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ORIGINAL PAPER

Synthetic utility of a heterocyclic *o*-aminoaldehyde: synthesis of pyrazolopyridopyrimidines, pyrazolonaphthyridines, and pyrazolopyrimidonaphthyridinones

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Abstract A series of various polysubstituted pyrazolo-[3,4-*h*][1,6]naphthyridines, benzo[*b*]pyrazolo[3,4-*h*][1,6]naphthyridines, and pyrazolo[4′,3′:5,6]pyrido[4,3-*d*]pyrimidines were synthesized by Friedländer condensation of 4-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (*o*-aminoaldehyde) with active methylene compounds. The *o*-aminoaldehyde was functionalized to *o*-aminonitrile and *o*-aminocarboxamide with malononitrile and cyanoacetamide, respectively, which on condensation with monosubstituted ureas and acetic anhydride, respectively, afforded pyrazolo[3,4-*h*]pyrimido[4,5-*b*][1,6]-naphthyridines.

Keywords Friedländer condensation · *o*-Aminoaldehyde · Active methylene compounds

Introduction

Pyrazoles are excellent precursors for the synthesis of condensed polyfunctionally substituted angular N-heterocycles [1–6] that play an important role in the drug discovery process because many drugs in late development are heterocycles [7, 8]. Therefore, it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received significant attention.

Pyrazolo-annulated heterocycles such as pyrazolopyridopyrimidines have attracted considerable interest because their derivatives display a wide range of pharmacological activities, e.g., as anticonvulsants [9], anti-malarial agents [10], anti-inflammatories, and central nervous system depressants [11]. Moreover, these types of compounds are inhibitors of cyclic guanosine-3′,5′-monophosphate phosphodiesterase (cGMP PDE), and are thereby agents against erectile dysfunction [12]; they also act as antiproliferative agents [13], have other physiological applications, and are colorants [14], heat/moisture resistant agents, thermal transfer printing agents [15], and photographic couplers [16]. The importance of these derivatives and our interest in this area led us to explore some new polysubstituted pyrazolo[3,4-*h*][1,6]naphthyridines, benzo[*b*]pyrazolo[3,4-*h*]-[1,6]naphthyridines, and pyrazolo[4′,3′:5,6]pyrido[4,3-*d*]-pyrimidines.

Results and discussion

The construction of ring structures from *ortho*-substituted aminoaldehyde starting material has wide applicability for the annulations of heterocyclic systems. This method controls the direction of ring growth and generally permits the direct and regiospecific introduction of functional groups and/or substituents in the newly formed heterocyclic ring. From the literature it was noted that *o*-aminoaldehydes, the first and best-known member of this class of compounds, have been utilized for the synthesis of various heterocycles [17–24] by Friedländer reaction [25–28]. Heterocyclic *o*-aminoaldehydes are important synthons to annulate a pyridine or pyrimidine nucleus by condensation reactions with various active methylene compounds. Recently, we reported the synthetic utility of heterocyclic *o*-aminoaldehydes, i.e., 5-aminopyrazol-4-carbaldehyde [25–28] and 4-amino-6-chloroquinoline-3-

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carbaldehyde [29]. In an earlier communication [30], we reported the use of 4-amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbaldehyde (*o*-aminoaldehyde, **1**) as a key intermediate for the synthesis of pyrazolo[3,4-*h*][1,6]naphthyridine derivatives. In this communication, we have extended the synthetic utility of *o*-aminoaldehyde **1** [17] for the synthesis of a new class of heterocycles.

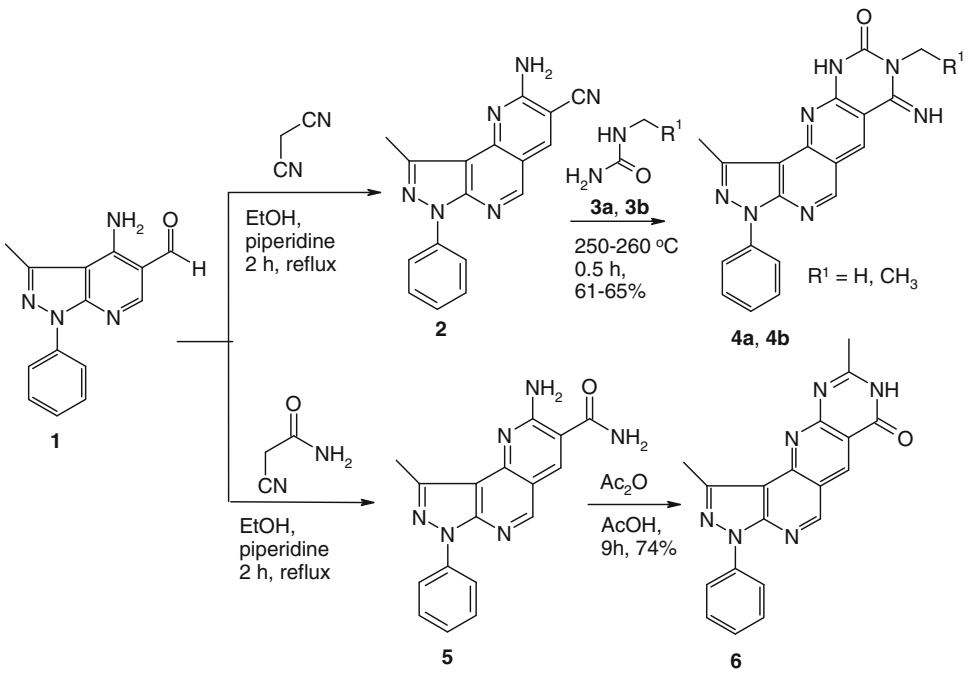
Malononitrile and cyanoacetamide are readily condensed with *o*-aminoaldehyde to form functionalized heterocyclic derivatives, which in turn are attractive starting materials for further ring annulations. Aromatic and heterocyclic *o*-aminocarbonitriles and *o*-aminocarboxamides are widely used and extensively studied [31–40] as building blocks for condensed nitrogen heterocycles, which prompted us to elaborate these by condensation of compound **1** with malononitrile and cyanocetamide. Thus, compound **1** and malononitrile were reacted in refluxing ethanol using a catalytic amount of piperidine, furnishing *o*-aminonitrile **2** in 75% yield, whereas the desired *o*-aminocarboxamide **5** was obtained by condensation of **1** with cyanoacetamide under similar reaction conditions (Scheme 1). In this condensation reaction, cyclization progressed via intramolecular addition of the amino group on the nitrile function to give the desired **2** and **5**.

It is well known [41] that heterocycles containing multifunctional groups like amino and nitriles as well as amino and carboxamide *ortho* to each other are useful starting materials in heterocyclic chemistry. Targeting towards the synthesis of pyrazolopyrimidonaphthyridinones, we have utilized compounds **2** and **5** for the construction of **4** and **6**, respectively. Thus, *o*-aminocarbonitrile **2** and monosubstituted urea **3** were heated together without using any base or solvent at 260–270 °C, furnishing compounds **4** in 61–65% yield after workup, which were characterized by spectral and analytical data. Requirement of high temperature for heterocyclization may be attributed due to the presence of conjugated electron-withdrawing substituents such as CN, which reduces the electron density around the amine nitrogen resulting in a greater decrease in nucleophilicity.

Analogously, *o*-aminocarboxamide **5** with acetic anhydride in refluxing acetic acid furnished pyrazolopyrimidonaphthyridinone **6** in 74% yield, as characterized by spectral and analytical data (Scheme 1).

After successful construction of pyrazolonaphthyridines by utilizing compound **1** with malononitrile and cyanoacetamide, we planned the next protocol elaborating a similar methodology to a series of pyrazolonaphthyridines, comparatively less reactive substrates. It was interesting to observe that decrease in the acidity of methylene protons of the substrate such as ketones or acetonitrile derivatives created a need to use a stronger base like potassium hydroxide instead of piperidine. The Friedländer condensation of *o*-aminoaldehyde **1** with propiophenone in refluxing ethanolic potassium hydroxide solution yielded 3,9-dimethyl-2,7-diphenyl-7*H*-pyrazolo[3,4-*h*][1,6]-naphthyridine (**7**). In the literature [42], it was noted that the reaction of dimethyl 1,3-acetonedicarboxylate with 5-aminopyrazolo-4-aldehyde resulted in the formation of two products comprising a thermally decarboxylated product; however, under similar reaction conditions we obtained compound **8** with both ester groups intact when

Scheme 1

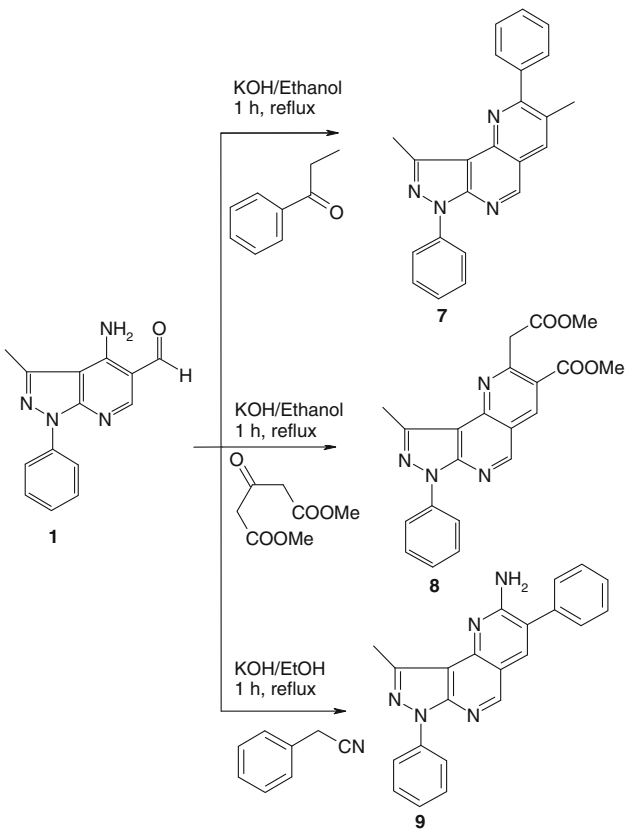


dimethyl 1,3-acetonedicarboxylate was condensed with *o*-aminoaldehyde **1**. Similarly the reaction of **1** with an active methylene nitrile such as phenylacetonitrile afforded naphthyridine **9** in 76% yield (Scheme 2).

Furthermore, the Friedländer condensation of *o*-aminoaldehyde **1** with cyclic ketones **10a**–**10f** under similar reaction condition produced corresponding **11a**–**11f**. However, reaction of **1** with dimedone (**10g**) was unsuccessful in ethanolic KOH because of its more enolic character; hence, this condensation was achieved by heating without solvent at 140–145 °C and afforded **11g** in 79% yield (Scheme 3). All compounds were characterized by spectral and analytical methods.

The condensation of *o*-aminoaldehyde **1** with neutral substrates such as amides **12** was unsuccessful in the presence of piperidine or potassium hydroxide; hence, higher temperature was used to induce the heterocyclization leading to fused pyrimidines. Thus, the neat reaction of **1** with formamide **12a** or benzamide **12b** at 170–175 °C furnished pyrazolo[4′,3′:5,6]pyrido[4,3-*d*]pyrimidines **13** in 62–67% yield as colorless solids, which were characterized by spectral and analytical data (Scheme 4).

In conclusion, we successfully utilized the condensation of 4-aminopyrazolo[3,4-*b*]pyridine-5-carbaldehyde (**1**) for the synthesis of various angular tricyclic or tetracyclic hetero-annulated compounds. The ready availability and wide choice of active methylene compounds, the ease of operation, and high yields obtained make this hetero-annulation sequence a versatile tool for the construction of multiple fused ring structures. It was observed that the strength of base and reactivity of active methylene compounds or neutral compounds are the major contributing factors for the heterocyclization. The reaction reported herein furnishes novel pyrazolo-annulated heterocycles, with high yields, simple workup, and clean products, and may be a valuable addition to the library of heterocyclic chemistry.



Scheme 2

Experimental

Melting points: Gallenkamp melting point apparatus; IR spectra (KBr-compression mould): Shimadzu IR-408; ^{1}H NMR (300 MHz), ^{13}C-NMR (75 MHz) spectra: Varian XL-300, DMSO-d_6, $CDCl_3$, TMS; mass spectra: HP 1100 LC/MSD mass spectral instrument (positive and negative APCI ion source, 50–200 V, nitrogen); elemental analyses (C, H, N, S) were conducted by using the HOSLI CH-analyser; the results were in agreement with calculated values. All reactions were monitored by thin-layer chromatography (TLC), carried out on 0.2-mm silica gel 60 F-254 plates (Merck) using UV light (254 and 366 nm) for detection. Common reagent grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

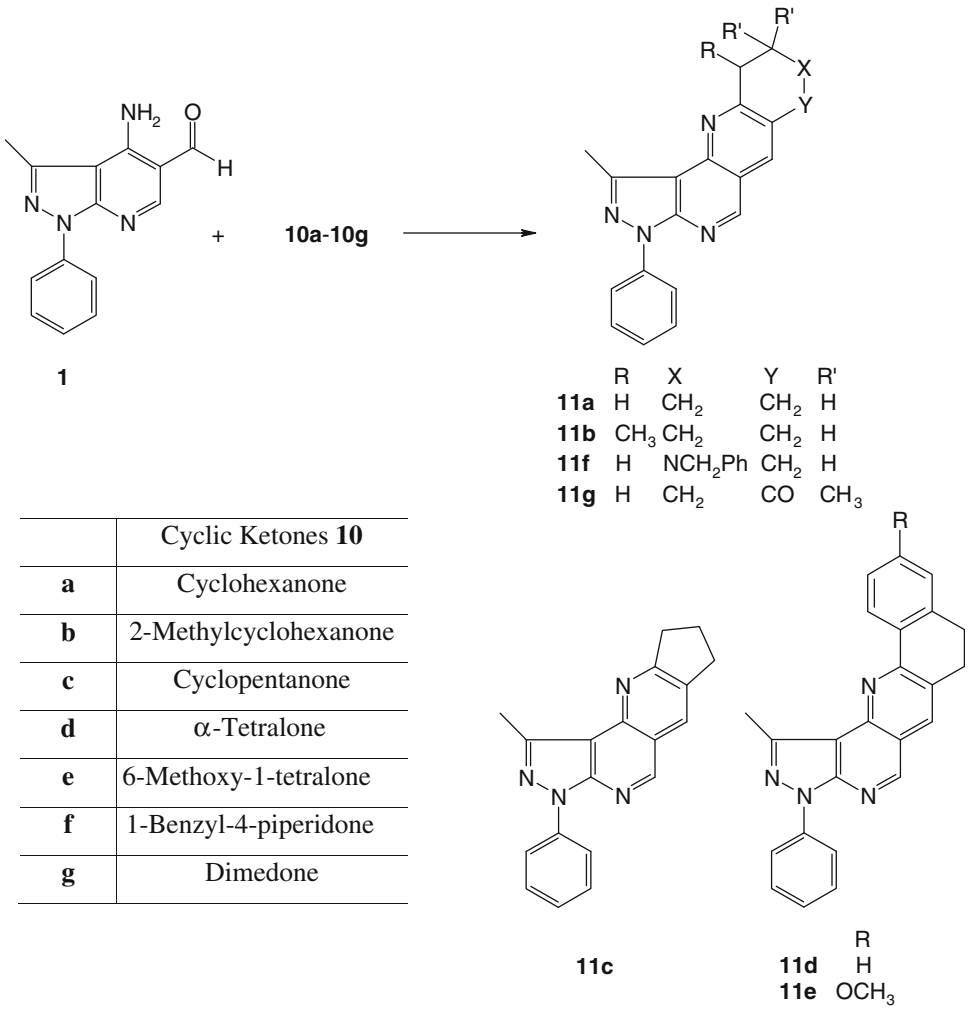
2-Amino-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]-naphthyridine-3-carbonitrile (**2**, $C_{17}H_{12}N_6$)

A solution of 200 mg **1** (0.792 mmol) and 52 mg malononitrile (0.792 mmol) was refluxed in 5 cm^3 ethanol in the presence of a catalytic amount of piperidine for 1 h (TLC check). The separated solid was then cooled to room temperature, collected by filtration, and crystallized from ethanol to yield 178 mg (75%) **2**. M.p.: 253–254 °C; IR: $\bar{\nu}$ = 3,455, 3,317, 2,311, 1,601, 1,521 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.79 (s, 3H, CH_3), 7.30 (t, J = 7.8 Hz, 1H, Ar-H), 7.51 (t, J = 7.8 Hz, 2H, Ar-H), 7.74 (s, 2H, –NH_2), 8.15 (d, J = 7.8 Hz, 2H, Ar-H), 8.82 (s, 2H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6): δ = 13.16, 108.27, 110.39, 116.89, 117.31, 120.24 (2C), 125.49, 128.01, 128.39 (2C), 138.28, 142.34, 143.83, 148.03, 150.38, 160.95 ppm; MS (70 eV): m/z = 323 (M + Na$^+$), 300 (M$^+$), 273, 182.

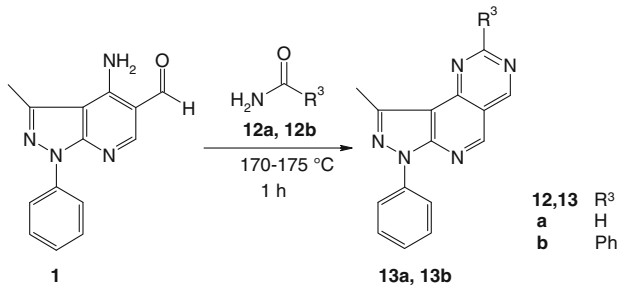
General procedure for the synthesis of compounds ***4***

A solution of 50 mg **2** (0.166 mmol) in substituted urea **3** (0.332 mmol) was heated at 250–260 °C for 30 min. Completion of the reaction was monitored by TLC. The molten mass was then cooled to room temperature, stirred

Scheme 3



	Cyclic Ketones **10**
a	Cyclohexanone
b	2-Methylcyclohexanone
c	Cyclopentanone
d	α-Tetralone
e	6-Methoxy-1-tetralone
f	1-Benzyl-4-piperidone
g	Dimedone



Scheme 4

in 2 cm^3 ethanol, and crystallized from dimethylformamide (DMF) to afford **4** in 61–65% yield.

3,7,8,10-Tetrahydro-7-imino-1,8-dimethyl-3-phenyl-9H-pyrazolo[3,4-h]pyrimido[4,5-b][1,6]naphthyridin-9-one (**4a**, $C_{19}H_{15}N_7O$)

Yield 39 mg (65%); m.p.: >300 °C; IR: $\bar{\nu}$ = 3,348, 3,239, 1,631, 1,604, 1,502 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.71 (d, J = 20.2 Hz, 3H, CH_3), 2.75 (s, 3H, CH_3), 7.19 (t, J = 7.2 Hz, 1H, Ar-H), 7.43 (t, J = 7.2 Hz, 2H, Ar-H), 8.15 (d, J = 7.2 Hz, 2H, Ar-H), 8.36 (s, 1H, NH), 8.77 (s, 1H, Ar-H), 9.18 (s, 1H, Ar-H), 11.32 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 12.16, 13.34, 35.78, 111.59, 112.94, 114.89, 199.96 (2C), 125.65, 128.73 (2C), 135.07, 138.12, 142.78, 144.13, 147.34, 148.06, 148.38, 150.21, 152.94 ppm; MS (70 eV): m/z = 357 (M^+), 328, 300, 237, 91.

8-Ethyl-3,7,8,10-tetrahydro-7-imino-1-methyl-3-phenyl-9H-pyrazolo[3,4-h]pyrimido[4,5-b][1,6]naphthyridin-9-one (**4b**, $C_{20}H_{17}N_7O$)

Yield 38 mg (61%); m.p.: >300 °C; IR: $\bar{\nu}$ = 3,352, 3,227, 1,614, 1,596, 1,542 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 1.06 (t, J = 6.4 Hz, 3H, CH_3), 2.77 (s, 3H, CH_3), 3.92 (q, J = 6.4 Hz, 2H, CH_2), 7.31 (t, J = 7.8 Hz, 1H, Ar-H), 7.49 (t, J = 7.8 Hz, 2H, Ar-H), 8.25 (d, J = 7.8 Hz, 2H, Ar-H), 8.45 (s, 1H, NH), 8.68 (s, 1H, Ar-H), 9.23 (s, 1H, Ar-H), 11.10 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 10.51, 15.01, 19.78, 42.89, 111.73, 112.84, 114.62, 120.12 (2C), 125.61, 128.37 (2C), 136.01, 139.21, 143.84, 144.03, 146.91, 148.02, 148.17, 149.98, 153.13 ppm; MS (70 eV): m/z = 371 (M^+), 356, 300, 251.

2-Amino-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]-naphthyridine-3-carboxamide (**5**, $C_{17}H_{14}N_6O$)
A solution of 100 mg **1** (0.396 mmol) and 33 mg cyanoacetamide (0.396 mmol) was refluxed in 3 cm^3 ethanol in the presence of a catalytic amount of piperidine for 1 h (TLC check). The reaction mass was then cooled to room temperature. The separated solid was collected by filtration and crystallized from ethanol to afford 91 mg (72%) **5**. M.p.: 286–287 °C; IR: $\bar{\nu}$ = 3,442, 3,412, 3,336, 1,629, 1,589, 1,555 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.83 (s, 3H, CH_3), 7.29 (t, J = 7.2 Hz, 1H, Ar-H), 7.51 (t, J = 8.4 Hz, 2H, Ar-H), 7.61 (bs, 2H, NH_2), 8.19 (d, J = 7.8 Hz, 2H, Ar-H), 8.25 (bs, 2H, NH_2), 8.72 (s, 1H, Ar-H), 8.78 (s, 1H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6): δ = 13.25, 111.02, 113.84, 115.01, 120.12 (2C), 125.91, 128.43 (2C), 139.16, 139.38, 140.63, 144.12, 148.17, 150.25, 161.13, 169.27 ppm; MS (70 eV): m/z = 341 ($M + Na^+$), 318 (M^+), 302, 227.

3,8-Dihydro-1,9-dimethyl-3-phenyl-7H-pyrazolo[3,4-h]-pyrimido[4,5-b][1,6]naphthyridin-7-one (**6**, $C_{19}H_{14}N_6O$)
A solution of 50 mg **5** (0.198 mmol), 1 cm^3 acetic anhydride, and 1 cm^3 acetic acid was refluxed under stirring for 9 h (TLC check). The reaction mass was then cooled to room temperature. The separated solid was collected by filtration, washed with cold ethanol, dried, and crystallized from ethanol/DMF (1:1) to yield 40 mg (74%) **6**. M.p.: >300 °C; IR: $\bar{\nu}$ = 3,389, 3,065, 1,601, 1,505 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.68 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 7.29 (t, J = 8.4 Hz, 1H, Ar-H), 7.38 (t, J = 8.4 Hz, 2H, Ar-H), 7.57 (bs, 1H, NH), 8.03 (d, J = 8.4 Hz, 2H, Ar-H), 9.22 (s, 1H, Ar-H), 9.34 (s, 1H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6): δ = 13.04, 24.79, 115.11, 115.34, 119.87 (2C), 122.53, 125.96, 128.74 (2C), 138.17, 139.29, 142.78, 143.91, 148.02, 150.24, 152.69, 153.82, 160.29 ppm; MS (70 eV): m/z = 342 (M^+), 300, 251, 210, 119.

*General procedure for the synthesis of **7–9***

A solution of 100 mg **1** (0.396 mmol), corresponding ketone (0.396 mmol), and 5 cm^3 ethanolic potassium hydroxide solution (2%) was refluxed for 1 h. Completion of the reaction was monitored by TLC. The reaction mass was then cooled to room temperature, the separated solid was collected by filtration and crystallized from ethanol to afford **7–9**.

3,9-Dimethyl-2,7-diphenyl-7H-pyrazolo[3,4-h][1,6]-naphthyridine (**7**, $C_{23}H_{18}N_4$)
Yield 116 mg (84%); m.p.: 187–188 °C; IR: $\bar{\nu}$ = 3,462, 3,045, 2,340, 1,605, 1,543 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.42 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 7.28 (t, J = 7.8 Hz, 1H, Ar-H), 7.32 (t, J = 8.2 Hz, 2H, Ar-H), 7.39 (m, 3H, Ar-H), 7.50 (t, J = 7.8 Hz, 2H, Ar-H), 7.86 (s, 1H, Ar-H), 8.18 (d, J = 7.8 Hz, 2H, Ar-H), 8.89 (s, 1H, Ar-H) ppm; ^{13}C-NMR (DMSO-d_6): δ = 13.21, 16.34, 114.52, 118.16, 119.87 (2C), 125.23, 126.47, 127.14 (2C), 128.91 (2C), 129.01 (2C), 132.54, 133.09, 136.13, 137.42, 141.93, 142.87, 147.59, 150.11, 159.24 ppm; MS (70 eV): m/z = 350 (M^+), 273, 259, 218, 76.

Methyl 3-(methoxycarbonyl)-9-methyl-7-phenyl-7H-pyrazolo[3,4-h][1,6]naphthyridin-2-acetate (**8**, $C_{21}H_{18}N_4O_4$)
Yield 96 mg (62%); m.p.: 138–139 °C; IR: $\bar{\nu}$ = 3,413, 2,826, 2,362, 1,720, 1,596, 1,537 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 3.02 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.49 (s, 2H, CH_2), 7.31 (t, J = 7.2 Hz, 1H, Ar-H), 7.53 (t, J = 7.2 Hz, 2H, Ar-H), 7.94 (s, 1H, Ar-H), 8.22 (d, J = 7.2 Hz, 2H, Ar-H), 8.91 (s, 1H, Ar-H) ppm; ^{13}C-NMR ($CDCl_3$): δ = 14.01, 36.27, 50.98, 51.03, 115.14, 117.81, 120.02 (2C), 125.37, 126.12, 128.03 (2C), 133.74, 137.19, 142.39, 146.21, 147.83, 150.34, 157.91, 167.28, 169.51 ppm; MS (70 eV): m/z = 390 (M^+), 331, 210.

9-Methyl-3,7-diphenyl-7H-pyrazolo[3,4-h][1,6]-naphthyridin-2-amine (**9**, $C_{22}H_{17}N_5$)
Yield 105 mg (76%); m.p.: 130–131 °C; IR: $\bar{\nu}$ = 3,465, 2,891, 2,345, 1,597, 1,551 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.89 (s, 3H, CH_3), 6.81 (s, 2H, –NH_2), 7.29 (t, J = 7.4 Hz, 1H, Ar-H), 7.41–7.55 (m, 7H, Ar-H), 8.06 (s, 1H, Ar-H), 8.27 (d, J = 7.4 Hz, 2H, Ar-H), 8.87 (s, 1H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6): δ = 17.20, 107.35, 113.63, 119.25 (2C), 121.15, 124.09, 126.67, 127.34 (2C), 127.66 (2C), 127.74 (2C), 135.71, 135.84, 138.07, 142.44, 146.13, 149.64, 150.70, 157.96 ppm; MS (70 eV): m/z = 351 (M^+), 335, 91.

*General procedure for the synthesis of **11a–11f***

A solution of 100 mg **1** (0.396 mmol), corresponding cyclic ketone **10** (0.396 mmol), and 5 cm^3 ethanolic potassium hydroxide solution (2%) was refluxed for 1 h (TLC check). The reaction mass was then cooled to room temperature, the separated solid was collected by filtration and recrystallized from ethanol to afford **11** in 71–82% yield.

7,8,9,10-Tetrahydro-1-methyl-3-phenyl-3H-benzo[b]-pyrazolo[3,4-h][1,6]naphthyridine (**11a**, $C_{20}H_{18}N_4$)
Yield 99 mg (79%); m.p.: 168–170 °C; IR: $\bar{\nu}$ = 3,417, 2,948, 2,371, 1,605, 1,492 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.91 (m, 2H, CH_2), 1.99 (m, 2H, CH_2), 2.97 (t, J = 6.0 Hz, 2H, CH_2), 3.02 (s, 3H, CH_3), 3.20 (t, J = 6.0 Hz, 2H, CH_2), 7.32 (t, J = 7.4 Hz, 1H, Ar-H), 7.53 (t, J = 7.4 Hz, 2H, Ar-H), 7.94 (s, 1H, Ar-H), 8.23 (d, J = 7.4 Hz, 2H, Ar-H), 8.92 (s, 1H, Ar-H) ppm; ^{13}C-NMR ($CDCl_3$): δ = 13.06, 20.99, 21.11, 27.30, 32.39,

108.09, 117.06, 120.06 (2C), 124.21, 127.23 (2C), 128.23, 133.58, 137.67, 142.61, 143.71, 147.98, 150.59, 162.75 ppm; MS (70 eV): $m/z = 314$ (M^+), 258, 167, 91.

7,8,9,10-Tetrahydro-1,10-dimethyl-3-phenyl-3H-benzo[b]pyrazolo[3,4-h][1,6]naphthyridine (**11b**, $C_{21}H_{20}N_4$)
Yield 107 mg (82%); m.p.: 121–122 °C; IR: $\bar{\nu} = 3{,}439$, 3,015, 2,345, 1,596, 1,508 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.56$ (d, $J = 6.3$ Hz, 3H, CH_3), 1.69 (m, 1H, CH), 1.84 (m, 1H, CH), 1.98 (m, 1H, CH), 2.18 (m, 1H, CH), 2.96 (t, $J = 6.3$ Hz, 2H, CH_2), 3.02 (s, 3H, CH_3), 3.16 (m, 1H, CH), 7.29 (t, $J = 7.8$ Hz, 1H, Ar-H), 7.50 (t, $J = 7.8$ Hz, 2H, Ar-H), 7.92 (s, 1H, Ar-H), 8.20 (d, $J = 7.8$ Hz, 2H, Ar-H), 8.91 (s, 1H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.07$, 18.80, 19.32, 27.95, 29.69, 35.76, 108.34, 116.89, 120.07 (2C), 124.21, 127.24 (2C), 128.01, 133.38, 137.69, 142.69, 143.66, 147.97, 150.53, 166.30 ppm; MS (70 eV): $m/z = 328$ (M^+), 313, 223, 105.

3,7,8,9-Tetrahydro-1-methyl-3-phenylcyclopenta[b]-pyrazolo[3,4-h][1,6]naphthyridine (**11c**, $C_{19}H_{16}N_4$)
Yield 87 mg (73%); m.p.: 188–189 °C; IR: $\bar{\nu} = 3{,}447$, 2,926, 2,398, 1,602, 1,519 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.21$ (m, 2H, CH_2), 2.82 (s, 3H, CH_3), 3.09 (t, $J = 6.2$ Hz, 2H, CH_2), 3.42 (t, $J = 6.2$ Hz, 2H, CH_2), 7.23 (t, $J = 7.6$ Hz, 1H, Ar-H), 7.36 (t, $J = 7.6$ Hz, 2H, Ar-H), 7.84 (d, $J = 7.6$ Hz, 2H, Ar-H), 8.77 (s, 1H, Ar-H), 9.09 (s, 1H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.24$, 24.81, 32.78, 34.26, 108.38, 117.29, 120.37 (2C), 124.17, 127.46 (2C), 128.75, 132.97, 137.28, 141.76, 144.06, 148.24, 151.21, 163.53 ppm; MS (70 eV): $m/z = 300$ (M^+), 258, 209.

7,8-Dihydro-1-methyl-3-phenyl-3H-naphtho[1,2-b]-pyrazolo[3,4-h][1,6]naphthyridine (**11d**, $C_{24}H_{18}N_4$)
Yield 107 mg (75%); m.p.: 192–193 °C; IR: $\bar{\nu} = 3{,}433$, 2,923, 2,376, 1,601, 1,499 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.99$ (t, $J = 6.0$ Hz, 2H, CH_2), 3.03 (s, 3H, CH_3), 3.05 (t, $J = 6.0$ Hz, 2H, CH_2), 7.28–7.34 (m, 2H, Ar-H), 7.46 (m, 2H, Ar-H), 7.54 (t, $J = 7.8$ Hz, 2H, Ar-H), 8.04 (s, 1H, Ar-H), 8.23 (d, $J = 8.2$ Hz, 2H, Ar-H), 8.63 (d, $J = 6.6$ Hz, 1H, Ar-H), 8.93 (s, 1H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.31$, 26.26, 26.63, 108.59, 117.42, 120.03 (2C), 124.24, 124.80, 125.62, 126.30, 127.25 (2C), 127.59, 128.92, 132.40, 132.56, 137.64, 138.06, 142.69, 144.59, 148.18, 150.26, 155.31 ppm; MS (70 eV): $m/z = 385$ ($M + Na^+$), 362 (M^+), 258, 197, 91.

7,8-Dihydro-10-methoxy-1-methyl-3-phenyl-3H-naphtho[1,2-b]pyrazolo[3,4-h][1,6]naphthyridine (**11e**, $C_{25}H_{20}N_4O$)
Yield 110 mg (71%); m.p.: 213–214 °C; IR: $\bar{\nu} = 3{,}427$, 2,939, 2,349, 1,599, 1,491 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.03$ (t, $J = 4.8$ Hz, 2H, CH_2), 3.13 (t, $J = 4.8$ Hz, 2H, CH_2), 3.18 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 6.82 (d, $J = 2.4$ Hz, 1H, Ar-H), 7.02 (dd, $J = 2.4$ Hz, 8.7 Hz, 1H, Ar-H), 7.33 (t, $J = 7.8$ Hz, 1H, Ar-H), 7.55 (t, $J = 7.8$ Hz, 2H, Ar-H), 8.08 (s, 1H, Ar-H), 8.26 (d, $J = 7.8$ Hz, 2H, Ar-H), 8.62 (d, $J = 8.7$ Hz, 1H, Ar-H), 8.98 (s, 1H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 14.04$, 28.19, 29.76, 54.08, 110.91, 111.02, 117.27, 119.79, 119.98 (2C), 124.01, 125.26, 127.34, 127.92 (2C), 131.23, 132.01, 137.46, 138.18, 142.05, 144.25, 148.17, 150.16, 156.34, 158.29 ppm; MS (70 eV): $m/z = 392$ (M^+), 361, 270, 134, 91.

8-Benzyl-7,8,9,10-tetrahydro-1-methyl-3-phenyl-3H-pyrido[4,3-b]pyrazolo[3,4-h][1,6]naphthyridine (**11f**, $C_{26}H_{23}N_5$)
Yield 116 mg (72%); m.p.: 171–172 °C; IR: $\bar{\nu} = 3{,}428$, 3,214, 3,036, 2,385, 1,602, 1,539 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.95$ (t, $J = 6.3$ Hz, 2H, CH_2), 2.99 (s, 3H, CH_3), 3.29 (t, $J = 6.0$ Hz, 2H, CH_2), 3.74 (s, 2H, CH_2), 3.83 (s, 2H, CH_2), 7.29 (t, $J = 8.4$ Hz, 1H, Ar-H), 7.37 (m, 5H, Ar-H), 7.50 (t, $J = 8.1$ Hz, 2H, Ar-H), 7.86 (s, 1H, Ar-H), 8.18 (d, $J = 7.8$ Hz, 2H, Ar-H), 8.89 (s, 1H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.08$, 32.14, 48.81, 53.55, 60.79, 108.08, 116.72, 120.15 (2C), 124.32, 125.57, 125.95, 126.65 (2C), 127.24 (4C), 131.55, 136.10, 137.59, 142.73, 144.23, 148.08, 150.69, 160.16 ppm; MS (70 eV): $m/z = 405.2$ (M^+), 300, 328, 105, 91.

3,8,9,10-Tetrahydro-1,9,9-trimethyl-3-phenyl-7H-benzo[b]pyrazolo[3,4-h][1,6]naphthyridine-7-one (**11g**, $C_{22}H_{20}N_4O$)
A mixture of 100 mg **1** (0.396 mmol) and 56 mg dimedone **10g** (0.396 mmol) was heated at 140–150 °C for 30 min. The molten mass on cooling was stirred in 2 cm^3 ethanol for 15 min. The separated solid was collected by filtration and crystallized from ethanol to afford 111 mg (79%) **11g**. M.p.: 244–245 °C; IR: $\bar{\nu} = 3{,}458$, 2,943, 1,726, 1,600, 1,554 cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 0.93$ (s, 6H, $(CH_3)_2$), 2.53 (s, 2H, CH_2), 2.82 (s, 3H, CH_3), 3.34 (s, 2H, CH_2), 7.24 (t, $J = 7.8$ Hz, 1H, Ar-H), 7.34 (t, $J = 7.8$ Hz, 2H, Ar-H), 7.75 (d, $J = 7.8$ Hz, 2H, Ar-H), 9.24 (s, 1H, Ar-H), 9.38 (s, 1H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 13.27$, 26.13 (2C), 32.59, 51.08, 53.71, 115.85, 120.18 (2C), 121.91, 125.87, 127.69 (2C), 133.01, 136.23, 138.95, 142.31, 144.05, 147.82, 150.96, 167.79, 194.91 ppm; MS (70 eV): $m/z = 379$ ($M + Na^+$), 356 (M^+), 300, 328, 272, 91.

*General procedure for the synthesis of **13***

Compound **1** (100 mg, 0.396 mmol) and corresponding amide **12** (1.98 mmol) were heated at 170–180 °C for 1 h (TLC check). The molten mass on cooling was stirred in 2 cm^3 ethanol for 15 min. The solid obtained on cooling was collected by filtration, washed with cold

ethanol, and crystallized from ethanol to afford **13** in 62–67% yield.

9-Methyl-7-phenyl-7H-pyrazolo[4′,3′:5,6]pyrido-[4,3-d]pyrimidine (**13a**, $C_{15}H_{11}N_5$)
Yield 64 g (62%); m.p.: 167–168 °C; IR: $\bar{\nu} = 3{,}426$, 2,973, 1,602, 1,542 cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 3.03$ (s, 3H, CH_3), 7.38 (t, $J = 7.8$ Hz, 1H, Ar-H), 7.55 (t, $J = 7.8$ Hz, 2H, Ar-H), 8.16 (d, $J = 7.8$ Hz, 2H, Ar-H), 9.17 (s, 1H, Ar-H), 9.52 (s, 1H, Ar-H), 9.54 (s, 1H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 13.47$, 112.76, 116.74, 120.13 (2C), 124.98, 127.64 (2C), 138.19, 142.54, 148.51, 149.27, 150.42, 153.68, 158.05 ppm; MS (70 eV): $m/z = 284$ ($M + Na^+$), 261 (M^+), 171, 91.

9-Methyl-2,7-diphenyl-7H-pyrazolo[4′,3′:5,6]pyrido-[4,3-d]pyrimidine (**13b**, $C_{21}H_{15}N_5$)
Yield 89 g (67%); m.p.: 193–194 °C; IR: $\bar{\nu} = 3{,}448$, 2,957, 1,599, 1,524 cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 3.01$ (s, 3H, CH_3), 7.40 (t, $J = 7.4$ Hz, 1H, Ar-H), 7.53–7.63 (m, 5H, Ar-H), 8.19 (d, $J = 7.4$ Hz, 2H, Ar-H), 8.66 (d, $J = 7.4$ Hz, 2H, Ar-H), 9.41 (s, 1H, Ar-H), 9.85 (s, 1H, Ar-H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 14.17$, 111.93, 115.71, 120.27 (2C), 125.35, 126.94 (2C), 128.61, 128.96 (2C), 129.13 (2C), 130.52, 138.94, 143.73, 148.38, 150.11, 151.26, 157.03, 163.82 ppm; MS (70 eV): $m/z = 337$ (M^+), 247, 205, 132.

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