(6)_{Bza}$ and $H(5)_{py}$); 7.71 (br.s, 1 H, NH). ^{13}C NMR, δ: 19.59 (C(4)Me); 24.05 (C(6)Me); 57.04 ($CH_2S(O)$), 106.26 ($C(3)_{py}$), 112.89 (CN_{py}), 126.22 ($C(5)_{py}$), 128.06 ($C(5)_{Bza}$), 128.10 ($C(6)_{Bza}$), 128.32 ($C(1)_{Bza}$), 129.79 ($C(3)_{Bza}$), 132.42 ($C(4)_{Bza}$), 136.17 (($C(2)_{Bza}$), 153.59 ($C(4)_{py}$), 162.15 ($C(6)_{py}$), 163.76 ($C(2)_{py}$), 169.56 (C=O).

2-{[(2-Aminocarbonyl)benzyl]sulfinyl}-3-cyano-5,6,7,8-tetrahydroquinoline (5b). Yield 0.75 g (73%), colorless crystals, m.p. 203—205 °C (acetone). Found (%): C, 63.84; H, 5.17; N, 12.25; S, 9.40. $C_{18}H_{17}N_3O_2S$. Calculated (%): C, 63.70; H, 5.05; N, 12.38; S, 9.45. IR, ν/cm^{-1}: 3393, 3309, 3255, 3206 (NH_2), 2942, 2229 (CN), 1658 (C=O), 1617, 1384, 1047, 1037 (S=O), 1023, 778. ^{1}H NMR, δ: 1.70—1.80 (m, 2 H, $C(6)H_{2(THQ)}$); 1.80—1.90 (m, 2 H, $C(7)H_{2(THQ)}$); 2.82 (t, 2 H, $C(5)H_{2(THQ)}$, J = 5.9 Hz); 2.92 (t, 2 H, $C(8)H_{2(THQ)}$, J = 5.9 Hz); 4.70 (d, 1 H, $CH_2S(O)$, J = 11.7 Hz); 4.82 (d, 1 H, $CH_2S(O)$, J = 11.7 Hz); 7.12—7.22 (m, 1 H, $H(3)_{Bza}$); 7.27 (br.s, 1 H, NH); 7.36 (m, 2 H,

H(4,5)$_{Bza}$); 7.52 (d, 1 H, H(6)$_{Bza}$, J = 7.3 Hz); 7.63 (br.s, 1 H, NH); 8.05 (s, 1 H, H(4)$_{py}$). ^{13}C NMR, δ: 21.21 (C(6)$_{THQ}$), 21.70 (C(7)$_{THQ}$), 27.54 (C(5)$_{THQ}$), 32.12 (C(8)$_{THQ}$), 56.87 ($CH_2S(O)$), 105.16 (C(3)$_{THQ}$), 114.03 (CN_{THQ}), 128.00 (C(1)$_{Bza}$), 128.10 (C(5)$_{Bza}$), 128.23 (C(6)$_{Bza}$), 129.80 (C(3)$_{Bza}$), 132.52 (C(4)$_{Bza}$), 135.29 (C(2)$_{Bza}$), 136.13 (C(4a)$_{THQ}$), 143.01 (C(4)$_{THQ}$), 160.32 (C(2)$_{THQ}$), 162.33 (C(8a)$_{THQ}$), 169.51 (C=O).

2-{[2-(Aminocarbonyl)benzyl]sulfinyl}-3-cyano-4,6-diphenylpyridine (5c). Yield 0.68 g (52%), colorless crystals, m.p. 247—249 °C (DMF—MeOH). Found (%): C, 71.55; H, 4.48; N, 9.49; S, 7.25. $C_{26}H_{19}N_3O_2S$. Calculated (%): C, 71.38; H, 4.38; N, 9.60; S, 7.33. IR, ν/cm^{-1}: 3478, 3396, 3291, 3239, 3178 (NH_2), 3066, 2223 (CN), 1670 (C=O), 1583, 1574, 1368, 1083, 1067 (S=O), 1058, 701. ^{1}H NMR, δ: 4.94 (s, 2 H, $CH_2S(O)$); 7.20—7.28 (m, 1 H, H(3)$_{Bza}$); 7.34—7.45 (m, 2 H, NH and H(5)$_{Bza}$); 7.48—7.68 (m, 9 H, H(4,6)$_{Bza}$, H(3,4,5)$_{6\text{-}Ph}$, H(3,4,5)$_{4\text{-}Ph}$ and NH); 7.70—7.78 (m, 2 H, H(2,6)$_{4\text{-}Ph}$); 8.22—8.32 (m, 3 H, H(2,6)$_{6\text{-}Ph}$ and H(5)$_{py}$). ^{13}C NMR, δ: 57.53 ($CH_2S(O)$), 105.22 (C(3)$_{py}$), 113.56 (CN_{py}), 122.03 (C(5)$_{py}$), 127.89 (C(3,5)$_{6\text{-}Ph}$), 128.17 (C(5)$_{Bza}$), 128.29 (C(6)$_{Bza}$), 128.55 (C(1)$_{Bza}$), 128.79 (C(3,5)$_{4\text{-}Ph}$), 128.95 (C(2,6)$_{4\text{-}Ph}$), 128.98 (C(2,6)$_{6\text{-}Ph}$), 129.96 (C(4)$_{4\text{-}Ph}$), 130.18 (C(4)$_{6\text{-}Ph}$), 131.16 (C(3)$_{Bza}$), 132.45 (C(4)$_{Bza}$), 135.19 (C(2)$_{Bza}$), 135.93 (C(1)$_{4\text{-}Ph}$), 136.07 (C(1)$_{6\text{-}Ph}$), 155.05 (C(4)$_{py}$), 158.69 (C(6)$_{py}$), 165.38 (C(2)$_{py}$), 169.60 (C=O).

2-{[2-(Aminocarbonyl)benzyl]sulfinyl}-3-cyano-4-trifluoromethyl-6-phenylpyridine (5d). Yield 1.03 g (80%), colorless crystals, m.p. 213—216 °C (acetone—hexane). Found (%): C, 58.92; H, 3.41; N, 9.63; S, 7.36. $C_{21}H_{14}F_3N_3O_2S$. Calculated (%): C, 58.74; H, 3.29; N, 9.79; S, 7.47. IR, ν/cm^{-1}: 3395, 3286, 3239, 3178 (NH_2), 3066, 2230 (CN), 1674 (C=O), 1583, 1574, 1368, 1061 (S=O), 1058, 701. ^{1}H NMR, δ: 4.87 (d, 1 H, $CH_2S(O)$, J = 12.5 Hz); 4.94 (d, 1 H, $CH_2S(O)$, J = 12.5 Hz); 7.22—7.30 (m, 1 H, H(3)$_{Bza}$); 7.33—7.45 (m, 3 H, H(4,5)$_{Bza}$ and NH); 7.52—7.67 (m, 4 H, H(6)$_{Bza}$ and H(3,4,5)$_{6\text{-}Ph}$); 7.79 (br.s, 1 H, NH); 8.24 (d, 2 H, H(2,6)$_{6\text{-}Ph}$, J = 6.6 Hz); 8.61 (s, 1 H, H(5)$_{py}$). ^{13}C NMR, δ: 57.84 ($CH_2S(O)$), 102.49 (C(3)$_{py}$), 110.73 (CN_{py}), 118.43 (q, C(5)$_{py}$, J = 4.4 Hz); 121.32 (q, CF_3, J_{CF} = = 275.3 Hz); 128.14 (C(5)$_{Bza}$), 128.22 (C(1)$_{Bza}$), 128.22 (C(3,5)$_{6\text{-}Ph}$), 128.29 (C(6)$_{Bza}$), 129.11 (C(2,6)$_{6\text{-}Ph}$), 129.95 (C(4)$_{6\text{-}Ph}$), 132.05 (C(3)$_{Bza}$), 132.64 (C(4)$_{Bza}$), 134.91 (C(2)$_{Bza}$), 135.81 (C(1)$_{6\text{-}Ph}$), 141.45 (q, C(4)$_{py}$, J = 33.2 Hz); 160.12 (C(6)$_{py}$), 167.15 (C(2)$_{py}$), 169.54 (C=O).

Synthesis of substituted 2-{[2-(aminocarbonyl)benzyl]sulfonyl}-3-cyanopyridines 7a—d (general procedure). To a stirred solution or suspension of benzamide **3a—d** (3 mmol) in AcOH (12—15 mL), finely ground $KMnO_4$ (0.76 g, 4.8 mmol) was added at such a rate to maintain the reaction temperature at 20—25 °C. The mixture was stirred for 40 min, decolorized by addition of a Na_2SO_3 solution, and poured into water (50 mL). The precipitated product was collected by filtration, washed with water, dried in air, and crystallized from the appropriate solvent.

2-{[2-(Aminocarbonyl)benzyl]sulfonyl}-3-cyano-4,6-dimethylpyridine (7a). Yield 0.47 g (48%), colorless crystals, m.p. 230—232 °C (DMF—MeOH). Found (%): C, 58.23; H, 4.71; N, 12.82; S, 9.61. $C_{16}H_{15}N_3O_3S$. Calculated (%): C, 58.35; H, 4.59; N, 12.76; S, 9.73. IR, ν/cm^{-1}: 3429, 3296, 3183 (NH_2), 3013, 2959, 2237 (CN), 1670, 1662 (C=O), 1609, 1592, 1381, 1311 (SO_2), 1300, 1148, 1132 (SO_2), 879, 778. ^{1}H NMR, δ: 2.52 (s, 3 H, C(4)Me); 2.61 (s, 3 H, C(6)Me); 5.42 (s, 2 H, CH_2SO_2); 7.31 (br.s, 1 H, NH); 7.40—7.48 (m, 3 H, H(3,4,5)$_{Bza}$); 7.52 (d, 1 H, H(6)$_{Bza}$, J = 6.6 Hz); 7.72 (s, 1 H, H(5)$_{py}$); 7.75 (br.s, 1 H, NH). ^{13}C NMR, δ: 20.09 (C(4)Me); 23.95 (C(6)Me); 53.77 (CH_2SO_2), 104.96 (C(3)$_{py}$), 112.72 (CN_{py}), 125.77 (C(1)$_{Bza}$), 127.94 (C(5)$_{py}$), 128.25 (C(5)$_{Bza}$), 128.52 (C(6)$_{Bza}$), 129.79 (C(3)$_{Bza}$), 133.44 (C(4)$_{Bza}$), 137.14 (C(2)$_{Bza}$), 154.88 (C(4)$_{py}$), 157.05 (C(2)$_{py}$), 161.72 (C(6)$_{py}$), 169.84 (C=O).

2-{[(2-Aminocarbonyl]benzyl]sulfonyl}-3-cyano-5,6,7,8-tetrahydroisoquinoline (7b). Yield 0.75 g (71%), colorless crystals, m.p. 241—243 °C (DMF—MeOH). Found (%): C, 60.70; H, 4.71; N, 11.77; S, 9.11. $C_{18}H_{17}N_3O_3S$. Calculated (%): C, 60.83; H, 4.82; N, 11.82; S, 9.02. IR, ν/cm^{-1}: 3432, 3338, 3290, 3209 (NH_2), 2950, 2232 (CN), 1669 (C=O), 1579, 1335, 1310 (SO_2), 1300, 1138 (SO_2), 782, 739. ^{1}H NMR, δ: 1.70—1.80 (m, 2 H, C(6)H$_{2(THQ)}$); 1.82—1.92 (m, 2 H, C(7)H$_{2(THQ)}$); 2.85 (t, 2 H, C(5)H$_{2(THQ)}$, J = 5.9 Hz); 2.96 (t, 2 H, C(8)H$_{2(THQ)}$, J = 5.9 Hz); 5.37 (s, 2 H, CH_2SO_2); 7.27 (br.s, 1 H, NH); 7.37—7.49 (m, 3 H, H(3,4,5)$_{Bza}$); 7.51 (d, 1 H, H(6)$_{Bza}$, J = 6.6 Hz); 7.67 (br.s, 1 H, NH); 8.20 (s, 1 H, H(5)$_{py}$). ^{13}C NMR, δ: 20.99 (C(6)$_{THQ}$), 21.56 (C(7)$_{THQ}$), 27.64 (C(5)$_{THQ}$), 31.99 (C(8)$_{THQ}$), 54.12 (CH_2SO_2), 104.35 (C(3)$_{py}$), 114.02 (CN_{py}), 125.95 (C(1)$_{Bza}$), 128.20 (C(5)$_{Bza}$), 128.47 (C(6)$_{Bza}$), 129.83 (C(3)$_{Bza}$), 133.45 (C(4)$_{Bza}$), 136.87 (C(4a)$_{THQ}$), 137.60 (C(2)$_{Bza}$), 143.99 (C(4)$_{THQ}$), 153.39 (C(2)$_{THQ}$), 162.08 (C(8a)$_{THQ}$), 169.66 (C=O).

2-{[2-(Aminocarbonyl)benzyl]sulfonyl}-3-cyano-4,6-diphenylpyridine (7c). Yield 0.98 g (72%), colorless crystals, m.p. 240—242 °C (MeOH). Found (%): C, 69.03; H, 4.17; N, 9.18; S, 7.14. $C_{26}H_{19}N_3O_3S$. Calculated (%): C, 68.86; H, 4.22; N, 9.27; S, 7.07. IR, ν/cm^{-1}: 3463, 3332, 3281, 3202 (NH_2), 3067, 2227 (CN), 1664 (C=O), 1585, 1575, 1386, 1320 (SO_2), 1142 (SO_2), 782, 756. ^{1}H NMR, δ: 5.65 (s, 2 H, CH_2SO_2); 7.33 (br.s, 1 H, NH); 7.43—7.68 (m, 10 H, H(3,4,5,6)$_{Bza}$, H(3,4,5)$_{6\text{-}Ph}$ and H(3,4,5)$_{4\text{-}Ph}$); 7.70—7.78 (m, 2 H, H(2,6)$_{4\text{-}Ph}$); 7.84 (br.s, 1 H, NH); 8.31 (d, 2 H, H(2,6)$_{6\text{-}Ph}$, J = 6.6 Hz); 8.47 (s, 1 H, H(5)$_{py}$). ^{13}C NMR, δ: 54.52 (CH_2SO_2), 104.02 (C$_{py}$(3)), 113.86 (CN_{py}), 124.17 (C(5)$_{py}$), 126.19 (C(1)$_{Bza}$), 128.57 (C(3,5)$_{6\text{-}Ph}$), 128.93 (C(5)$_{Bza}$), 129.18 (C(6)$_{Bza}$), 129.30 (C(3,5)$_{4\text{-}Ph}$), 129.67 (C(2,6)$_{4\text{-}Ph}$), 129.72 (C(2,6)$_{6\text{-}Ph}$), 130.43 (C(4)$_{4\text{-}Ph}$), 130.82 (C(4)$_{6\text{-}Ph}$), 132.06 (C(3)$_{Bza}$), 134.09 (C(4)$_{Bza}$), 135.75 (C(1)$_{4\text{-}Ph}$), 135.84 (C(1)$_{6\text{-}Ph}$), 137.80 (C(2)$_{Bza}$), 157.34 (C(4)$_{py}$), 158.38 (C(6)$_{py}$), 159.55 (C(2)$_{py}$), 170.51 (C=O).

2-{[2-(Aminocarbonyl)benzyl]sulfonyl}-3-cyano-4-trifluoromethyl-6-phenylpyridine (7d). Yield 1 g (75%), colorless crystals, m.p. 230—232 °C (MeOH). Found (%): C, 56.77; H, 3.11; N, 9.31; S, 7.08. $C_{21}H_{14}F_3N_3O_3S$. Calculated (%): C, 56.63; H, 3.17; N, 9.43; S, 7.20. IR, ν/cm^{-1}: 3477, 3331, 3280, 3196, 3184 (NH_2), 3076, 2237 (CN), 1665 (C=O), 1590, 1429, 1380, 1326 (SO_2), 1269, 1189, 1149 (SO_2), 779. ^{1}H NMR, δ: 5.55 (s, 2 H, CH_2SO_2); 7.27 (br.s, 1 H, NH); 7.42—7.68 (m, 7 H, H(3,4,5,6)$_{Bza}$ and H(3,4,5)$_{6\text{-}Ph}$); 7.79 (br.s, 1 H, NH); 8.25 (d, 2 H, H(2,6)$_{6\text{-}Ph}$, J = 6.6 Hz); 8.76 (s, 1 H, H(5)$_{py}$). ^{13}C NMR, δ: 55.38 (CH_2SO_2), 101.67 (C(3)$_{py}$), 111.70 (CN_{py}), 120.97 (q, C(5)$_{py}$, J = 5.5 Hz), 121.78 (q, CF_3, J_{CF} = 277.6 Hz); 126.06 (C(1)$_{Bza}$), 128.87 (C(5)$_{Bza}$), 128.92 (C(3,5)$_{6\text{-}Ph}$), 129.33 (C(6)$_{Bza}$), 129.78 (C(2,6)$_{6\text{-}Ph}$), 130.57 (C(4)$_{6\text{-}Ph}$), 132.97 (C(3)$_{Bza}$), 134.12 (C(4)$_{Bza}$), 134.93 (C(1)$_{6\text{-}Ph}$), 137.35 (C(2)$_{Bza}$), 143.25 (q, C(4)$_{py}$, J = 33.2 Hz); 160.00 (C(2)$_{py}$), 160.43 (C(6)$_{py}$), 170.34 (C=O).

Synthesis of substituted 5-aminopyrido[3′,2′:4,5]thieno[3,2-*c*]-isoquinoline oxides 6a—d (general procedure). To a solution of benzamide **5a—d** (2 mmol) in anhydrous DMF (4 mL), potassium *tert*-butoxide (0.34 g, 3 mmol) was added. The reaction mixture was stirred at 55—60 °C for 50 min and poured into water (20 mL). The products were extracted with $CHCl_3$ (3×15 mL).

The combined organic layers were washed with water (3×20 mL), dried with $MgSO_4$, and concentrated. The target products were purified by silica gel column chromatography (elution with $CHCl_3$) and subsequent crystallization from appropriate solvent. Chromatographic purification of the products obtained by the reaction of benzamide **5d** with Bu^{t}OK gives also 0.1 g (13%) of compound **4d**.

5-Amino-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline 11-oxide (6a). Yield 0.44 g (75%), yellow crystals, m.p. 272—274 °C (DMF—MeOH). Found (%): C, 64.81; H, 4.36; N, 14.12; S, 10.97. $C_{16}H_{13}N_3OS$. Calculated (%): C, 65.07; H, 4.44; N, 14.23; S, 10.85. IR, ν/cm^{-1}: 3344, 3240 (NH_2), 3168, 2920, 1632, 1616, 1592, 1568, 1544, 1504, 1420, 1368, 1000 (S=O), 968, 752. ^{1}H NMR, δ: 2.51 (s, 3 H, C(7)Me); 2.82 (s, 3 H, C(9)Me); 7.23 (s, 1 H, H(8)$_{PTI}$); 7.55 (t, 1 H, H(3)$_{PTI}$, J = 7.3 Hz); 7.78 (t, 1 H, H(2)$_{PTI}$, J = 7.3 Hz); 7.81 (s, 2 H, NH_2); 7.97 (d, 1 H, H(1)$_{PTI}$, J = 8.1 Hz); 8.31 (d, 1 H, H(4)$_{PTI}$, J = 8.1 Hz). ^{13}C NMR, δ: 18.48 (C(7)Me); 23.53 (C(9)Me); 116.10 (C(4a)$_{PTI}$), 118.91 (C(11a)$_{PTI}$), 122.43 (C(4)$_{PTI}$), 125.47 (C(3)$_{PTI}$), 126.53 (C(6b)$_{PTI}$), 126.76 (C(1)$_{PTI}$), 128.26 (C(8)$_{PTI}$), 132.51 (C(2)$_{PTI}$), 133.83 (C(11b)$_{PTI}$), 146.01 (C(6a)$_{PTI}$), 151.20 (C(7)$_{PTI}$), 158.58 (C(5)$_{PTI}$), 160.75 (C(9)$_{PTI}$), 166.06 (C(10a)$_{PTI}$).

5-Amino-8,9,10,11-tetrahydroisoquinolino[3′,4′:4,5]thieno-[2,3-*b*]quinoline 13-oxide (6b). Yield 0.45 g (70%), yellow crystals, m.p. 288—290 °C (DMF—MeOH). Found (%): C, 67.45; H, 4.77; N, 12.88; S, 9.83. $C_{18}H_{15}N_3OS$. Calculated (%): C, 67.27; H, 4.70; N, 13.07; S, 9.98. IR, ν/cm^{-1}: 3328, 3264, 3216 (NH_2), 2920, 2952, 1640, 1616, 1568, 1536, 1504, 1432, 1388, 1000 (S=O), 768. ^{1}H NMR, δ: 1.70—1.80 (m, 2 H, C(9)H$_{2(THIQTQ)}$); 1.80—1.90 (m, 2 H, C(10)H$_{2(THIQTQ)}$); 2.83—2.98 (m, 4 H, C(8,11)H$_{2(THIQTQ)}$); 7.58 (t, 1 H, H(3)$_{THIQTQ}$, J = 8.1 Hz); 7.76—7.83 (m, 2 H, H(2,7)$_{THIQTQ}$), 7.95 (s, 2 H, NH_2); 8.00 (d, 1 H, H(1)$_{THIQTQ}$, J = 8.1 Hz); 8.44 (d, 1 H, H(4)$_{THIQTQ}$, J = 8.8 Hz). ^{13}C NMR, δ: 21.91 (C(9)$_{(THIQTQ)}$); 22.34 (C(10)$_{(THIQTQ)}$); 28.58 (C(8)$_{(THIQTQ)}$); 32.18 (C(11)$_{(THIQTQ)}$); 117.02 (C(4a)$_{THIQTQ}$), 119.86 (C(13a)$_{THIQTQ}$), 122.49 (C(4)$_{THIQTQ}$), 125.59 (C(3)$_{THIQTQ}$), 126.86 (C(1)$_{THIQTQ}$), 129.33 (C(6b)$_{THIQTQ}$), 130.54 (C(7)$_{THIQTQ}$), 132.62 (C(2)$_{THIQTQ}$), 133.76 (C(13b)$_{THIQTQ}$), 135.82 (C(7a)$_{THIQTQ}$), 149.04 (C(6a)$_{THIQTQ}$), 158.73 (C(5)$_{THIQTQ}$), 161.31 (C(11a)$_{THIQTQ}$), 163.14 (C(12a)$_{THIQTQ}$).

5-Amino-7,9-diphenylpyrido[3′,2′:4,5]thieno[3,2-c]isoquinoline 11-oxide (6c). Yield 0.23 g (27%), yellow crystals, m.p. 182—186 °C (DMF—MeOH). Found (%): C, 74.58; H, 4.01; N, 9.91; S, 7.77. $C_{26}H_{17}N_3OS$. Calculated (%): C, 74.44; H, 4.08; N, 10.02; S, 7.64. IR, ν/cm^{-1}: 3444, 3426, 3319 (NH_2), 3207, 3057, 2906, 1640, 1615, 1588, 1576, 1542, 1502, 1417, 1359, 1027, 1015 (S=O), 759, 696. ^{1}H NMR, δ: 7.36 (br.s, 1 H, NH_2); 7.51—7.63 (m, 7 H, H(3,4,5)$_{9\text{-}Ph}$, H(3,4,5)$_{7\text{-}Ph}$ and H(3)$_{PTI}$); 7.74—7.81 (m, 2 H, H(2,6)$_{7\text{-}Ph}$); 7.85 (t, 1 H, H(2)$_{PTI}$, J = 7.3 Hz); 8.05 (s, 1 H, H(8)$_{PTI}$); 8.11 (d, 1 H, H(1)$_{PTI}$, J = 7.3 Hz); 8.26—8.34 (m, 2 H, H(2,6)$_{9\text{-}Ph}$); 8.38 (d, 1 H, H(4)$_{PTI}$, J = 7.3 Hz). ^{13}C NMR, δ: 116.62 (C(4a)$_{PTI}$), 120.10 (C(11a)$_{PTI}$), 122.59 (C(4)$_{PTI}$), 124.61 (C(8)$_{PTI}$), 125.40 (C(3)$_{PTI}$), 126.30 (C(6b)$_{PTI}$), 126.89 (C(1)$_{PTI}$), 127.00 (C(3,5)$_{9\text{-}Ph}$), 127.52 (C(3,5)$_{7\text{-}Ph}$), 128.84 (C(4)$_{7\text{-}Ph}$), 128.94 (C(2,6)$_{7\text{-}Ph}$), 129.97 (C(4)$_{9\text{-}Ph}$), 130.05 (C(2,6)$_{9\text{-}Ph}$), 132.33 (C(2)$_{PTI}$), 133.63 (C(11b)$_{PTI}$), 136.07 (C(1)$_{7\text{-}Ph}$), 136.80 (C(1)$_{9\text{-}Ph}$); 148.09 (C(6a)$_{PTI}$), 149.69 (C(7)$_{PTI}$), 155.94 (C(9)$_{PTI}$), 159.82 (C(5)$_{PTI}$), 168.12 (C(10a)$_{PTI}$).

Substituted 5-aminopyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline dioxides 8a—d were synthesized similarly to compounds **4a—d**.

5-Amino-7,9-dimethylpyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline 11,11-dioxide (8a). Yield 0.51 g (82%), yellow crystals, m.p. 340—342 °C (DMF—MeOH). Found (%): C, 61.88; H, 4.16; N, 13.50; S, 10.21. $C_{16}H_{13}N_3O_2S$. Calculated (%): C, 61.72; H, 4.21; N, 13.50; S, 10.30. IR, ν/cm^{-1}: 3472, 3416, 3376 (NH_2), 2928, 1616, 1544, 1504, 1424, 1280 (SO_2), 1152 (SO_2), 1116, 752. ^{1}H NMR, δ: 2.57 (s, 3 H, C(7)Me); 2.91 (s, 3 H, C(9)Me); 7.43 (s, 1 H, H(8)$_{PTI}$); 7.64 (t, 1 H, H(3)$_{PTI}$, J = 8.1 Hz); 7.86—7.93 (m, 2 H, H(1,2)$_{PTI}$); 8.18 (s, 2 H, NH_2); 8.41 (d, 1 H, H(4)$_{PTI}$, J = 8.8 Hz). ^{13}C NMR, δ: 19.38 (C(7)Me); 23.56 (C(9)Me); 111.63 (C(11a)$_{PTI}$), 115.77 (C(4a)$_{PTI}$), 121.73 (C(4)$_{PTI}$), 122.35 (C(6b)$_{PTI}$), 125.69 (C(3)$_{PTI}$), 127.43 (C(1)$_{PTI}$), 129.84 (C(11b)$_{PTI}$), 129.87 (C(8)$_{PTI}$), 133.25 (C(2)$_{PTI}$), 146.72 (C(6a)$_{PTI}$), 147.05 (C(7)$_{PTI}$), 157.56 (C(10a)$_{PTI}$), 160.03 (C(5)$_{PTI}$), 161.46 (C(9)$_{PTI}$).

5-Amino-8,9,10,11-tetrahydroisoquinolino[3′,4′:4,5]thieno-[2,3-*b*]quinoline 13,13-dioxide (8b). Yield 0.49 g (72%), light yellow crystals, m.p. 322—324 °C (DMF—MeOH). Found (%): C, 64.31; H, 4.39; N, 12.33; S, 9.61. $C_{18}H_{15}N_3O_2S$. Calculated (%): C, 64.08; H, 4.48; N, 12.45; S, 9.50. IR, ν/cm^{-1}: 3456, 3408, 3320, 3248 (NH_2), 3216, 2952, 1640, 1624, 1616, 1584, 1564, 1544, 1512, 1432, 1384, 1292 (SO_2), 1136 (SO_2), 1024, 768. ^{1}H NMR, δ: 1.70—1.80 (m, 2 H, C(9)H$_{2(THIQTQ)}$); 1.82—1.92 (m, 2 H, C(10)H$_{2(THIQTQ)}$); 2.86—3.00 (m, 4 H, C(8,11)H$_{2(THIQTQ)}$); 7.65 (t, 1 H, H(3)$_{THIQTQ}$, J = 8.1 Hz); 7.87—7.93 (m, 2 H, H(1,2)$_{THIQTQ}$); 7.96 (s, 1 H, H(8)$_{THIQTQ}$); 8.25 (br.s, 2 H, NH_2); 8.44 (d, 1 H, H(4)$_{THIQTQ}$, J = 8.8 Hz). ^{13}C NMR, δ: 21.75 (C(9)$_{(THIQTQ)}$); 22.21 (C(10)$_{(THIQTQ)}$); 28.79 (C(8)$_{(THIQTQ)}$); 32.26 (C(11)$_{(THIQTQ)}$); 112.49 (C(13a)$_{THIQTQ}$), 116.75 (C(4a)$_{THIQTQ}$), 121.74 (C(4)$_{THIQTQ}$), 124.94 (C(6b)$_{THIQTQ}$), 125.84 (C(3)$_{THIQTQ}$), 127.53 (C(1)$_{THIQTQ}$), 129.83 (C(13b)$_{THIQTQ}$), 130.51 (C(7)$_{THIQTQ}$), 133.36 (C(2)$_{THIQTQ}$), 137.81 (C(7a)$_{THIQTQ}$), 144.80 (C(6a)$_{THIQTQ}$), 154.81 (C(12a)$_{THIQTQ}$), 160.12 (C(5)$_{THIQTQ}$), 162.01 (C(11a)$_{THIQTQ}$).

5-Amino-7,9-diphenylpyrido[3′,2′:4,5]thieno[3,2-c]isoquinoline 11,11-dioxide (8c). Yield 0.67 g (77%), yellow crystals, m.p. 336—338 °C (DMF—MeOH). Found (%): C, 71.61; H, 4.04; N, 9.76; S, 7.25. $C_{26}H_{17}N_3O_2S$. Calculated (%): C, 71.71; H, 3.95; N, 9.65; S, 7.36. IR, ν/cm^{-1}: 3472, 3432, 3376 (NH_2), 1616, 1600, 1592, 1584, 1576, 1544, 1424, 1284 (SO_2), 1132 (SO_2), 760. ^{1}H NMR, δ: 7.45—7.60 (m, 6 H, H(3,4,5)$_{9\text{-}Ph}$ and H(3,4,5)$_{7\text{-}Ph}$); 7.65 (t, 1 H, H(3)$_{PTI}$, J = 8.1 Hz); 7.68 (br.s, 2 H, NH_2); 7.70—7.78 (m, 2 H, H(2,6)$_{7\text{-}Ph}$); 7.93 (t, 1 H, H(2)$_{PTI}$, J = 7.3 Hz); 8.00 (d, 1 H, H(1)$_{PTI}$, J = 8.1 Hz); 8.12 (s, 1 H, H(8)$_{PTI}$); 8.22—8.30 (m, 2 H, H(2,6)$_{9\text{-}Ph}$); 8.43 (d, 1 H, H(4)$_{PTI}$, J = 8.1 Hz). ^{13}C NMR, δ: 112.47 (C(11a)$_{PTI}$), 116.34 (C(4a)$_{PTI}$), 122.00 (C(4)$_{PTI}$), 122.36 (C(6b)$_{PTI}$), 124.82 (C(8)$_{PTI}$), 125.73 (C(3)$_{PTI}$), 126.32 (C(4)$_{7\text{-}Ph}$), 127.30 (C(3,5)$_{9\text{-}Ph}$), 127.76 (C(1)$_{PTI}$), 127.82 (C(3,5)$_{7\text{-}Ph}$), 129.31 (C(2,6)$_{7\text{-}Ph}$), 129.79 (C(11b)$_{PTI}$), 130.19 (C(2,6)$_{9\text{-}Ph}$), 130.68 (C(4)$_{9\text{-}Ph}$), 133.32 (C(2)$_{PTI}$), 136.28 (C(1)$_{7\text{-}Ph}$), 136.44 (C(1)$_{9\text{-}Ph}$), 145.80 (C(7)$_{PTI}$), 148.79 (C(6a)$_{PTI}$), 157.36 (C(9)$_{PTI}$), 159.09 (C(10a)$_{PTI}$), 160.70 (C(5)$_{PTI}$).

5-Amino-7-trifluoromethyl-9-phenylpyrido[3′,2′:4,5]thieno-[3,2-*c*]isoquinoline 11,11-dioxide (8d). Yield 0.67 g (78%), yellow crystals, m.p. > 350 °C ($CHCl_3$—MeOH). Found (%): C, 58.83; H, 2.97; N, 9.96; S, 7.43. $C_{21}H_{12}F_3N_3O_2S$. Calculated (%): C, 59.02; H, 2.83; N, 9.83; S, 7.50. IR, ν/cm^{-1}: 3405, 3308 (NH_2), 3069, 2928, 1689, 1619, 1555, 1510, 1473, 1434, 1269 (SO_2), 1152 (SO_2), 1108, 871, 767, 757, 689. ^{1}H NMR, δ: 6.89 (br.s, 2 H, NH_2); 7.40—7.53 (m, 4 H, H(3,4,5)$_{9\text{-}Ph}$ and H(3)$_{PTI}$); 7.74 (t, 1 H, H(2)$_{PTI}$, J = 7.3 Hz); 7.81 (d, 1 H, H(1)$_{PTI}$, J = 7.3 Hz); 7.99 (d, 2 H, H(2,6)$_{9\text{-}Ph}$, J = 8.1 Hz); 8.27 (d, 1 H, H(4)$_{PTI}$, J = 7.3 Hz); 8.30 (s, 1 H, H(8)$_{PTI}$).

2-(Chloromethyl)benzoyl chloride (13). To a solution of *o*-toluoyl chloride (9.3 g, 60 mmol) in CCl_4 (20 mL), sulfuryl

chloride (9.7 g, 72 mmol) and diazoisobutyronitrile (0.25 g, 1.5 mmol) were added. The reaction mixture was refluxed for 4 h, cooled down, filtered, and concentrated *in vacuo*. Vacuum distillation of the residue afforded 9.8 g (87%) of chloride **13**, b.p. 172—174 °C (36 Torr) (*cf.* Ref. 17: b.p. 135 °C (14 Torr)).

4-[2-(Chloromethyl)benzoyl]morpholine (12). To a stirred solution of 2-(chloromethyl)benzoyl chloride **13** (2.84 g, 15 mmol) in $CHCl_3$ (20 mL), a solution of morpholine (2.78 g, 32 mmol) in $CHCl_3$ (20 mL) was added dropwise at 0—5 °C. The reaction mixture was stirred at this temperature for 30 min and after warming up to room temperature was poured into water (60 mL). The organic layer was separated, washed with water (2×30 mL), dried with $MgSO_4$, and the solvent was removed *in vacuo*. Purification of the residue by silica gel column chromatography afforded 2.95 g (82%) of compound **12**, viscous oil. Found (%): C, 60.32; H, 5.97; N, 5.73; Cl, 14.71. $C_{12}H_{14}ClNO_2$. Calculated (%): C, 60.13; H, 5.89; N, 5.84; Cl, 14.79. IR, ν/cm^{-1}: 3479, 3255, 3060, 2967, 2920, 2856, 1633 (C=O), 1456, 1279, 1259, 1114, 1019, 846, 775, 741, 680. ^{1}H NMR, δ: 3.16 (t, 2 H, CH_2N, J = 4.4 Hz); 3.53 (t, 2 H, CH_2N, J = 4.4 Hz); 3.66 (t, 4 H, CH_2OCH_2, J = 4.4 Hz); 4.66—4.86 (m, 2 H, CH_2Cl); 7.32 (t, 1 H, $H(5)_{Bza}$, J = 6.6 Hz); 7.34—7.42 (m, 2 H, $H(3,4)_{Bza}$); 7.47 (d, 1 H, $H(6)_{Bza}$, J = 6.6 Hz).

3-Cyano-4,6-dimethyl-2-{[2-(4-morpholinocarbonyl)benzyl]thio}pyridine (14). To a suspension of pyridinethione **1a** (1.64 g, 10 mmol) in $CHCl_3$ (15 mL), Et_3N (1.5 mL, 15 mmol) and amide **12** (2.4 g, 10 mmol) were added. The reaction mixture was refluxed for 1 h, cooled down, washed with water (2×20 mL), and dried with $MgSO_4$. Removal of the solvent *in vacuo* and purification of the residue by silica gel column chromatography (elution with $CHCl_3$) afforded 3.1 g (84%) of amide **14**, colorless crystals, m.p. 158—160 °C (MeOH). Found (%): C, 65.49; H, 5.82; N, 11.38; S, 8.61. $C_{20}H_{21}N_3O_2S$. Calculated (%): C, 65.37; H, 5.76; N, 11.44; S, 8.72. IR, ν/cm^{-1}: 2969, 2920, 2861, 1622 (C=O), 1582, 1445, 1434, 1275, 1112, 1013, 781. ^{1}H NMR, δ: 2.40 (s, 3 H, C(4)Me); 2.53 (s, 3 H, C(6)Me); 3.19 (t, 2 H, CH_2N, J = 4.4 Hz); 3.56 (t, 2 H, CH_2N, J = 4.4 Hz); 3.62 (t, 4 H, CH_2OCH_2, J = 4.4 Hz); 4.55 (s, 2 H, CH_2S); 7.13 (s, 1 H, $H(5)_{py}$); 7.29 (t, 1 H, $H(5)_{Bza}$, J = 6.6 Hz); 7.30—7.40 (m, 2 H, $H(2,3)_{Bza}$); 7.55 (d, 1 H, $H(4)_{Bza}$, J = 7.3 Hz). ^{13}C NMR, δ: 19.58 (C(4)Me); 24.26 (C(6)Me); 30.69 (CH_2S), 41.51 (CH_2N), 47.28 (CH_2N), 65.82 (CH_2OCH_2), 103.42 ($C(3)_{py}$), 114.88 (CN_{py}), 120.58 ($C(5)_{py}$), 126.51 ($C(5)_{Bza}$), 127.40 ($C(6)_{Bza}$), 129.00 ($C(3)_{Bza}$), 130.68 ($C(4)_{Bza}$), 134.50 ($C(2)_{Bza}$), 135.65 ($C(1)_{Bza}$), 152.56 ($C(4)_{py}$), 160.01 ($C(2)_{py}$), 161.44 ($C(6)_{py}$), 168.02 (C=O).

7,9-Dimethyl-5-(morpholin-4-yl)pyrido[3′,2′:4,5]thieno[3,2-*c*]isoquinoline (15). To a solution of compound **14** (0.55 g, 1.5 mmol) in DMF (3 mL), Bu^tOK (0.25 g, 2.23 mmol) was added. The reaction mixture was stirred at room temperature for 40 min, poured into water (15 mL), and extracted with $CHCl_3$. The organic layer was washed with water (2×20 mL) and dried with $MgSO_4$. Removal of the solvent *in vacuo* and purification of the residue by silica gel column chromatography (elution with $CHCl_3$) afforded 0.22 g (43%) of compound **15**, yellow crystals, m.p. 226—228 °C (DMF). Found (%): C, 68.89; H, 5.43; N, 12.13; S, 9.05. $C_{20}H_{19}N_3OS$. Calculated (%): C, 68.74; H, 5.48; N, 12.02; S, 9.17. IR, ν/cm^{-1}: 3064, 3052, 2957, 2915, 2851, 2837, 1582, 1563, 1396, 1367, 1265, 1247, 1118, 1021, 897, 763. ^{1}H NMR, δ: 2.60 (s, 3 H, C(4)Me); 3.00 (s, 3 H, C(6)Me); 3.45 (t, 4 H, CH_2NCH_2, J = 4.4 Hz); 3.94 (t, 4 H, CH_2OCH_2, J = 4.4 Hz); 7.19 (s, 1 H, $H(8)_{PTI}$); 7.71 (t, 1 H, $H(3)_{PTI}$, J = 8.1 Hz); 7.86 (t, 1 H, $H(2)_{PTI}$, J = 8.1 Hz); 8.03 (d, 1 H, $H(1)_{PTI}$, J = 8.8 Hz); 8.28 (d, 1 H, $H(4)_{PTI}$, J = 8.1 Hz).

References

1. M. Cushman, M. Jayaraman, J. A. Vroman, A. K. Fukunaga, B. M. Fox, G. Kohlhagen, D. Strumbergt, Y. Pommier, *J. Med. Chem.*, 2000, **43**, 3688.
2. D. Strumberg, Y. Pommier, K. Paull, M. Jayaraman, P. Nagafuji, M. Cushman, *J. Med. Chem.*, 1999, **42**, 446.
3. Pat. WO 00/21537; *Chem. Abstr.*, 2000, **132**, 293675t.
4. C. Szabo, V. L. Dawson, *Trends Pharmacol. Sci.*, 1998, **19**, 287.
5. U.S. Pat. 7393955; *Chem. Abstr.*, 2008, **149**, 128753.
6. Pat. WO 2006069182; *Chem. Abstr.*, 2006, **145**, 83249.
7. V. E. Kalugin, A. M. Shestopalov, *Tetrahedron Lett.*, 2011, **52**, 1557.
8. V. E. Kalugin, A. M. Shestopalov, *Russ. Chem. Bull.*, 2014, **63**, 2478.
9. V. E. Kalugin, A. M. Shestopalov, *Russ. Chem. Bull.*, 2014, **63**, 426.
10. V. E. Kalugin, A. M. Shestopalov, *Russ. Chem. Bull.*, 2017, **66**, 523.
11. V. E. Kalugin, A. M. Shestopalov, *Russ. Chem. Bull.*, 2015, **64**, 878.
12. L. F. Tietze, G. Brasche, K. M. Gericke, in *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006, p. 617.
13. K. Gewald, M. Hentschel, U. Illgen, *J. Pract. Chem.*, 1974, **316**, 1030.
14. L. A. Rodinovskaya, E. V. Belukhina, A. M. Shestopalov, V. P. Litvinov, *Russ. Chem. Bull.*, 1994, **43**, 449.
15. A. A. Krauze, Z. A. Bomika, A. M. Shestopalov, L. A. Rodinovskaya, Yu. É. Pelcher, G. Ya. Dubur, Yu. A. Sharanin, V. K. Promonenkov, *Chem. Heterocycl. Compd.*, 1981, **17**, 279.
16. L. A. Rodinovskaya, Yu. A. Sharanin, V. P. Litvinov, A. M. Shestopalov, V. K. Promonenkov, B. M. Zolotarev, B. Yu. Mortikov, *Zh. Org. Khim.* [*Russ. J. Org. Chem.*], 1985, **21**, 2439 (in Russian).
17. I. G. Hinton, F. G. Mann, *J. Chem. Soc.*, 1959, 599.

Received September 13, 2017;
in revised form May 7, 2018;
accepted May 11, 2018