

Research Article

A Facile Synthesis of Pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine and Pyrido[2',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazine Bearing a Thiophene Moiety

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Pyridinone derivative **8** was synthesized and transformed into the respective chloropyridine **9**, which was allowed to react with hydrazine hydrate to afford pyrazolo[3,4-*b*]pyridin-3-amine derivative **11**. Compound **11** was used as a key intermediate for a facile synthesis of the title compounds **14**, **15**, **17**, **21a,b**, and **24a-c** where the reaction of **11** with some 1,3-dielectrophiles resulted in the formation of pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidines **14**, **15**, and **17**, whereas diazotization of compound **11** gave the respective diazonium salt **18** which was coupled with some active methylene-containing compounds to give the corresponding hydrazones **19a,b** and **22a-c**. Cyclization of the latter hydrazones yielded the pyrido[2',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazines **21a,b** and **24a-c**, respectively.

1. Introduction

Thiophene moiety is present in a large number of bioactive molecules having diverse biological activities such as anti-inflammatory [1], anticonvulsant [2], antibacterial [3], and anti-tumor [4] activities. Moreover, thiophene moiety is a well-known isostere for benzene; for example, the replacement of benzene ring of the antidepressant drug, Viloxazine, (**I**, Figure 1) led to a prolongation of half-life [5].

On the other hand, several pyrazolo[3,4-*b*]pyridines revealed interesting biological properties including antimicrobial [6], antiviral [7], anti-inflammatory [8], analgesic [9], and antitumor activities [10]. In addition, pyrazolo[3,4-*b*]pyridines represent the skeleton of pharmaceuticals possessing significant biological activities as represented by Etazolate (**II**, EHT-0202, Figure 1), an anxiolytic drug, which is now in clinical trials for the treatment of Alzheimer's

disease [11], and by Glicaramide (**III**, Figure 1), a potent antidiabetic agent [12].

Following a program dealing with the development of bioactive heterocyclic derivatives [13–15], we report herein a facile synthesis of new pyrazolo[3,4-*b*]pyridines **14**, **15**, **17**, **21a,b**, and **24a-c**, bearing a thiophene moiety, as new bioactive candidates.

2. Experimental

2.1. General. Melting points were determined on a Galenkamp melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded as KBr disks using the Perkin Elmer FT-IR Spectrum BX apparatus. NMR Spectra were measured in DMSO-*d*₆ on a Jeol-NMR spectrometer operating at 400 MHz for ¹H NMR and at 100 MHz

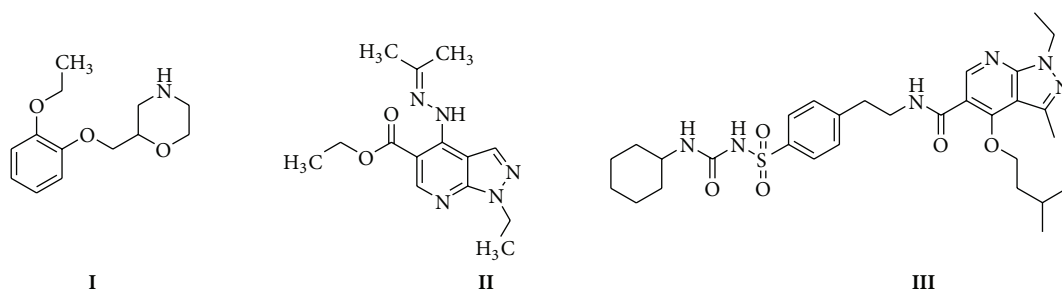


FIGURE 1: Chemical structures of Viloxazine (I), Etazolate (II), and Glicaramide (III).

for ^{13}C NMR. Chemical shifts are expressed in δ values (ppm) relative to TMS as an internal standard. Coupling constants (J) are expressed in Hz. D_2O was added to confirm the exchangeable protons. Mass spectra were measured on Agilent Triple Quadrupole 6410 QQQ LC/MS with ESI (Electrospray ionization) source.

2.2. Synthesis of 5,6-Dimethyl-2-oxo-4-(2-thienyl)-1,2-dihydropyridine-3-carbonitrile (8). A mixture of thiophene-2-carbaldehyde (1) (11.2 g, 0.1 mol), ethyl 2-cyanoacetate (2a) (11.3 g, 0.1 mol), 2-butanone (3) (7.2 g, 0.1 mol), and ammonium acetate (45.0 g, 0.6 mol) in absolute ethanol (150 mL) was heated to reflux for 12 h. The precipitate formed after cooling to rt was filtered, washed with ethanol, and dried. Crystallization from ethanol gave compound 8 as yellow crystals in 72% yield; mp 152–154°C; IR (KBr): ν 3102 (NH), 2219 (C \equiv N), 1654 (C=O) cm^{-1} ; ^1H NMR (DMSO- d_6): δ 1.84 (s, 3H, CH $_3$), 2.32 (s, 3H, CH $_3$), 7.21–7.32 (m, 2H, thiophene H3 and H4), 7.85 (d, J = 5.2 Hz, 1H, thiophene H5), 12.85 (s, D_2O exch., 1H, NH); ^{13}C NMR (DMSO- d_6): δ 15.60, 25.30, 115.25, 122.07, 127.76, 128.12, 128.30, 129.77, 135.31, 136.42, 159.45, 168.32; ESI MS m/z : 230.8 [M] $^+$.

2.3. Synthesis of 2-Chloro-5,6-dimethyl-4-(2-thienyl)nicotinonitrile (9). A solution of pyridinone derivative 8 (2.3 g, 10 mmol) in phosphorous oxychloride (10 mL) was refluxed gently for 5 h. It was then left to cool to rt and poured carefully onto crashed-ice with stirring. The solid obtained was filtered, washed with water, dried, and recrystallized from ethanol to give compound 9 as pale yellow crystals in 87% yield. Mp 285–287°C; IR (KBr): ν 2228 (C \equiv N), 1600 (C=N) cm^{-1} ; ^1H NMR (DMSO- d_6): δ 2.16 (s, 3H, CH $_3$), 2.58 (s, 3H, CH $_3$), 7.26–7.35 (m, 2H, thiophene H3 and H4), 7.89 (d, J = 5.2 Hz, 1H, thiophene H5); ^{13}C NMR (DMSO- d_6): δ 15.62, 24.15, 119.23, 122.19, 127.75, 128.30, 128.33, 129.75, 135.28, 136.41, 149.65, 159.45; ESI MS m/z : 249.0 [M] $^+$.

2.4. Synthesis of 5,6-Dimethyl-4-(2-thienyl)-1H-pyrazolo[3,4-b]pyridin-3-amine (II). A mixture of 2-chloro-5,6-dimethyl-4-(thiophen-2-yl)nicotinonitrile (9) (0.248 g, 1 mmol) and hydrazine hydrate (0.5 mL, 99%) in absolute ethanol (25 mL) was refluxed for 16 h. The reaction mixture was cooled to rt and poured onto an ice/water mixture. The precipitate that formed was filtered, washed with water, dried, and

recrystallized from EtOH to give compound II as yellow crystals in 69% yield. Mp 301–303°C; IR (KBr): ν 3301–3134 (NH $_2$, NH), 1664 (C=N) cm^{-1} ; ^1H NMR (DMSO- d_6): δ 2.10 (s, 3H, CH $_3$), 2.52 (s, 3H, CH $_3$), 4.91 (s, D_2O exch., 2H, NH $_2$), 7.15–7.28 (m, 2H, thiophene H3 and H4), 7.82 (d, J = 5.2 Hz, 1H, thiophene H5), 11.98 (s, D_2O exch., 1H, NH); ^{13}C NMR (DMSO- d_6): δ 15.71, 24.60, 103.73, 122.24, 128.19, 128.30, 128.68, 135.40, 136.46, 147.25, 151.01, 158.08; ESI MS m/z : 244.5 [M] $^+$.

2.5. General Procedure for the Synthesis of Compounds 14 and 15. To a solution of compound II (0.24 g, 1 mmol) in glacial acetic acid (25 mL), acetyl acetone (12a) and/or ethyl acetoacetate (12b) (1 mmol) were added. The mixture was refluxed for 14 h and then allowed to cool to rt. The solid formed was filtered, washed with ethanol, and recrystallized from EtOH/DMF to afford the corresponding pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine derivatives 14 and 15.

2.5.1. 2,4,8,9-Tetramethyl-10-(2-thienyl)pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine (14). Yield 77%; yellow crystals; mp 220–222°C; IR (KBr): ν 1665 (C=N) cm^{-1} ; ^1H NMR (DMSO- d_6): δ 2.29 (s, 3H, CH $_3$), 2.43 (s, 3H, CH $_3$), 2.68 (s, 3H, CH $_3$), 2.81 (s, 3H, CH $_3$), 7.26–7.28 (m, 3H, pyrimidine H, thiophene H3 and H4), 7.8 (d, J = 5.2 Hz, 1H, thiophene H5); ^{13}C NMR (DMSO- d_6): δ 16.47, 17.78, 24.85, 25.71, 103.09, 113.29, 124.24, 127.56, 127.75, 129.35, 136.12, 136.65, 141.89, 145.30, 156.34, 158.54, 163.43; ESI MS m/z : 308.9 [M] $^+$.

2.5.2. 2,8,9-Trimethyl-4-hydroxy-10-(2-thienyl)pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine (15). Yield 73%; yellow powder; mp 241–243°C; IR (KBr): ν 3350–2850 (OH), 1664 (C=N) cm^{-1} ; ^1H NMR (DMSO- d_6): δ 2.21 (s, 3H, CH $_3$), 2.62 (s, 3H, CH $_3$), 2.74 (s, 3H, CH $_3$), 6.67 (s, 1H, pyrimidine H), 7.23–7.28 (m, 2H, thiophene H3 and H4), 7.80 (d, J = 5.2 Hz, 1H, thiophene H5), 11.40 (s, D_2O exch., 1H, OH); ^{13}C NMR (DMSO- d_6): δ 16.36, 17.84, 25.71, 123.37, 123.47, 127.88, 127.99, 129.15, 129.25, 136.15, 136.25, 148.78, 157.10, 158.20, 160.45, 163.42; ESI MS m/z : 310.6 [M] $^+$.

2.6. Synthesis of 4-Amino-8,9-dimethyl-10-(2-thienyl)pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine-2(1H)-one (17). A mixture of compound II (0.24 g, 1 mmol) and ethyl cyanoacetate

(**2a**) (0.34 g, 30 mmol) was heated to reflux for 15 min. and then left to cool to rt. The solid separated was collected by filtration, washed with ethanol, and finally recrystallized from EtOH/DMF to afford compound **17** as a brown powder in 84% yield. Mp > 360°C; IR (KBr): ν 3340–3150 (NH, NH₂), 1685 (C=O), 1664 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 2.21 (s, 3H, CH₃), 2.68 (s, 3H, CH₃), 4.01 (s, D₂O exch., 2H, NH₂), 7.22–7.46 (m, 3H, pyrimidine H, thiophene H3 and H4), 7.76–7.92 (m, 2H, –CONH and thiophene H5); ¹³C NMR (DMSO-*d*₆): δ 14.44, 25.05, 102.35, 115.66, 122.34, 127.46, 127.67, 128.85, 135.95, 136.13, 148.45, 158.24, 160.43, 164.88, 168.34; ESI MS *m/z*: 311.6 [M]⁺.

2.7. General Procedure for the Synthesis of Hydrazones 19a,b and 22a–c. A solution of 5,6-dimethyl-4-(thiophen-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-3-amine (**11**) (0.24 g, 1 mmol) in glacial acetic acid (10 mL) obtained by heating was cooled to 5°C and hydrochloric acid (15 mL) was added. A solution of sodium nitrite (0.07 g, 1 mmol) in water (10 mL) was then gradually added with stirring. The resulting solution was added gradually within 2 h to a stirred cold solution (0–5°C) of the appropriate active methylene-containing compounds **12a,b** and **2a–c** (1 mmol) and sodium acetate trihydrate (0.26 g, 20 mmol) in ethanol (50 mL) and then left for 8 h in a refrigerator (4°C). The resulting solid was collected by filtration, washed thoroughly with water, and dried to give the respective crude hydrazones **19a,b** and **22a–c** which were used without any further purification in the next step.

2.8. General Procedure for the Synthesis of Pyrido[2',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazines 21a,b and 24a–c. The crude hydrazones **19a,b** and **22a–c** (1 mmol) were refluxed in pyridine (20 mL) for 1 h and then left to cool to rt. The reaction mixture was then added to cold water and the formed solid was filtered, washed with ethanol, and finally recrystallized from EtOH/DMF to afford the corresponding 1,2,4-triazines **21a,b** and **24a–c**, respectively.

2.8.1. 3-Acetyl-4,8,9-trimethyl-10-(2-thienyl)pyrido[2',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazine (21a). Yield 68%; yellow powder; mp 210–212°C; IR (KBr): ν 1694 (C=O), 1663 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 2.39 (s, 3H, CH₃), 2.76 (s, 3H, CH₃), 2.84 (s, 3H, CH₃), 3.13 (s, 3H, CH₃), 7.35–7.37 (m, 2H, thiophene H3 and H4), 7.91 (d, *J* = 5.2 Hz, 1H, thiophene H5); ¹³C NMR (DMSO-*d*₆): δ 14.03, 16.50, 25.86, 29.51, 104.87, 128.11, 128.53, 128.53, 128.70, 129.79, 136.95, 137.46, 142.00, 144.00, 159.35, 166.50, 199.38; ESI MS *m/z*: 337.5 [M]⁺.

2.8.2. Ethyl 4,8,9-Trimethyl-10-(2-thienyl)pyrido[2',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazine-3-carboxylate (21b). Yield 62%; yellow powder; mp 180–183°C; IR (KBr): ν 1710 (C=O), 1664 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 1.39 (t, *J* = 7.5 Hz, 3H, CH₃), 2.42 (s, 3H, CH₃), 2.81 (s, 3H, CH₃), 3.16 (s, 3H, CH₃), 4.40 (q, *J* = 7.5 Hz, 2H, CH₂), 7.23–7.28 (m, 2H, thiophene H3 and H4), 7.81 (d, *J* = 5.2 Hz, 1H, thiophene H5); ¹³C NMR (DMSO-*d*₆): δ 14.45, 14.61, 16.77, 25.90, 62.66, 128.07, 128.69, 129.82, 135.52, 136.97, 137.90, 138.37, 140.13, 141.86, 144.04, 159.00, 164.42, 166.37; ESI MS *m/z*: 367.6 [M]⁺.

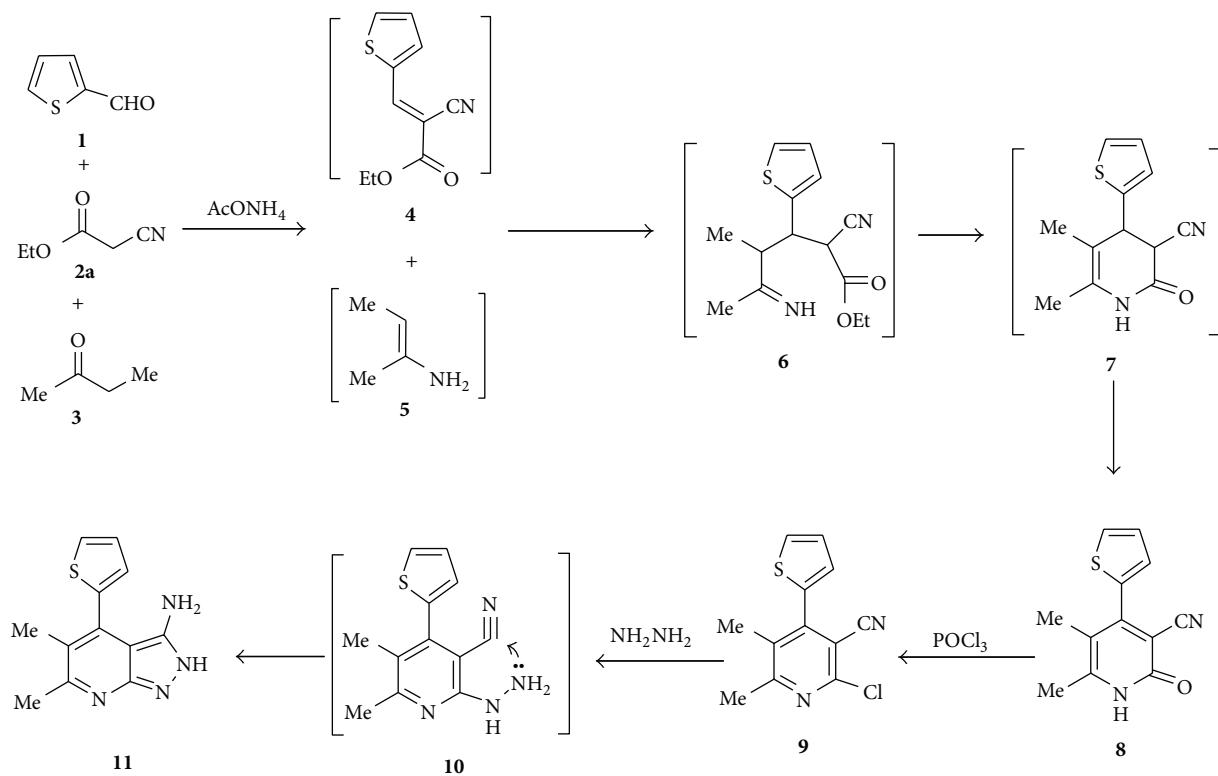
2.8.3. Ethyl 4-Amino-8,9-dimethyl-10-(2-thienyl)pyrido[2',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazine-3-carboxylate (24a). Yield 67%; yellow powder; mp 310–312°C; IR (KBr): ν 3143 (NH₂), 1694 (C=O), 1663 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 1.22 (t, *J* = 7.5 Hz, 3H, CH₃), 2.09 (s, 3H, CH₃), 2.62 (s, 3H, CH₃), 4.17 (q, *J* = 7.5 Hz, 2H, CH₂), 6.90 (s, D₂O exch., 2H, NH₂); 7.07–7.19 (m, 2H, thiophene H3 and H4), 7.70 (d, *J* = 5.2 Hz, 1H, thiophene H5); ¹³C NMR (DMSO-*d*₆): δ 14.44, 16.06, 24.89, 62.51, 116.13, 125.88, 128.43, 128.70, 129.36, 136.03, 137.12, 138.40, 140.38, 143.75, 159.03, 161.15, 166.95; ESI MS *m/z*: 368.6 [M]⁺.

2.8.4. 4-Amino-8,9-dimethyl-10-(2-thienyl)pyrido[2',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazine-3-carbo-nitrile (24b). Yield 63%; yellow powder; mp 304–306°C; IR (KBr): ν 3292 (NH₂), 2224 (C≡N), 1664 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 2.35 (s, 3H, CH₃), 2.75 (s, 3H, CH₃), 6.49 (s, D₂O exch., 2H, NH₂), 7.30–7.31 (m, 2H, thiophene H3 and H4), 7.86 (d, *J* = 5.2 Hz, 1H, thiophene H5); ¹³C NMR (DMSO-*d*₆): δ 16.70, 25.99, 115.25, 127.85, 128.74, 130.33, 134.35, 137.25, 138.42, 141.99, 143.75, 155.65, 160.12, 159.11, 164.42; ESI MS *m/z*: 322.1 [M]⁺.

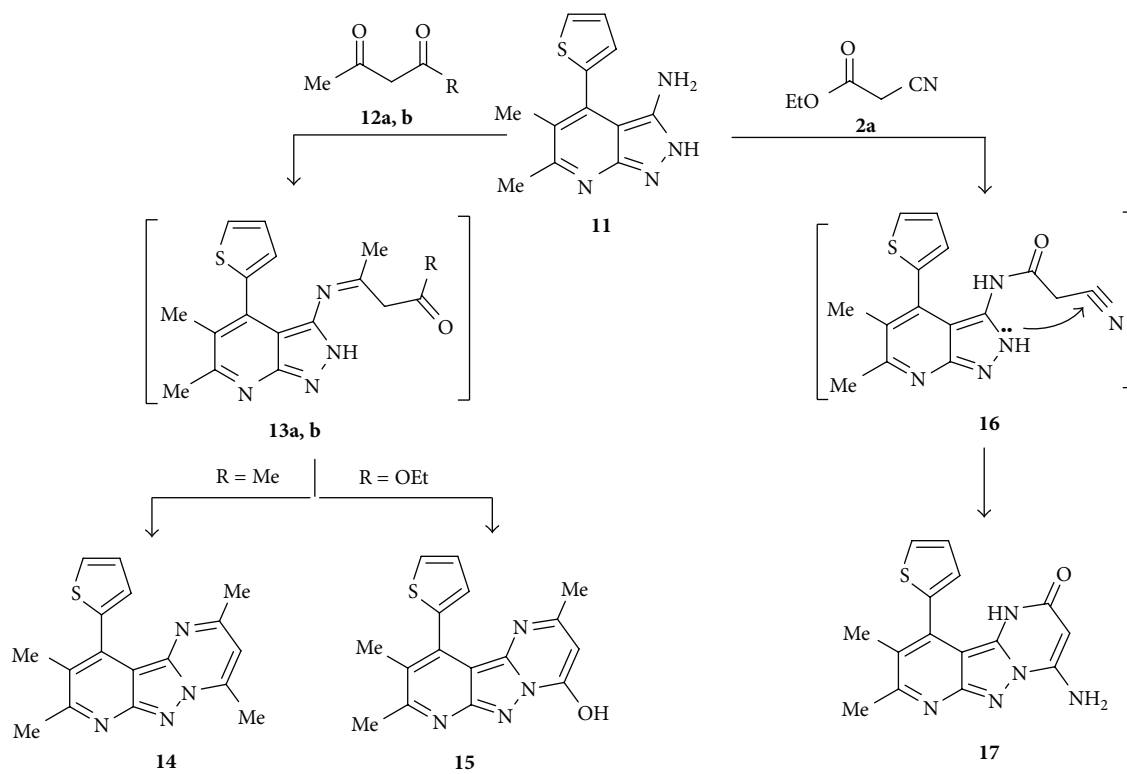
2.8.5. 3-(1H-Benzo[d]imidazole-2-yl)-8,9-dimethyl-10-(2-thienyl)pyrido[2',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazine-4-amine (24c). Yield 64%; yellow powder; mp 317–319°C; IR (KBr): ν 3300–3197 (NH+NH₂), 1635 (C=N) cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 2.16 (s, 3H, CH₃), 2.64 (s, 3H, CH₃), 7.27–7.41 (m, 6H, thiophene H3 and H4+2H ArH+2H NH₂), 7.54 (d, *J* = 7.4 Hz, 1H, ArH), 7.80 (d, *J* = 7.4 Hz, 1H, ArH), 7.87 (d, *J* = 5.2 Hz, 1H, thiophene H5), 11.98 (s, D₂O exch., 1H, imidazole NH); ¹³C NMR (DMSO-*d*₆): δ 16.15, 24.92, 122.64, 123.30, 127.78, 128.39, 129.53, 130.01, 131.12, 133.75, 134.56, 135.25, 150.62, 153.15, 155.02, 158.65, 161.73, 166.33, 167.14; ESI MS *m/z*: 413.2 [M]⁺.

3. Results and Discussion

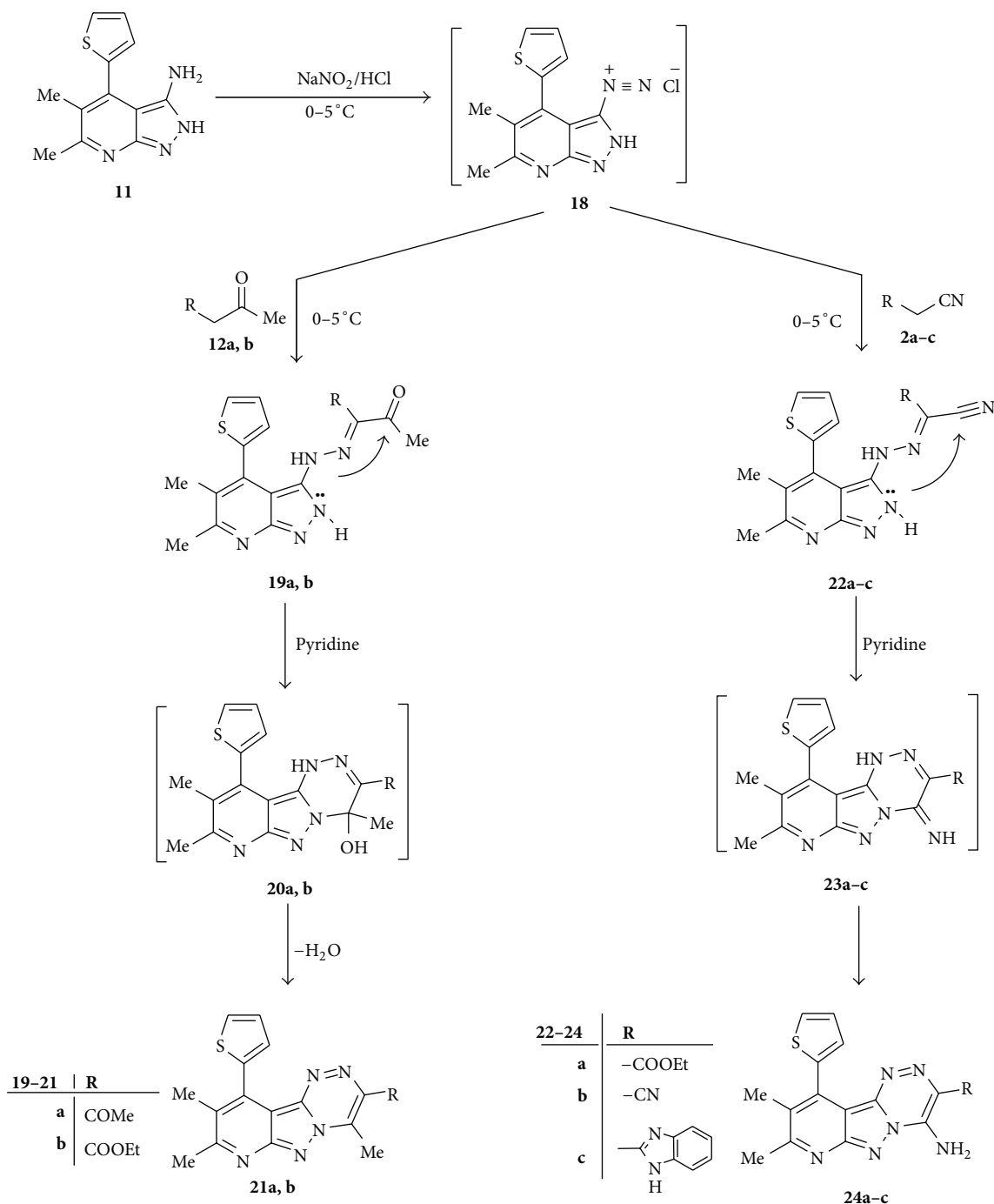
Heating a mixture of thiophene-2-carbaldehyde (**1**), ethyl 2-cyanoacetate (**2a**), and 2-butanone (**3**) in absolute ethanol, in the presence of ammonium acetate, pyridinone derivative **8** was achieved (Scheme 1). The latter four-component reaction produced the intermediate **4** via Knoevenagel condensation between thiophene-2-carbaldehyde (**1**) and ethyl 2-cyanoacetate (**2a**). The intermediate **5** was instead produced by the condensation of 2-butanone (**3**) with ammonium acetate. Reaction between **4** and **5** eventually gave the intermediate **6**. Cyclization of **6** gave the dihydropyridine derivative **7**, which was oxidized to pyridinone derivative **8** as the final product. The IR spectrum of compound **8** exhibited the characteristic sharp absorption band of carbonitrile functionality at 2219 cm⁻¹ in addition to NH and C=O absorption bands at 3102 and 1654 cm⁻¹, respectively. ¹H NMR spectrum of **8** showed three singlet signals at δ 1.84 and 2.32 and 12.85 due to two methyl groups and a NH group, respectively, while thiophene protons signals appeared at δ 7.21–7.32 and 7.85. The ESI mass analysis of the pyridinone **8** exhibited a molecular ion peak at *m/z* = 230.8.



SCHEME 1: Synthetic protocol to achieve the pivotal intermediate pyrazolo[3,4-*b*]pyridine derivative **11**.



SCHEME 2: Synthetic pathway to achieve pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidines **14**, **15** and **17**.

SCHEME 3: Synthesis of pyrido[2',3':3,4]pyrazolo[5,1-c][1,2,4]triazines **21a,b** and **24a-c**.

Subsequently, reaction of pyridinone derivative **8** with phosphorous oxychloride gave the corresponding 2-chloropyridine **9** (Scheme 1) in 87% yield. The reaction of compound **9** with hydrazine hydrate in ethanol at reflux gave the corresponding 5,6-dimethyl-4-(2-thienyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (**11**) (Scheme 1). The IR spectrum of **11** showed absorption bands due to NH and NH₂ functionalities in the region 3301–3134 cm⁻¹. The

signals of protons of NH and NH₂ groups appeared at δ 11.98 and 4.91, respectively, and disappeared after D₂O exchange.

The reaction of the pyrazolo[3,4-*b*]pyridine derivative **11** with acetylacetone (**12a**) or ethyl acetoacetate (**12b**) in glacial acetic acid gave, in both cases, a single product. The reaction products were identified as pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidines **14** and **15**, respectively (Scheme 2). The structures of the latter compounds were established on the basis of

their spectral data. For example, the ^1H NMR of compound **14** showed four singlet signals of methyl groups in the region δ 2.29–2.81 in addition to a singlet signal due to the pyrimidine proton around δ 7.27, while its ^{13}C NMR exhibited four signals in the region δ 16.47–25.17 due to four methyl groups. The mass spectrum of **14** showed a peak corresponding to its molecular ion at m/z 308.9 $[\text{M}]^+$.

The reaction of compound **11** with ethyl cyanoacetate (**2a**) gave the pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine-2(1*H*)-one derivative **17** (Scheme 2). The IR spectrum of **17** showed bands due to NH_2 and NH functionalities in the region 3340–3150 cm^{-1} in addition to a carbonyl band at 1685 cm^{-1} . ^1H NMR spectrum of **17** revealed two signals (D_2O -exchangeable) around δ 4.0 and 7.8 which were assigned to NH_2 and NH protons, respectively.

Furthermore, diazotization of compound **11** furnished the respective diazonium salt **18** which was smoothly coupled with acetyl acetone (**12a**), ethyl acetoacetate (**12b**), ethyl cyanoacetate (**2a**), malononitrile (**2b**), and 2-(1*H*-benzo[*d*]imidazol-2-yl)acetonitrile (**2c**) to give the corresponding hydrazones **19a,b** and **22a–c**, respectively.

The hydrazones **19a,b** and **22a–c** underwent intramolecular cyclization in boiling pyridine to yield the fused systems **21a,b** and **24a–c**, respectively (Scheme 3). The IR spectra lack the characteristic bands of NH groups for products **21a** and **21b** and the nitrile absorption bands for compounds **24a** and **24c**. On the other hand, the mass spectra of compounds **21a,b** and **24a–c** showed a peak corresponding to their molecular ions. Mechanistically, compounds **19a** and **19b** underwent an intramolecular cyclization via loss of a water molecule from the intermediates **20a** and **20b** to give compounds **21a** and **21b**, respectively. Michael-addition of the endocyclic NH of the hydrazones **22a–c** to their nitrile functionality gave the corresponding compounds **24a–c**, as reported in the literature for an analogous system [16].

4. Conclusion

Pyrazolo[3,4-*b*]pyridine derivative **11** acts as a key intermediate for the straightforward synthesis of the title compounds **14**, **15**, **17**, **21a,b**, and **24a–c**. These derivatives were synthesized starting from readily available reagents using convenient procedures. Further chemical and biological studies on such compounds will be reported in a due course.

Conflict of Interests

The authors have declared that there is no conflict of interests.

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