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Synthesis of some fused heterocyclic systems and their nucleoside candidates

Hassan A. El-Sayed · Said A. Said · Abd El-Galil E. Amr

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Abstract A series of pyridofuro compounds were synthesized from 4-(4-chlorophenyl)-1,2-dihydro-2-oxo-6-(thiophen-2-yl)pyridine-3-carbonitrile **(1)** as starting material. Alkylation of **1** with ethyl bromoacetate gave the corresponding ester **2**, which was condensed with hydrazine hydrate to afford the corresponding acid hydrazide derivative **3**. Thrope-Ziegler cyclization of **2** with sodium methoxide gave furo[2,3-b]pyridine derivative **4**, which was reacted with thiosemicarbazide, allyl isothiocyanate, formamide or hydrazine hydrate to give furopyridine derivatives **5–8,** respectively. The latter compound **8** was cyclized with acetylacetone or formic acid to give the corresponding compounds **9** and **10**, respectively. Furthermore, sulfurization of **1** with P_2S_5 gave the corresponding thioxopyridine **11**, which was reacted with glycosyl (or galactosyl) bromide, morpholine or piperidine to give the corresponding thioglycoside **12a**,**b** and Mannich base **14a**,**b** derivatives. The deacetylation of **12a**,**b** gave the corresponding deacetylated thioglycosides **13a**,**b**, respectively. All the newly synthesized compounds were characterized by the elemental analyses and spectroscopic evidences (IR, ^{1}H- and ^{13}C NMR).

Keywords Pyridine-2(1H)-one · Furo[2,3-b]pyridine · Thioglycoside · Mannich bases

H. A. El-Sayed · S. A. Said
Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt

A. E.-G. E. Amr (✉)
Pharmaceutical Chemistry Department, Drug Exploration and Development Chair, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia
e-mail: aamr1963@yahoo.com

A. E.-G. E. Amr
Applied Organic Chemistry Department, National Research Center, El Dokki, Cairo, Egypt

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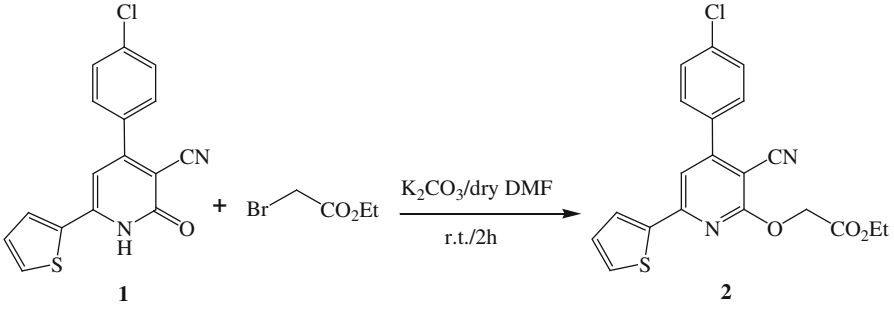
Introduction

Furopyridines and heterocycles derived from them are found to be associated with diverse pharmacological activities [1–4]. They are also reported to possess significant antipsychotic [5], antianaphlactic [3], antiproliferative [6], anticonvulsant [7], and anthelmintic [8] activities, and they can be used as calcium influx promoters [9], HIV-1 nonnucleoside reverse transcriptase inhibitors [10], acetylcholinesterase inhibitors [11], antioxidant, anti-inflammatory [12], broad-spectrum human herpes virus polymerase inhibitors [13], anticancer [14], and 5-HT_6receptor antagonists [15]. Moreover, 2-thioxopyridines and their derivatives have been evaluated to possess good antimicrobial [16], antiviral [17, 18], and anti-inflammatory activity [19]. On the other hand, glycosylsulfanyl heterocycles have attracted much attention because of their biological activity as antitumor [20], antimicrobial [21, 22], antiviral [23], and in particular their inhibition of the activity of enzymes [24–31]. In view of these reports and as a continuation of our research program in the chemistry of pyridines [32], we report here the synthesis of additional new numbers of these derivatives that are required in medicinal chemistry programs.

Results and discussion

4-(4-Chlorophenyl)-2-oxo-6-(thien-2-yl)-1,2-dihydropyridine-3-carbonitrile (**1**) was synthesized as starting material according to the literature procedure [32]. Alkylation of **1** with ethyl bromoacetate in the presence of K_2CO_3 in *DMF* afforded the corresponding ethyl ester derivative **2** (Scheme 1). The IR spectrum of ester **2** showed an absorption band at 1732 cm^{-1} characteristic for (C=O, ester), in addition to the disappearance of the amide carbonyl band, which means the formation of an O-alkylated derivative and not the N-analogues. Its ^1H NMR spectrum showed triplet, quartet, and singlet signals at δ 1.24, 4.21, and 5.11 ppm corresponding to OC_2H_5 and CH_2O protons, respectively. ^{13}C NMR spectrum of **2** showed four signals at δ 14.15, 60.76, 63.67, and 167.9 ppm corresponding to (C_2H_5), CH_2O ,and (C=O, ester), respectively.

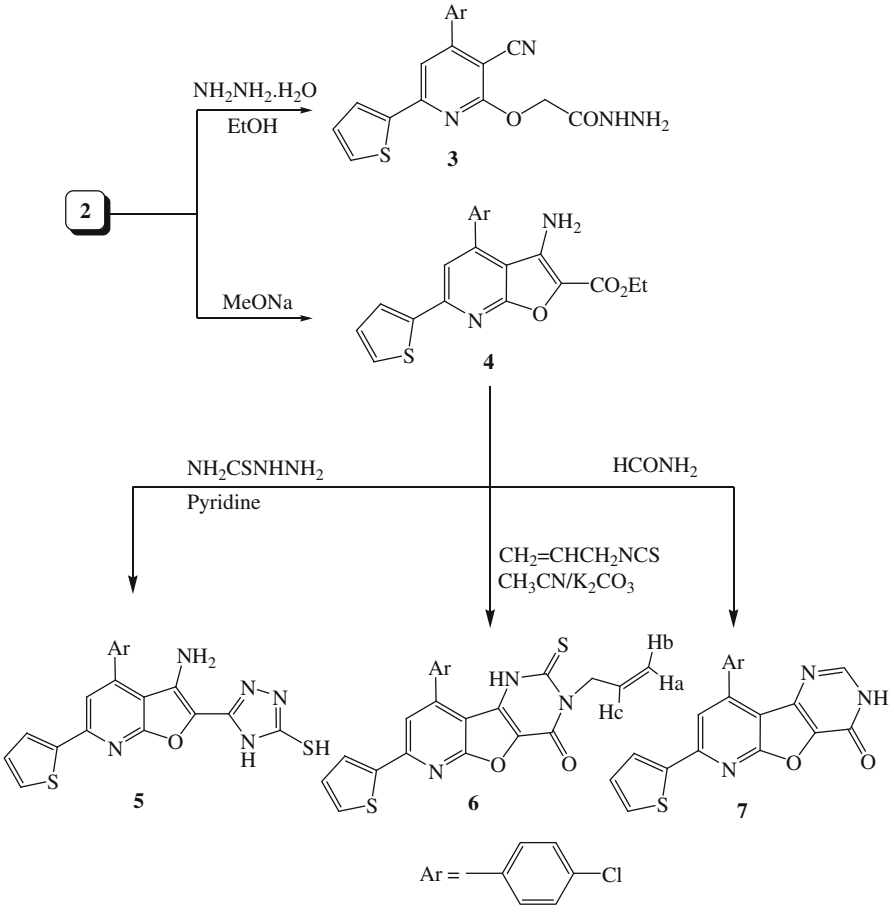


Scheme 1 Synthetic pathway for compound **2**

Condensation of ester **2** with hydrazine hydrate afforded the corresponding acid hydrazide derivative **3** (Scheme 2). The IR spectrum of **3** showed absorption bands at 1636 and 3416 cm^{-1} characterized to amid carbonyl, NH, and NH_2 groups, respectively. Its ^1H NMR spectrum showed two singlets at δ 4.62 and 8.48 ppm corresponding to NH_2 and NH protons, respectively. ^{13}C NMR spectrum of **3** showed the disappearance of the ethoxy carbon atoms. Upon treatment of ester **2** with sodium methoxide in methanol, it underwent interamolecular Thrope-Ziegler condensation to furnish ethyl 3-amino-4-(4-chlorophenyl)-6-(thien-2-yl)furo[2,3-b]pyridine-2-carboxylate (**4**) (Scheme 2). The IR spectrum of compound **4** showed an absorption band at 1734 and 3449 cm^{-1} characteristic for carbonyl ester and NH_2, in addition to the disappearance of the C≡N band. Its ^1H NMR spectrum showed triplet, quartet, and singlet broad signals at δ 1.20, 4.10, and 5.03 ppm corresponding to ethoxy and NH_2 protons, respectively, with the disappearance of the signal of the CH_2O protons. Heterocyclization of furo[2,3-b]pyridine **4** with thiosemicarbazide, allylisothiocyanate, and formamide afforded 5-(3-amino-4-(4-chlorophenyl)-6-(thien-2-yl)furo[2,3-b]pyridin-2-yl)-4H-1,2,4-triazole-3-thiol (**5**), 3-allyl-9-(4-chlorophenyl)-4-oxo-1,2,3,4-tetrahydro-7-(thien-2-yl)-2-thioxopyrido[3′,2′:4,5]furo[3,2-d]pyrimidine (**6**), and 9-(4-chlorophenyl)-4-oxo-3,4-dihydro-7-(thien-2-yl)pyrido-[3′,2′:4,5]furo[3,2-d]pyrimidine (**7**), respectively (Scheme 2). The IR spectra of compounds **5**–**7** showed the absence of a carbonyl ester band and the presence of bands at 3444–3448 cm^{-1} corresponding to NH groups, in addition, two bands at 1638 and 1654 cm^{-1} corresponded to the amide carbonyl of compounds **6** and **7**, respectively. The ^1H NMR spectrum of triazole derivative **5** showed two singlets at δ 8.79 and 13.21 ppm corresponding to NH and SH protons. The ^1H NMR spectrum of allyl derivative **6** showed two doublet signals at δ 4.8 and 5.23 ppm with coupling constants 5.43 and 10.14 Hz, corresponding to NCH_2 and Ha, respectively, in addition, there was a doublet signal at δ 5.31 ppm with a coupling constant 17.5 Hz for Hb, and a multiplet signal at δ 5.80 ppm for Hc. Its ^{13}C NMR spectrum showed signals at δ 62.91, 110.9, and 118.0 ppm corresponding to NCH_2, (=CH_2), and (CH=), respectively. The ^1H NMR spectrum of furopyrimidine **7** showed two singlets at δ 4.94 and 7.69 ppm for the NH and pyrimidine-H-2 protons, respectively.

Condensation of ester **4** with hydrazine hydrate afforded the acid hydrtazide derivative **8**, which was cyclized with acetyl acetone and formic acid and gave (3-amino-4-(4-chlorophenyl)-6-(thien-2-yl)furo[2,3-b]pyridin-2-yl)(3,5-dimethyl-1H-pyrazol-1-yl)methanone (**9**) and 9-(4-chlorophenyl)-3-formylamino-4-oxo-3,4-dihydro-7-(thien-2-yl)pyrido[3′,2′:4,5]furo[3,2-d]pyrimidine (**10**), respectively (Scheme 3). The IR spectra of compounds **9** and **10** showed absorption bands at 1619 and 1694 cm^{-1}, respectively, corresponding to the amide carbonyl. The ^1H NMR spectrum of pyrazole derivative **9** showed three singlets at 2.27, 2.87, and 6.25 ppm corresponding to $2CH_3$ protons and a pyrazole ring proton, respectively, while the ^1H NMR spectrum of compound **10** showed three singlets at δ 7.81, 9.8, and 10.01 ppm corresponding to pyrimidine-H-2, CHO, and NH protons, respectively.

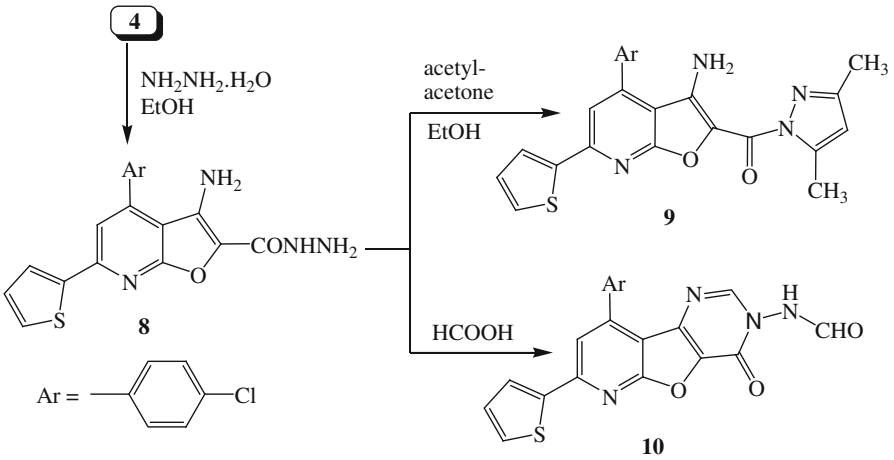
Sufurization of **1** with P_2S_5 gave the corresponding thioxopyridine derivative **11**, which was glycosylated with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco/galactopyranosyl bormide to give the corresponding thioglycosides **12a**,**b**, respectively (Scheme 4). The IR spectrum of **12a** showed characteristic absorption band at 1750 cm^{-1} corresponding



Scheme 2 Synthetic pathway for compounds **3**–**7**

to the acetyl carbonyl groups and the ^{1}H NMR spectra of **12a**,**b** showed the anomeric proton of the sugar moiety at δ 6.40 and 6.09 ppm as doublet, with coupling constants 8.78 and 8.76 Hz, respectively, indicating the β-orientation of the thioglycosidic bond. The attachment of the glycosyl residues to the sulfur rather than to the nitrogen has been supported by the value of the chemical shift of the anomeric protons which otherwise should appear at a lower field. The anomeric proton of β-N-glucosides having an adjacent C=S, was reported to appear at higher chemical shift (δ 6.9–7.2 ppm) due to the anisotropic deshielding effect of the C=S. Furthermore, the ^{13}C NMR spectrum of **12a**,**b** showed a signals at δ 81.5 and 80.2 ppm, respectively, corresponding to the anomeric carbons, in addition to, the absence of C=S carbon peak indicates that the attachment of the sugar at the sulfur atom and not the nitrogen atom.

When the glycosides **12a**,**b** were treated with triethyamine in the presence of a few drops of water in methanol, the deacetylated thioglycoside derivatives **13a**,**b** were obtained in good yields (Scheme 4). The IR spectra of compounds **13a**,**b** showed



Scheme 3 Synthetic pathway for compounds **8**–**10**

characteristic absorption bands corresponding to the OH groups at 3423 and 3421 cm^{-1}, respectively, and their ^{1}H NMR agreed with the assigned structures.

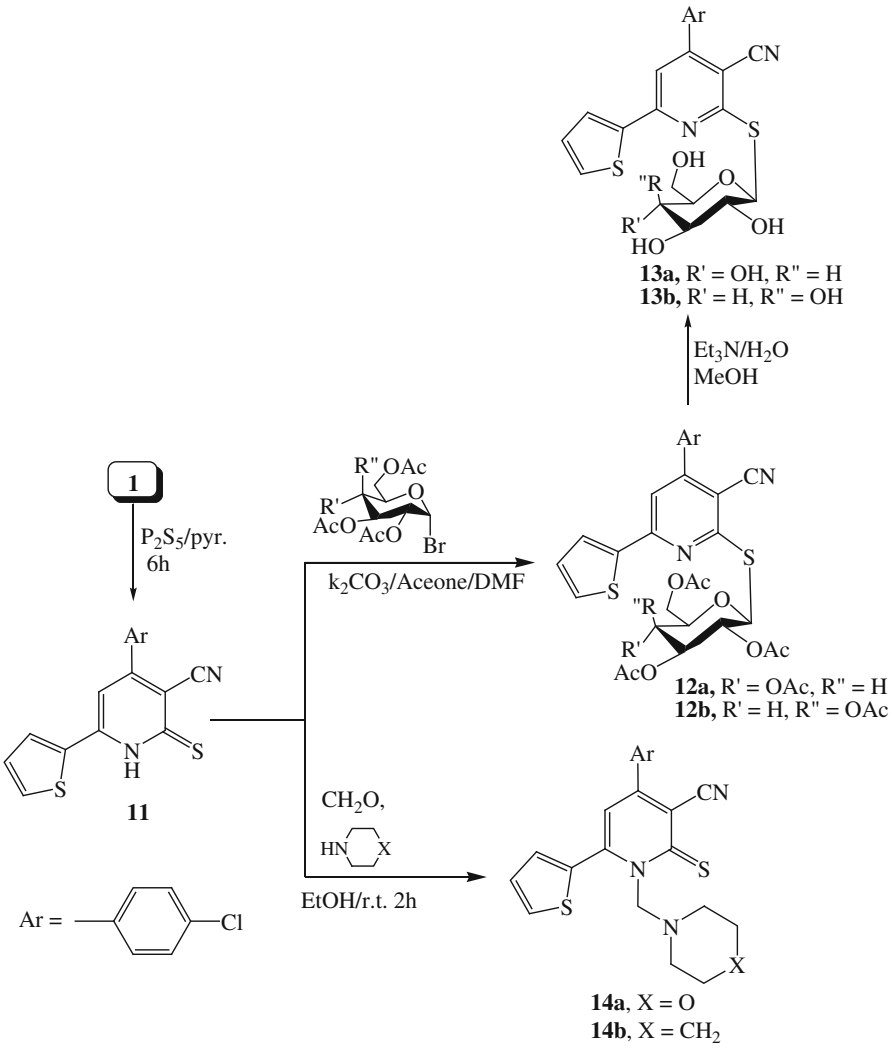
Transformation of 4-(4-chlorophenyl)-6-(thien-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**11**) into Mannich bases is an important reaction to confirm the regeio-selectivity of the previous glycosylation reaction at the sulfur atom and not the nitrogen atom. The one-pot multi-component Mannich reaction involved the thioxopyridine derivative **11**, the formaldehyde and the secondary amines (namely, morpholine and pipridine) in ethanol at room temperature to give the corresponding Mannich base derivatives **14a**,**b** (Scheme 4). The IR spectrua of compounds **14a**,**b** showed absorption bands at 1353 and 1372 cm^{-1} corresponding to the amidic thiocarbonyl (C=S). Their ^{13}C NMR spectra showed absorption peaks at δ 185.2 and 183.5 ppm corresponding to C=S carbon.

Experimental

All melting points are uncorrected and were measured using an Electro thermal IA 9100 apparatus. TLC was performed on Merck Silica Gel $60F_{254}$ with detection by UV light and by charring for glycosides after seperating with 10 % EtOH solution of H_2SO_4. The IR spectra were recorded on a Pye Unicam Sp-3-300 or a Shimadzu FTIR 8101 PC infrared spectrophotometer. The ^{1}H and ^{13}C NMR spectra were determined with a JEOL-JNM-LA 500 MHz spectrometer. The chemical shifts are expressed on the δ (ppm) scale using *TMS* as the standard reference. Elemental analysis determined on a Perkin Elmer 240 (microanalysis), Microanalysis Center, Cairo University, Cairo, Egypt.

Ethyl 2-(4-(4-chlorophenyl)-3-cyano-6-(thien-2-yl)pyridin-2-yloxy)acetate (**2**)

A mixture of pyridin-2(1H)-one (**1**) (0.01 mol) and anhydrous potassium carbonate (0.01 mol) in dry DMF (15 mL) was stirred for 1 h, then (0.011 mol) of ethyl



Scheme 4 Synthetic pathway for compounds **11**–**14**

bromoacetate was added. The reaction mixture was stirred for an additional 2 h at room temperature, filtered off, concentrated under reduced pressure, and poured into ice water. The obtained product was filtered off, dried, and crystallized from ethanol to give the title product **2** as pale yellow crystals. Yield 95 %, mp 135–136 °C. IR (KBr, cm^{-1}): 2219 (C≡N) and 1732 (C=O, ester). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.24$ (t, 3H, $J = 7.0$ Hz, $C\underline{H}_3CH_2$), 4.21 (q, 2H, $J = 7.0$ Hz, $C\underline{H}_2CH_3$), 5.11 (s, 2H, CH_2), 7.25 (t, 1H, $J = 4.55$, 3.62 Hz, thiophene-H), 7.69 (d, 2H, $J = 8.50$ Hz, Ar–H), 7.77 (d, 2H, $J = 8.50$ Hz, Ar–H), 7.83 (s, 1H, pyridine-H-5), 7.86 (d, 1H, $J = 4.55$ Hz, thiophene-H), 8.13 (d, 1H, $J = 3.62$ Hz, thiophene-H). ^{13}C NMR (DMSO-d_6, ppm): $\delta = 14.15$ ($\underline{C}H_3CH_2$), 60.76 ($CH_3\underline{C}H_2$), 63.67 (CH_2), 91.1,

112.7, 114.8 (C≡N), 128.9, 129.0, 130.5, 131.8, 134.2, 135.1, 148.0, 142.0, 152.6, 155.1, 162.8 and 167.9 (Ar–C and C=O). Anal. Calcd. for $C_{20}H_{15}ClN_2O_3S$ (398.86): C, 60.22; H, 3.79; N, 7.02;. Found: C, 60.19; H, 3.83; N, 7.09.

2-(4-(4-Chlorophenyl)-3-cyano-6-(thien-2-yl)pyridin-2-yloxy)acetohydrazide (**3**)

A mixture of compound **2** (0.01 mol) and hydrazine hydrate 98 % (1 mL, 0.04 mol) in absolute ethanol (25 mL) was refluxed for 1 h. After cooling, the formed precipitate was filtered off, dried, and crystallized from methanol to give compound **3** as yellow crystals. Yield 80 %, mp 192–194 °C. IR (KBr, cm^{-1}): 3416 (NH and NH_2), 2206 (C≡N) and 1636 (C=O, amide). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 4.62$ (s, 2H, NH_2), 4.98 (s, 2H, CH_2), 7.31 (t, 1H, $J = 4.12$, 3.24 Hz, thiophene-H), 7.65 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.70 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.72 (s, 1H, pyridine-H-5), 7.80 (d, 1H, $J = 4.12$ Hz, thiophene-H), 8.03 (d, 1H, $J = 3.24$ Hz, thiophene-H), 8.48 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, ppm): $\delta = 65.1$ (CH_2), 107.6, 113.0, 115.2 (C≡N), 128.0, 128.6, 128.7, 130.2, 130.5, 134.6, 141.1, 144.8, 154.6, 156.2, 161.4 and 166.3 (Ar–C and C=O). Anal. Calcd. for $C_{18}H_{13}ClN_4O_2S$ (384.84): C, 56.18; H, 3.40; N, 14.56. Found: C, 56.23; H, 3.44; N, 14.55.

Ethyl 3-amino-4-(4-chlorophenyl)-6-(thien-2-yl)furo[2,3-b]pyridine-2-carboxylate (**4**)

Compound **2** (0.01 mol) was suspended in sodium methoxide solution (0.12 g sodium in 30 mL methanol) and heated under reflux for 30 min. The reaction mixture was cooled, poured into ice water and acidified with HCl; the formed solid was filtered off, dried, and crystallized from ethanol to give compound **4** as pale yellow crystals; Yield 78 %, mp 231–233 °C. IR (KBr, cm^{-1}): 3449 (NH_2) and 1734 (C=O, ester). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.20$ (t, 3H, $J = 7.14$ Hz, $C\underline{H}_3CH_2$), 4.10 (q, 2H, $J = 7.14$ Hz, $CH_2\underline{C}H_3$), 5.03 (s, 2H, NH_2), 7.23 (t, 1H, $J = 4.58$, 3.50 Hz, thiophene-H), 7.68 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.77 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.81 (s, 1H, pyridine-H-5), 7.83 (d, 1H, $J = 4.58$ Hz, thiophene-H), 8.09 (d, 1H, $J = 3.50$ Hz, thiophene-H). ^{13}C NMR (DMSO-d_6, ppm): $\delta = 16.02$ ($\underline{C}H_3CH_2$), 63.5 ($CH_3\underline{C}H_2$), 91.1, 112.0, 112.5, 127.5, 128.9, 129.0, 130.4, 131.3, 131.6, 134.3, 135.1, 142.1, 152.6, 155.0, 163.0 and 169.3 (Ar–C and C=O). Anal. Calcd. for $C_{20}H_{15}ClN_2O_3S$ (398.86): C, 60.22; H, 3.79; N, 7.02. Found: C, 60.20; H, 3.76; N, 6.97.

5-(3-Amino-4-(4-chlorophenyl)-6-(thien-2-yl)furo[2,3-b]pyridin-2-yl)-4H-1,2,4-triazole-3-thiol (**5**)

A mixture of compound **4** (0.01 mol) and thiosemicarbazide (0.015 mol) in pyridine (30 mL) was refluxed for 6 h. The reaction mixture was cooled, poured into ice water and acidified with HCl, the formed solid was filtered off, dried, and crystallized from ethanol to give compound **5** as yellow crystals; Yield 82 %, mp 125–127 °C. IR (KBr, cm^{-1}): 3444 (NH and NH_2). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 5.05$ (s, 2H, NH_2), 7.24 (t, 1H, $J = 4.57$, 3.50 Hz, thiophene-H), 7.69 (d, 2H,

$J = 7.80$ Hz, Ar–H), 7.74 (d, 2H, $J = 7.80$ Hz, Ar–H), 7.79 (s, 1H, pyridine-H-5), 7.84 (d, 1H, $J = 4.57$ Hz, thiophene-H), 8.10 (d, 1H, $J = 3.50$ Hz, thiophene-H), 8.79 (s, 1H, NH), 13.21 (s, 1H, SH). ^{13}C NMR (DMSO-d_6, ppm): $\delta = 91.16$, 112.5, 127.6, 128.3, 128.9, 129.0, 129.8, 130.5, 131.7, 132.0, 134.3, 135.1, 138.0, 142.1, 152.6, 155.1 and 163.0 (Ar–C). Anal. Calcd. for $C_{19}H_{12}ClN_5OS_2$ (425.91): C, 53.58; H, 2.84; N, 16.44; Found: C, 53.60; H, 2.81; N, 16.47.

3-Allyl-9-(4-chlorophenyl)-4-oxo-1,2,3,4-tetrahydro-7-(thien-2-yl)-2-thioxopyrido[3′,2′:4,5]furo-[3,2-d]pyrimidine (**6**)

A mixture of furopyridine **4** (0.01 mol), allyl isothiocyanate (0.011 mol) and anhydrous potassium carbonate (0.012 mol) in dry acetonitrile (30 mL) was refluxed for 12 h. The reaction mixture was concentrated under reduced pressure, cooled, and poured into ice water; the formed solid was filtered off, dried, and crystallized from ethanol to give compound **6** as yellow crystals. Yield 65 %, mp 130–132 °C. IR (KBr, cm^{-1}): 3438 (NH), 1638 (C=O, amide). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 4.8$ (d, 2H, $J = 5.43$ Hz, NCH_2), 5.23 (d, 1H, $J = 10.14$ Hz, H-a), 5.31 (d, 1H, $J = 17.5$ Hz, H-b), 5.80 (m, 1H, H–c), 7.18 (t, 1H, $J = 4.83$, 3.72 Hz, thiophene-H), 7.75 (d, 2H, $J = 7.84$ Hz, Ar–H), 7.78 (d, 2H, $J = 7.84$ Hz, Ar–H), 7.80 (s, 1H, pyridine-H-8), 7.84 (d, 1H, $J = 4.83$ Hz, thiophene-H), 8.15 (d, 1H, $J = 3.72$ Hz, thiophene-H), 10.2 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, ppm): $\delta = 62.91$ (NCH_2), 110.9 (=CH_2), 118.0 (CH =), 128.1, 128.6, 128.9, 129.2, 129.8, 130.0, 130.4, 131.7, 132.1, 134.0, 135.1, 142.8, 148.2, 153.3, 155.5, 160.2 and 168.3 (Ar–C, C=O and C=S). Anal. Calcd. for $C_{22}H_{14}ClN_3O_2S_2$ (451.95): C, 58.47; H, 3.12; N, 9.30. Found: C, 58.46; H, 3.15; N, 9.28.

9-(4-Chlorophenyl)-4-oxo-3,4-dihydro-7-(thien-2-yl)pyrido[3′,2′:4,5]furo[3,2-d]pyrimidine (**7**)

A solution of furopyridine **4** (0.01 mol) in formamide (20 mL) was heated under reflux for 4 h. The reaction mixture was cooled and poured into ice water; the formed precipitate was filtered off, dried, and crystallized from ethanol to give compound **7** as yellow crystals. Yield 70 %, mp 163–165 °C. IR (KBr, cm^{-1}): 3448 (NH) and 1654 (C=O, amide). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 7.23$ (t, 1H, $J = 5.0$, 3.50 Hz, thiophene-H), 7.69 (s, 1H, pyrimidine-H-2), 7.76 (d, 2H, $J = 8.50$ Hz, Ar–H), 7.81 (d, 2H, $J = 8.50$ Hz, Ar–H), 7.82 (s, 1H, pyridine-H-8), 7.84 (d, 1H, $J = 5.0$ Hz, thiophene-H), 8.06 (d, 1H, $J = 3.5$ Hz, thiophene-H), 10.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, ppm): $\delta = 91.8$, 112.1, 128.2, 128.9, 129.6, 130.4, 131.5, 132.7, 134.4, 135.0, 142.2, 148.3, 152.6, 154.9, 155.6, 162.9 and 168.8 (Ar–C and C=O). Anal. Calcd for $C_{19}H_{10}ClN_3O_2S$ (379.82): C, 60.08; H, 2.65; N, 11.06. Found: C, 60.11; H, 2.61; N, 11.08.

3-Amino-4-(4-chlorophenyl)-6-(thien-2-yl)furo[2,3-b]pyridine-2-carbohydrazide (**8**)

A mixture of furopyridine **4** (0.01 mol) and hydrazine hydrate 98 % (1 mL, 0.04 mol) in absolute ethanol was refluxed for 3 h, then the reaction mixture was cooled, the formed precipitate was filtered off, dried, and crystallized from methanol to give

compound **8** as yellow crystals. Yield 75 %, mp 178–180 °C. ^{1}H NMR (DMSO-d_6, ppm): $\delta = 4.09$ (s, 2H, furan-NH_2), 4.63 (s, 2H, NHN$\underline{H}_2$), 7.25 (t, 1H, $J = 5.12$, 3.71 Hz, thiophene-H), 7.68 (d, 2H, $J = 8.26$ Hz, Ar–H), 7.74 (d, 2H, $J = 8.26$ Hz, Ar–H), 7.80 (s, 1H, pyridine-H-5), 7.85 (d, 1H, $J = 5.12$ Hz, thiophene-H), 8.06 (d, 1H, $J = 3.71$ Hz, thiophene-H), 8.48 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, ppm): $\delta = 92.8$, 112.8, 127.5, 128.1, 128.7, 129.4, 129.6, 131.4, 131.9, 132.6, 135.0, 135.3, 141.2, 154.4, 159.8 and 168.5 (Ar–C and C=O). Anal. Calcd for $C_{18}H_{13}ClN_4O_2S$ (384.84): C, 56.18; H, 3.40; N, 14.56. Found: C, 65.15; H, 3.42; N, 14.59.

(3-Amino-4-(4-chlorophenyl)-6-(thien-2-yl)furo[2,3-b]pyridin-2-yl)(3,5-dimethyl-1H-pyrazol-1-yl)methanone (**9**)

A mixture of hydrazide **8** (0.01 mol) and acetylacetone (0.02 mol) in ethanol (30 mL) was heated under reflux for 8 h. The reaction mixture was cooled and poured into ice water. The formed precipitate was filtered off, dried, and crystallized from ethanol to give compound **9** as yellow crystals. Yield 81 %, mp 148–150 °C. IR (KBr, cm^{-1}): 3433 (NH_2) and 1619 (C=O, amide). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 2.27$ (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 4.92 (s, 2H, NH_2), 6.25 (s, 1H, pyrazole-H), 7.24 (t, 1H, $J = 4.96$, 3.85 Hz, thiophene-H), 7.64 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.84 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.88 (s, 1H, pyridine-H-5), 7.96 (d, 1H, $J = 4.96$ Hz, thiophene-H), 8.16 (d, 1H, J = 3.85 Hz, thiophene-H). ^{13}C NMR (DMSO-d_6, ppm): $\delta = 12.82$, 13.32 ($2CH_3$), 98.9, 109.3, 127.9, 128.5, 128.8, 129.2, 129.4, 130.1, 130.8, 131.5, 134.4, 135.0, 141.5, 141.9, 149.5, 152.6, 152.9, 155.6 and 168.7 (Ar–C and C=O). Anal. Calcd for $C_{23}H_{17}ClN_4O_2S$ (448.92): C, 61.54; H, 3.82; N, 12.48. Found: C, 61.57; H, 3.80; N, 12.51.

9-(4-Chlorophenyl)-3-formylamino-4-oxo-3,4-dihydro-7-(thien-2-yl)pyrido[3′,2′:4,5]furo[3,2-d]pyrimidine (**10**)

A solution of hydrazide **8** (0.01 mol) in formic acid (20 mL) was heated under reflux for 3 h. The reaction mixture was cooled and poured into ice water. The formed precipitate was filtered off, dried, and recrystallized from ethanol to give compound **10** as yellow crystals. Yield 67 %, mp 160–162 °C. IR (KBr, cm^{-1}): 3434 (NH) and 1694 (C=O, amide). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 7.22$ (t, 1H, $J = 4.82$, 3.64 Hz, thiophene-H), 7.56 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.69 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.75 (s, 1H, pyridine-H-8), 7.81 (s, 1H, pyrimidine-H-2), 7.88 (d, 1H, $J = 4.82$ Hz, thiophene-H), 8.07 (d, 1H, $J = 3.64$ Hz, thiophene-H), 9.8 (s, 1H, NH), 10.09 (s, 1H, C$\underline{H}$O). ^{13}C NMR (DMSO-d_6, ppm): $\delta = 113.3$, 127.5, 127.6, 127.9, 128.4, 128.6, 128.8, 129.0, 129.3, 129.5, 130.4, 130.6, 131.2, 143.9, 152.4, 154.0, 160.8 and 166.8 (Ar–C, HC=O and C=O). Anal. Calcd for $C_{20}H_{11}ClN_4O_3S$ (422.84): C, 56.81; H, 2.62; N, 13.25. Found: C, 56.79; H, 2.63; N, 13.28.

4-(4-Chlorophenyl)-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glycopyranosylmercapto)-6-(thien-2-yl)nicotinonitrile (**12a**,**b**)

A mixture of pyridin-2-thione **(11)** (0.01 mol) and anhydrous potassium carbonate (0.01 mol) was stirred in dry acetone/DMF (15 mL) for 1 h, then 0.011 mol of

glucosyl/or galactosyl bromide was added. The reaction mixture was stirred overnight at room temperature, and then refluxed for 3–5 h, filtered off, and the solvent was evaporated under reduced pressure; the obtained products were dried and crystallized from the ethanol to give compounds **12a**,**b**.

4-(4-Chlorophenyl)-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosylmercapto)-6-(thien-2-yl)nicotinonitrile (**12a**)

Orange crystals, yield 76 %, mp 140–142 °C. IR (KBr, cm^{-1}): 2216 (C≡N) and 1750 (C=O, acetoxy). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.87$, 1.98, 2.08 and 2.17 (4 s, 12H, 4 C$\underline{H}_3$CO), 3.95 (dd, 1H, $J_{5',6'} = 4.34$, $J_{6',6''} = 12.07$ Hz, H-6′), 4.12 (dd, 1H, $J_{5',6'} = 4.15$, $J_{6',6''} = 12.07$ Hz, H-6″), 4.52 (m, 1H, H-5′), 5.25 (t, 1H, $J = 9.12$ Hz, H-4′), 5.48 (dd, 1H, $J_{1',2'} = 8.78$, $J_{2',3'} = 9.52$ Hz, H-2′), 5.59 (dd, 1H, $J_{2',3'} = 9.52$, $J_{3',4'} = 9.12$ Hz, H-3′), 6.40 (d, 1H, $J_{1',2'} = 8.78$ Hz, H-1′), 7.29 (t, 1H, $J = 5.18$, 3.63 Hz, thiophene-H), 7.70 (d, 2H, $J = 7.92$ Hz, Ar–H), 7.76 (d, 2H, $J = 7.92$ Hz, Ar–H), 7.81 (s, 1H, pyridine-H-5), 7.95 (d, 1H, $J = 5.18$ Hz, thiophene-H), 8.15 (d, 1H, $J = 3.63$ Hz, thiophene-H). ^{13}C NMR (DMSO-d_6, ppm): $\delta = 19.9$, 20.2, 20.3 and 20.4 (4$\underline{C}H_3$CO), 61.6 (C-6′), 66.1 (C-4′), 67.7 (C-3′), 70.9 (C-2′), 73.8 (C-5′), 82.5 (C-1′), 114.1 (C≡N), 117.2, 128.9, 129.0, 129.1, 130.5, 130.6, 132.0, 132.2, 134.1, 135.2, 141.6, 153.9, 157.5, 169.0, 169.6, 170.2 and 171.0 (Ar–C, C=N and 4 C=O). Anal. Calcd. for $C_{30}H_{27}ClN_2O_9S_2$ (659.13): C, 54.67; H, 4.13; N, 4.25. Found: C, 54.71; H, 4.10; N, 4.21.

4-(4-Chlorophenyl)-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosylmercapto)-6-(thien-2-yl)nicotinonitrile (**12b**)

Orange crystals, yield 78 %, mp 191–193 °C. ^{1}H NMR (DMSO-d_6, ppm): $\delta = 2.0$, 2.04, 2.05 and 2.12 (4 s, 12H, 4 C$\underline{H}_3$CO), 4.05 (dd, 1H, $J_{5',6'} = 5.26$, $J_{6',6''} = 11.25$ Hz, H-6′), 4.12 (dd, 1H, $J_{5',6''} = 6.30$, $J_{6',6''} = 11.25$ Hz, H-6″), 4.25 (m, 1H, H-5′), 5.09 (t, 1H, $J_{3',2'} = 9.58$, $J_{3',4'} = 2.81$ Hz, H-3′), 5.28 (t, 1H, $J_{2',1'} = 8.96$, $J_{2',3'} = 9.58$ Hz, H-2′), 5.62 (t, 1H, $J_{4',3'} = 2.81$, $J_{4',5'} = 2.38$ Hz, H-4′), 6.09 (d, 1H, $J_{1',2'} = 8.96$, Hz, H-1′), 7.29 (t, 1H, $J = 5.16$, 4.45 Hz, thiophene-H), 7.68 (d, 2H, $J = 8.50$ Hz, Ar–H), 7.77 (d, 2H, $J = 8.50$ Hz, Ar–H), 7.92 (d, 1H, $J = 5.16$ Hz, thiophene-H), 7.99 (s, 1H, pyridine-H5), 8.20 (d, 1H, $J = 4.45$ Hz, thiophene-H). ^{13}C NMR (DMSO-d_6, ppm): $\delta = 20.04$, 20.30, 20.35 and 20.60 (4$\underline{C}H_3$CO), 61.6 (C-6′), 67.9 (C-4′), 68.6 (C-2′), 73.1 (C-3′), 75.4 (C-5′), 80.2 (C-1′), 102.8, 115.1, 115.4 (C≡N), 128.9, 129.1, 129.4, 130.5, 132.1, 134.1, 135.2, 142.1, 153.0, 154.0, 159.1, 169.3, 169.5, 169.8 and 170.3 (Ar–C, C=N and 4C=O). Anal. Calcd. for $C_{30}H_{27}ClN_2O_9S_2$ (659.13): C, 54.67; H, 4.13; N, 4.25. Found: C, 54.65; H, 4.18; N, 4.23.

4-(4-Chlorophenyl)-2-(β-D-glycopyranosylmercapto)-6-(thien-2-yl)nicotinonitrile (**13a**,**b**)

Triethylamine (1 mL) was added to a solution of glycosides **12a,b** (0.01 mol) in methanol (20 mL) and a few drops of water. The reaction mixture was stirred

overnight at room temperature for 5 h, evaporated under reduced pressure, and the residue was washed with methanol until the triethylamine was removed. The residue was crystallized from ethanol to give compounds **13a**,**b**.

4-(4-Chlorophenyl)-2-(β-D-glucopyranosylmercapto)-6-(thien-2-yl)nicotinonitrile (**13a**)

Orange crystals, yield 88 %, mp 189–191 °C. IR (KBr, cm^{-1}): 3423 (4 OH) and 2212 (C≡N). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 3.04$ (m, 6H, H-6′, H-6″, H-5′, H-4′, H-3′ and H-2′), 3.45 (t, 1H, $J = 3.52$ Hz, OH-6′), 4.27 (d, 1H, $J = 4.23$ Hz, OH-4′), 5.10 (d, 1H, $J = 4.20$ Hz, OH-3′), 5.43 (d, 1H, $J = 4.54$ Hz, OH-2′), 5.98 (d, 1H, $J_{1',2'} = 8.53$ Hz, H-1′), 7.21 (t, 1H, $J = 4.92$, 3.80 Hz, thiophene-H), 7.65 (d, 2H, $J = 8.40$ Hz, Ar–H), 7.72 (d, 2H, $J = 8.40$ Hz, Ar–H), 7.90 (s, 1H, pyridine-H-5), 7.96 (d, 1H, $J = 4.92$ Hz, thiophene-H), 8.16 (d, 1H, $J = 3.80$ Hz, thiophene-H). Anal. Calcd. for $C_{22}H_{19}ClN_2O_5S_2$ (490.98): C, 53.82; H, 3.90; N, 5.71;. Found: C, 53.78; H, 3.92; N, 5.77.

4-(4-Chlorophenyl)-2-(β-D-galatcopyranosylmercapto)-6-(thien-2-yl)nicotinonitrile (**13b**)

Orange crystals, yield 90 %, mp 205–207 °C. IR (KBr, cm^{-1}): 3421 (4 OH) and 2218 (C≡N). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 3.21$ (m, 3H, H-3′, H-6′, H-6″), 3.50 (m, 3H, H-2′, H-4′, H-5′), 4.52 (m, 2H, OH-4′, OH-6′), 4.80 (d, 1H, $J = 5.12$ Hz, OH-3′), 5.18 (d, 1H, $J = 4.74$ Hz, OH-2′), 5.56 (d, 1H, $J_{1',2'} = 8.28$ Hz, H-1′), 7.19 (t, 1H, $J = 4.90$, 3.85 Hz, thiophene-H), 7.55 (d, 2H, $J = 8.42$ Hz, Ar–H), 7.68 (d, 2H, $J = 8.42$ Hz, Ar–H), 7.72 (s, 1H, pyridine-H-5), 7.75 (d, 1H, $J = 4.90$ Hz, thiophene-H), 8.15 (d, 1H, $J = 3.85$ Hz, thiophene-H). Anal. Calcd. for $C_{22}H_{19}ClN_2O_5S_2$ (490.98): C, 53.82; H, 3.90; N, 5.71;. Found: C, 53.84; H, 3.93; N, 5.70.

General synthetic procedure for Mannich bases (**14a**,**b**)

A mixture of **11a**,**b** (0.01 mol), morpholine or piperidine (0.015 mol) and formaldehyde (37 %, 1 mL) in ethanol (20 mL) was stirred at room temperature for 2 h, then 10 mL of cooled water was added. The formed precipitate was filtered off, dried, and crystallized from ethanol to give compounds **14a**,**b**.

4-(4-Chlorophenyl)-1-(morpholinomethyl)-6-(thien-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**14a**)

Orange crystals, yield 90 %, mp 110–112 °C. IR (KBr, cm^{-1}): 2214 (C≡N) and 1353 (C=S). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 2.40$ (t, 4H, $J = 4.48$ Hz, 2C$\underline{H}_2$-morpholine), 3.56 (t, 4H, $J = 4.48$ Hz, 2CH_2–morpholine), 5.25 (s, 2H, N–CH_2–N), 7.23 (t, 1H, $J = 5.0$, 3.92 Hz, thiophene-H), 7.72 (d, 2H, $J = 8.10$ Hz, Ar–H), 7.79 (d, 2H, $J = 8.10$ Hz, Ar–H), 7.85 (s, 1H, pyridine-H-5), 8.13 (d, 1H, $J = 5.0$ Hz, thiophene-H), 8.24 (d, 1 H, $J = 3.92$ Hz, thiophene-H). ^{13}C NMR (DMSO-d_6,

ppm): $\delta = 51.5$, 66.0 (4$\underline{C}H_2$-morpholine), 79.6 (N–CH_2–N), 107.6, 115.6 (C≡N), 117.2, 129.0, 129.2, 129.5, 130.5, 132.2, 135.3, 141.6, 153.3, 154.4 157.5 and 185.2 (Ar–C and C=S). Anal. Calcd. for $C_{21}H_{18}ClN_3OS_2$ (427.97): C, 58.94; H, 4.24; N, 9.82; Found: C, 58.96; H, 4.23; N, 9.80.

4-(4-Chlorophenyl)-1-(piperidin-1-ylmethyl)-6-(thien-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**14b**)

Orange crystals, yield 92 %, mp 170–172 °C. IR (KBr, cm^{-1}): 2214 (C≡N) and 1372 (C=S). ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.50$ (m, 6H, 3$\underline{C}H_2$-piperidine), 2.58 (t, 4H, $J = 4.74$ Hz, 2$\underline{C}H_2$-piperidine), 4.08 (s, 2H, N–CH_2–N), 7.23 (t, 1H, $J = 4.97$, 3.80 Hz, thiophene-H), 7.71 (d, 2H, $J = 8.15$ Hz, Ar–H), 7.78 (d, 2H, $J = 8.15$ Hz, Ar–H), 7.82 (s, 1H, pyridine-H-5), 8.02 (d, 1H, $J = 4.97$ Hz, thiophene-H), 8.12 (d, 1 H, $J = 3.80$ Hz, thiophene-H). ^{13}C NMR (DMSO-d_6, ppm): $\delta = 48.5$, 50.8, 51.5 (5$\underline{C}H_2$-piperidine), 66.1 (N–CH_2–N), 107.6, 115.6 (C≡N), 117.2, 129.0, 129.2, 129.5, 130.5, 130.6, 132.2, 135.3, 141.6, 153.3, 154.4 and 183.5 (Ar–C and C=S). Anal. Calcd. for $C_{22}H_{20}ClN_3S_2$ (426.00): C, 62.03; H, 4.73; N, 9.86. Found: C, 62.05; H, 4.74; N, 9.82.

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