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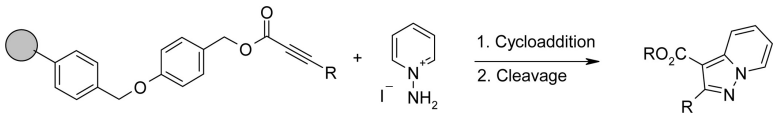

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Solid-Phase Synthesis of Pyrazolopyridines from Polymer-Bound Alkyne and Azomethine Imines

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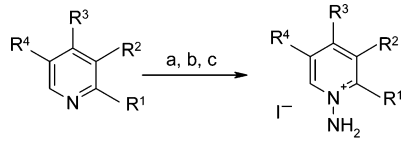
Study was made of the 1,3-dipolar cycloaddition of polymer-bound alkynes to azomethine imines generated in situ from *N*-aminopyridine iodides. Aromatization of the cycloadducts gives polymer-bound pyrazolopyridines that can be released from the resin as carboxylic acids with trifluoroacetic acid or as methyl esters with sodium methoxide.

Introduction

Pyrazolopyridines are nitrogen heterocycles that can be synthesized via 1,3-dipolar cycloaddition reaction from azomethine imines and alkynes. In the course of the cycloaddition reaction, a five-membered ring is formed, and a fused two-ring system is obtained. Pyrazolopyridines exhibit a wide range of biological activities, including dopamine D3 receptor antagonist and partial agonist,[1] dopamine D4 antagonist,[2] adenosine A1 receptor antagonist,[3] and antiherpetic[4] and antiallergic[5] properties. Solid-phase methods have recently been used in a variety of applications, providing a new approach to the synthesis of combinatorial libraries of compounds. 1,3-Dipolar cycloaddition reactions have also been performed on solid supports having either a dipole or dipolarophile attached to the resin.[6] Our goal was to develop an efficient solid-phase synthesis of pyrazolopyridines from polymer-bound alkyne and azomethine imines to provide focused compound libraries for biological screening.

Polymer-bound alkynes have been employed in 1,3-dipolar cycloadditions to synthesize triazoles[7] and isoxazoles.[8] Only a few reports exist on the corresponding solid-phase synthesis of pyrazole derivatives. Pyrazoles have been obtained by the reaction of azomethine imines with polymer-bound vinyl sulfones.[9] Traceless synthesis of pyrazoles has been reported from polymer-supported azomethine imines obtained via a silatropic shift.[10] The pyrazole ring has also been formed in 1,3-dipolar cycloaddition of polymer-bound enamine to nitrile imine.[11] In this paper, we report the results of a parallel solid-phase synthesis of pyrazolopyridines from polymer-bound alkyne and azomethine imines.

Scheme 1. Preparation of *N*-Aminopyridine Iodides **2**[a]



1 **2**

[a] Reagents and conditions: (a) substituted pyridine **1** (3 equiv), hydroxylamine-*O*-sulfonic acid (1 equiv), water, 90 °C, 0.5−2 h; (b) K_2CO_3 (1 equiv), water evaporation, ethanol extraction; (c) HI (1 equiv).

Results and Discussion

Synthesis of pyrazolopyridines from alkynes and azomethine imines in solution was first reported by Huisgen et al.[12] *N*-Aminopyridine iodides **2** can be obtained from the corresponding pyridine reagent **1** and hydroxylamine-*O*-sulfonic acid (Scheme 1).[13] We synthesized *N*-aminopyridine iodides using a 12-place reaction station in a parallel fashion and applied them as such, without recrystallization, in cycloaddition reactions. Polymer-bound alkyne was prepared from propiolic acid and 4-(bromomethyl)phenoxymethyl polystyrene resin **3** (bromo-Wang, Scheme 2).[14] The reaction was monitored by FT-IR. Appearance of strong alkyne bands (3270 and 2115 cm^{-1}) and the ester band (1710 cm^{-1}) was an indication of a successful reaction. Comparison of the bromo-Wang resin with the Wang resin, which differ only in having the bromo or OH substituent, indicated the probable band due to the bromo substituent, that is, 1100 cm^{-1}. This disappeared after successful ester bond formation. The polymer-bound alkyne **4** reacted with various *N*-aminopyridine iodide salts **2**, and polymer-bound pyrazolopyridine derivatives **5** were obtained in a parallel fashion in sealed plastic syringes equipped with filters and valves. The disappearance of the alkyne band was easily monitored by FT-IR.

Cleavage of the polymer-bound pyrazolopyridines with TFA provided the corresponding pyrazolopyridines as carboxylic acids **6**. The cleavage of the products was performed

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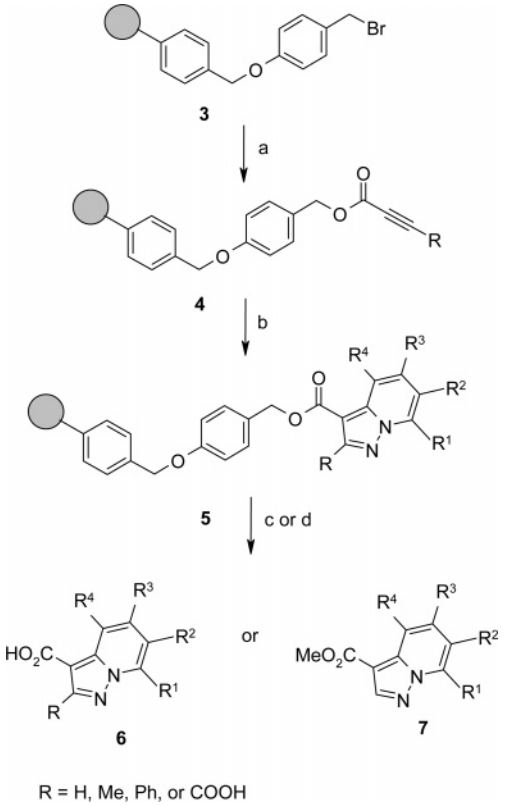
Scheme 2. Solid-Phase Synthesis of Pyrazolopyridines **6** and **7**[a]



[a] Reagents and conditions: (a) propiolic acid, 2-butynoic acid, phenylpropiolic acid, or acetylenedicarboxylic acid (1.5 equiv), DIPEA (1.5 equiv), CsI (1 equiv), DMF, rt, 72 h; (b) *N*-aminopyridine iodide **2** (3 equiv), K_2CO_3 (2 equiv), DMF, rt, 20−40 h; (c) TFA−DCM 4:1, rt, 2 × 1 h, and overnight; (d) NaOMe (0.5 equiv), THF−MeOH 4:1, 70 °C, overnight.

three times with 80% TFA−DCM. Use of 10−50% TFA−DCM did not give as good yields. After the final acidic treatment, the residual resins were analyzed by FT-IR, and only traces of the ester bands or typical pyrazolopyridine bands (1530−1550 cm^{-1}) were then detected. Instead, a strong trifluoroacetate band at ∼1770−1780 cm^{-1} was detected, indicating successful release. Treatment of the polymer-bound pyrazolopyridines with sodium methoxide gave pyrazolopyridines as methyl esters **7** (Scheme 3, Table 1).[15]

The cycloaddition method we developed was extended to other polymer-bound alkynes. 2-Butynoic acid, phenylpropiolic acid, and acetylenedicarboxylic acid were attached to bromo-Wang resin, and cycloadditions with various *N*-aminopyridine iodides were performed. Cleavage with trifluoroacetic acid gave substituted pyrazolopyridines **6**.

LC−MS analyses of the crude products gave us information about the side products formed in the cycloaddition reaction. UV detection (210 nm) indicated that purities of the crude products were mostly over 80%. In almost every crude product, the corresponding decarboxylated products were detected as major side products (∼5−15%). Additionally, minor quantities of *N*-aminopyridine starting material were sometimes found. Compound **6f** was obtained as a more complex mixture, even after chromatographic purification; traces of a nonaromatized compound, differing by two mass units, were detected, for example. Compounds **6o**−**6r** were formed after the decarboxylation of the cycloadduct, and only

Scheme 3. Pyrazolopyridines Prepared on Solid Support

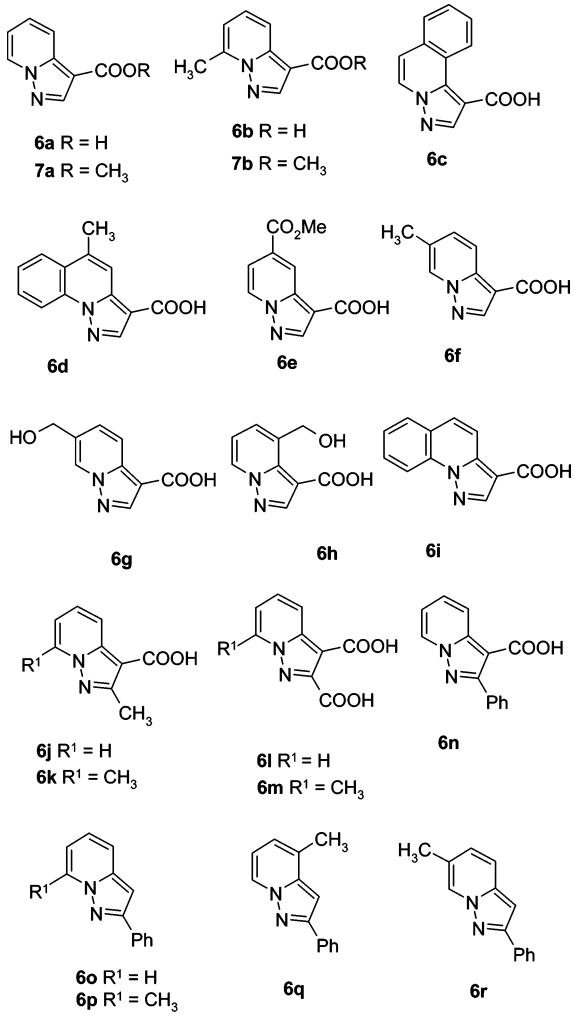


Table 1. Yields and Purities of Pyrazolopyridines **6** and **7**

product	yield[a] (%)	purity[b] (%)	product	yield[a] (%)	purity[b] (%)
6a	44	>98	**6k**	52	>90
6b	40	87	**6l**	traces	<10
6c	15	94	**6m**	traces	<10
6d	57	>98	**6n**	traces	<5
6e	11	>95	**6o**	79	>97
6f	14	74	**6p**	52	>95
6g + **6h**	33	*c*	**6q** + **6r**	32	*d*
6i	36	>98	**7a**	40	>98
6j	74	>95	**7b**	31	>95

[a] Overall isolated yields are based on the theoretically corrected original loadings of the resins. [b] Purities are evaluated on the basis of analytical data. [c] About 2:1 mixture of regioisomers **6g** and **6h**. [d] About 2:1 mixture of **6q** and **6r**.

traces of carboxylic group-substituted pyrazolopyridine **6n** were detected by LC−MS. Acetylenedicarboxylic acid underwent partial decarboxylation while attached to the resin, and only traces of dicarboxylic acids **6l** and **6m** were detected by LC−MS.

When 2- and 4-substituted *N*-aminopyridine salts react in cycloaddition with alkynes having an ester group, only the regioisomer with an electron-withdrawing group at position 3 is formed. The other regioisomer has usually been synthesized via hydrolysis and selective decarboxylation of the diester group of the cycloadduct obtained from dimethyl

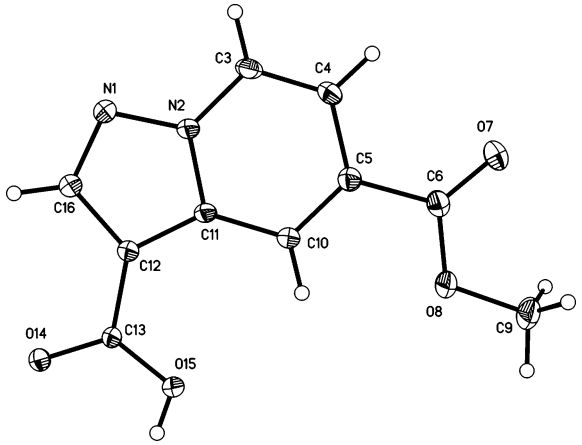


Figure 1. Molecular structure of **6e**.

acetylenedicarboxylate.[16] 3-Substituted *N*-aminopyridine salts may give two different regioisomers, depending on the site of the ring formation. In solution, the ring formation is reported to occur on the same side as the substituent unless sterically hindering groups are present.[17] Analysis of the regiochemistry of the ring formation is based on the ^{1}H NMR coupling systems. In compounds **6f** and **6g**, which were the major regioisomers isolated from the crude products, the ring appears to have formed on the less hindered side. Compounds **6q** and **6r** were formed in a 2:1 ratio, and interestingly, the crystallized product was the minor regioisomer **6r**. In compound **6c**, in turn, the ring formed on the same side as the substituent, as reported in the literature.[18]

Confirmation of the regiochemistry of the carboxylic group was obtained by X-ray crystal structure analysis of **6e** (Figure 1). Additional information was provided by ^{1}H NMR signals of the singlet proton (H-2) of the pyrazole ring, which for all compounds appeared at 8.2−8.6 ppm.[18] Regiochemistry of the phenyl group of compound **6r** was also confirmed by X-ray crystal structure analysis. The singlet proton (H-3) in all phenyl-substituted compounds appeared at 7.0−7.1 ppm. Further confirmation of the regiochemistry of the phenyl- and methyl-substituted cycloadducts was obtained with NOESY experiments.

In summary, we have developed a solid-phase synthesis of pyrazolopyridines, in which pyrazolopyridines are obtained in high purities and moderate or high yields. Most of the yields are comparable to the yields reported in solution.[19]

Experimental Section

The resin was purchased from Novabiochem (4-(bromomethyl)phenoxymethyl polystyrene **1**, 100−200 mesh, cross-linked with 1% divinylbenzene, catalog number 01-64-0186). Parallel syntheses were carried out using a Radleys Carousel 12-place reaction station. Thin-layer chromatography was performed with Merck TLC aluminum sheets and silica gel 60 F_{254}. Column chromatography was peformed with a Biotage Sp4 automated purification system or a Biotage Quad3 parallel automated purification system, with flash 12+M silica cartridges. Melting points were measured with an Electrothermal IA9100 digital melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 Plus or a Bruker Avance 300 spectrometer. Chemical shifts (δ) are given in parts per million relative to the NMR solvent signals (DMSO-d_6 2.5 and 39.51 ppm). IR spectra were recorded on a Bruker Vertex 70 FT-IR spectrometer with KBr technique. LC−MS analyses were performed using an HP1100 instrument with UV detector wavelength of 210 nm and XTerra MS RP18 (4.6 × 30 mm, 2.5 μm) column and using a PE SCIEX API 3000 triple quadrupole LC−/MS/MS mass spectrometer with ESI ion source and 5 mM ammonium acetate buffer (pH 4.5)/acetonitrile as mobile phase increasing from 95:5 to 10:90. A Q-TOF Micro (quadrupole time-of-flight) mass spectrometer (The Waters Micromass) with electrospray ionization in positive ion mode was used for accurate LC−MS analyses (HRMS). Elemental analyses were performed by Robertson Microlit Laboratories Inc., Madison, NJ.

Preparation of *N*-Aminopyridine Iodides 2. A solution of hydroxylamine-*O*-sulfonic acid (2 g, 1 equiv), water (10 mL), and pyridine reagent **1** (5.2−7.0 mL, 3 equiv) was heated at 90 °C for 20 min−2 h. Potassium carbonate (1.22 g, 1 equiv) was added, and the water was evaporated. Ethanol (20−30 mL) was added to the solid residue, and insoluble potassium sulfate was filtered out. Hydroiodic acid (57−67%, 1.7−2.3 mL, 1 equiv) was added to the filtrate, and the resulting solution was placed in a freezer. The precipitate was filtered out, washed with ethanol, and dried in vacuo. Isolated products were used as such in the cycloaddition reaction. The approximate purities of the crude products were analyzed with ^{1}H NMR. The analytical samples were recrystallized from 2-propanol, and the purities of the samples were determined with LC−MS.

Preparation of Polymer-Bound Alkyne 4. A mixture of 4-(bromomethyl)phenoxymethyl polystyrene **3** (0.76−1.7 mmol/g, 1 equiv), cesium iodide (1 equiv), alkyne (1.5 equiv), and *N*-ethyldiisopropylamine (1.5 equiv) in DMF (∼5 mL/g resin) was stirred at room temperature for 72 h. The resin was washed with DMF (2×), H_2O (2×), DMF−H_2O (2×), MeOH (3×), THF (3×), and DCM (3×) and dried in vacuo. FT-IR (KBr, cm^{-1}): 3270, 2115, and 1700 (propiolic acid), 2215 and 1699 (phenylpropiolic acid), 2238 and 1700 (2-butynoic acid).

Preparation of Polymer-Bound Pyrazolopyridines 5. Polymer-bound alkyne **4** (0.76−1.7 mmol/g, 1 equiv), potassium carbonate (2 equiv), and *N*-aminopyridine derivative **2** (3−5 equiv) in DMF (∼10 mL/g resin) were stirred at room temperature for 20−40 h. The resin was filtered and washed with DMF (2×), H_2O (2×), DMF−H_2O (2×), MeOH (3×), THF (3×), and DCM (3×) and dried in vacuo. FT-IR (KBr, cm^{-1}): 1530−1560 and 1350−1360.

Cleavage of the Polymer-Bound Pyrazolopyridines as Carboxylic Acids 6. Polymer-bound pyrazolopyridines **5** were treated with TFA−DCM 4:1 (∼5 mL/g resin) at room temperature (2 × 1 h, and overnight). The filtrate was evaporated and dried in vacuo. The crude products were purified by column chromatography, except compounds **6i**−**6k**, which were recrystallized from ethyl acetate(−acetic acid).

Cleavage of the Polymer-Bound Pyrazolopyridines as Esters 7. Polymer-bound pyrazolopyridines **5** were treated

with sodium methoxide (0.5 equiv) in THF−MeOH 4:1 (∼20 mL/g resin) at 70 °C for ∼20 h. HCl (10%) was added, and the resin was filtered. The filtrate was concentrated, and the crude product was extracted with ethyl acetate. The filtrate was evaporated and dried in vacuo. The crude products were purified by column chromatography.

1-Amino-2-methylpyridinium Iodide. Yield 1.68 g (36%, purity >95%), recrystallized sample (purity >95%); mp 148−149 °C (lit. 152 °C[20]). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.81 (d, J = 6.3 Hz, 1H), 8.22 (td, J = 7.8 and 1.2 Hz, 1H), 8.01 (broad s, 2H), 7.97−8.01 (overlapping d, 1H), 7.88 (td, J = 8.0 and 1.8 Hz, 1 H), 2.72 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 150.3, 140.2, 139.6, 129.1, 125.7, 18.5. FT-IR (KBr, cm^{-1}): 3243, 1630, 1491, 1035, 781. LC−MS: $[M - I]^+$, m/z 109 (t_r = 1.1 min). Calcd for $C_6H_9N_2I$: C, 30.53%; H, 3.84%; N, 11.87%. Found: C, 30.07%; H, 3.06%; N, 12.00%.

2-Aminoisoquinolinium Iodide. Yield 2.96 g (62%, purity ∼40%), recrystallized sample (purity 96%); mp 165−166 °C (lit. 177.5−178.5 °C[21]). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.69 (s, 1H), 8.50−8.57 (m, 4H), 8.43 (d, J = 8.1 Hz, 1H), 8.30 (d, J = 8.1 Hz, 1H), 8.12 (td, J = 7.2 and 1.2 Hz, 1H), 8.01 (td, J = 7.2 and 1.2 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 140.7, 134.8, 134.0, 131.8, 131.1, 129.0, 127.3, 127.3, 126.3. FT-IR (KBr, cm^{-1}): 3228, 1645, 1504, 1371, 805. LC−MS: $[M - I]^+$, m/z 145 (t_r = 1.7 min). Calcd for $C_9H_9N_2I$: C, 39.73%; H, 3.33%; N, 10.30%. Found: C, 39.48%; H, 2.60%; N, 9.71%.

1-Amino-4-methylquinolinium Iodide. Yield 535 mg (21%, purity ∼85%), recrystallized sample (purity 97%); mp 188 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.19 (d, J = 6.0 Hz, 1H), 8.59 (d, J = 8.7 Hz, 1H), 8.49 (dd, J = 8.7 and 1.5 Hz, 1H), 8.25 (td, J = 6.9 and 1.2 Hz, 1H), 8.18 (broad s, 2H), 8.05 (td, J = 7.8 and 0.9 Hz, 1H), 7.94 (d, J = 6.3 Hz, 1H), 2.95 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 154.0, 143.1, 136.5, 134.4, 129.9, 128.9, 126.5, 122.3, 118.7, 19.2. FT-IR (KBr, cm^{-1}): 3224, 1604, 1519, 1366, 768. LC−MS: $[M - I]^+$, m/z 159 (t_r = 2.2 min). Calcd for $C_{10}H_{11}N_2I$: C, 41.92%; H, 3.88%; N, 9.79%. Found: C, 42.07%; H, 3.22%; N, 9.25%.

1-Amino-4-methoxycarbonylpyridinium Iodide. Yield 2.45 g (49%, purity <50%). LC−MS: $[M - I]^+$, m/z 153 (t_r = 1.2 min). The mixture was used as such in the cycloaddition reaction, but the product could not be isolated. On the basis of the analytical data, the main isolated product seems to be the hydroiodide salt of methyl isonicotinate.

1-Amino-3-methylpyridinium Iodide. Yield 1.57 g (38%, purity >95%), recrystallized sample (purity >98%); mp 75−76 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.66 (s, 1H), 8.62 (d, J = 7.2 Hz, 1H), 8.36 (broad s, 2H), 8.14 (d, J = 8.1 Hz, 1H), 7.92 (dd, J = 8.1 and 6.3 Hz, 1 H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 140.4, 138.8, 137.8, 135.8, 127.4, 17.8. FT-IR (KBr, cm^{-1}): 3435, 1618, 1522, 1459, 799. LC−MS: $[M - I]^+$, m/z 109 (t_r = 1.1 min). Calcd for $C_6H_9N_2I$: C, 30.53%; H, 3.84%; N, 11.87%. Found: C, 30.32%; H, 3.59%; N, 11.97%.

1-Amino-3-(hydroxymethyl)pyridinium Iodide. Yield 2.19 g (49%, purity ∼85%), recrystallized sample (purity >98%); mp 98−99 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.71 (s, 1H), 8.66 (d, J = 6.3 Hz, 1H), 8.47 (broad s, 2H), 8.17 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 8.1 and 6.3 Hz, 1H), 5.82 (broad s, 1H), 4.69 (s, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 143.6, 137.1, 136.5, 135.4, 127.5, 59.3. FT-IR (KBr, cm^{-1}): 3292, 1386, 1175, 1047, 812. LC−MS: $[M - I]^+$, m/z 125 (t_r = 0.9 min). Calcd for $C_6H_9N_2OI$: C, 28.59%; H, 3.60%; N, 11.11%. Found: C, 28.74%; H, 3.39%; N, 11.02%.

1-Aminoquinolinium Iodide. Yield 4.09 g (17%, purity 66%), recrystallized sample (purity 74%); mp 168−169 °C (lit. 188 °C[16a]). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.32 (dd, J = 6.0 and 1.2 Hz, 1H), 9.06 (d, J = 8.4 Hz, 1H), 8.57 (d, J = 9.0 Hz, 1H), 8.44 (overlapping broad s and d, J = 7.5 Hz, 3H), 8.26 (td, J = 7.2 and 1.2 Hz, 1H), 8.02−8.11 (m, 2H). FT-IR (KBr, cm^{-1}): 3220, 1634, 1517, 812, 771. LC−MS: $[M - I]^+$, m/z 145 (t_r = 1.1 min).

Pyrazolo[1,5-*a*]pyridine-3-carboxylic Acid 6a. Yield 48 mg (44%), R_f = 0.3 (DCM−EtOAc−AcOH 90:10:1); mp 217−219 °C (lit. 223−224 °C[19a]). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.3−12.5 (broad s, 1H), 8.85 (dt, J = 6.9 and 1.2 Hz, 1H), 8.40 (s, 1H), 8.08 (dt, J = 8.7 and 1.2 Hz, 1H), 7.56 (ddd, J = 8.1; 6.9 and 1.2 Hz, 1H), 7.13 (td, J = 6.9 and 1.5 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.0, 144.5, 140.2, 129.8, 127.9, 118.2, 114.1, 103.6. FT-IR (KBr, cm^{-1}): 1700, 1530, 1284, 1218, 745. LC−MS: $[M + H]^+$, m/z 163 (t_r = 3.4 min). Calcd for $C_8H_6N_2O_2$: C, 59.26%; H, 3.73%; N, 17.28%. Found: C, 59.21%; H, 3.55%; N, 17.24%. HRMS $[M + H]^+$ calcd 163.0508, found 163.0512.

7-Methylpyrazolo[1,5-*a*]pyridine-3-carboxylic Acid 6b. Yield 19 mg (40%, purity 87%), R_f = 0.3 (DCM−EtOAc−AcOH 90:10:1), mp 189−190 °C (lit. 211 °C[19b]). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.0−12.4 (broad s, 1H), 8.43 (s, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.50 (dd, J = 9.0 and 6.9 Hz, 1H), 7.06 (d, J = 6.9 Hz, 1H), 2.73 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.2, 144.0, 140.5, 139.1, 127.9, 115.8, 113.3, 103.9, 17.3. FT-IR (KBr, cm^{-1}): 1663, 1536, 1255, 1170, 789. LC−MS: $[M + H]^+$, m/z 177 (t_r = 4.6 min). Calcd for $C_9H_8N_2O_2$: C, 61.36%; H, 4.58%; N, 15.90%. Found: C, 61.28%; H, 4.58%; N, 15.76%. HRMS $[M + H]^+$ calcd 177.0664, found 177.0664.

Pyrazolo[5,1-*a*]isoquinoline-1-carboxylic Acid 6c. Yield 20 mg (15%, purity 94%), R_f = 0.4 (DCM−EtOAc−AcOH 80:20:1), mp 199−200 °C (lit. 229 °C[16a]). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.81−9.84 (m, 1H), 8.59 (d, J = 7.2 Hz, 1H), 8.47 (s, 1H), 7.97−8.00 (m, 1H), 7.72−7.77 (m, 2H), 7.46 (d, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.7, 145.5, 137.4, 130.3, 129.5, 127.8, 127.4, 127.3, 127.0, 123.7, 114.5, 108.4. FT-IR (KBr, cm^{-1}): 1689, 1529, 1451, 1279, 1216. LC−MS: $[M + H]^+$, m/z 213 (t_r = 5.7 min). Calcd for $C_{12}H_8N_2O_2$: C, 67.92%; H, 3.80%; N, 13.20%. Found: C, 67.09%; H, 3.51%; N, 11.77%. HRMS $[M + H]^+$ calcd 213.0664, found 213.0670.

5-Methylpyrazolo[1,5-*a*]quinoline-3-carboxylic Acid 6d. Yield 43 mg (57%), R_f = 0.3 (DCM−EtOAc−AcOH 90:10:1), mp 249−250 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.5−12.7 (broad s, 1H), 8.57 (dd, J = 8.1 and 0.9 Hz, 1H), 8.41 (s, 1H), 8.11 (dd, J = 8.1 and 1.2 Hz, 1H), 7.91 (s, 1H), 7.86 (td, J = 7.2 and 1.5 Hz, 1H), 7.67 (td, J

= 8.4 and 1.2 Hz, 1H), 2.69 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.2, 143.5, 138.2, 136.1, 133.3, 130.4, 125.9, 125.9, 123.3, 115.5, 115.2, 105.8, 18.9. FT-IR (KBr, cm^{-1}): 1677, 1626, 1549, 1309, 1124. LC−MS: [M + H]$^+$, *m*/*z* 227 (t_r = 6.5 min). Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02%; H, 4.46%; N, 12.38%. Found: C, 68.74%; H, 4.22%; N, 12.15%. HRMS [M + H]$^+$ calcd 227.0821, found 227.0820.

Pyrazolo[1,5-*a*]pyridine-3,5-dicarboxylic Acid 5-Methyl Ester 6e. Yield 15 mg (11%), R_f = 0.7 (EtOAc−AcOH 99:1), mp 240−241 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.96 (dd, J = 7.5 and 0.9 Hz, 1H), 8.66 (d, J = 1.2 Hz, 1H), 8.54 (s, 1H), 7.48 (dd, J = 6.9 and 1.8 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.6, 163.7, 145.5, 139.2, 130.3, 128.2, 120.1, 112.5, 106.5, 52.9. FT-IR (KBr, cm^{-1}): 1730, 1678, 1532, 1306, 1113. LC−MS: [M + H]$^+$, *m*/*z* 221 (t_r = 4.4 min). Calcd for $C_{10}H_8N_2O_4$: C, 54.55%; H, 3.66%; N, 12.72%. Found: C, 55.54%; H, 3.31%; N, 11.20%. HRMS [M + H]$^+$ calcd 221.0562, found 221.0572.

6-Methylpyrazolo[1,5-*a*]pyridine-3-carboxylic Acid 6f. Yield 9 mg (14%, purity 74%), R_f = 0.3 (DCM−EtOAc−AcOH 90:10:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.68 (dd, J = 2.1 and 0.9 Hz, 1H), 8.31 (s, 1H), 7.97 (dd, J = 9.0 and 0.6 Hz, 1H), 7.42 (dd, J = 9.6 and 1.5 Hz, 1H), 2.34 (s, 3H). LC−MS: [M + H]$^+$, *m*/*z* 177 (t_r = 4.6 min). HRMS [M + H]$^+$ calcd 177.0664, found 177.0666.

6-Hydroxymethylpyrazolo[1,5-*a*]pyridine-3-carboxylic Acid 6g and 4-Hydroxymethylpyrazolo[1,5-*a*]pyridine-3-carboxylic Acid 6h. Yield 47 mg (33%, ∼2:1 mixture of regioisomers **6g** and **6h**). Analytical samples **6g**: (purity 90%), R_f = 0.1 ($CHCl_3$−AcOH, 95:5), mp 191−192 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.58 (s, 1H), 8.20 (s, 1H), 8.12 (d, J = 9 Hz, 1H), 7.38 (d, J = 9.3 Hz, 1H), 4.54 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 166.0, 144.0, 139.0, 128.0, 126.3, 126.0, 118.4, 108.2, 60.2. FT-IR (KBr, cm^{-1}): 3400, 1660, 1527, 1224, 810. LC−MS: [M + H]$^+$, *m*/*z* 193 (t_r = 3.2 min). Calcd for $C_9H_8N_2O_3$: C, 56.25%; H, 4.20%; N, 14.58%. Found: C, 54.11%; H, 3.59%; N, 12.93%. HRMS [M + H]$^+$ calcd 193.0613, found 193.0605. **6h**: (purity 86%), R_f = 0.3 ($CHCl_3$−AcOH, 95:5), ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.64 (d, J = 6.6 Hz, 1H), 8.33 (s, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 4.87 (s, 2H). LC−MS: [M + H]$^+$, *m*/*z* 193 (t_r = 3.2 min). HRMS [M + H]$^+$ calcd 193.0613, found 193.0623.

Pyrazolo[1,5-*a*]quinoline-3-carboxylic Acid 6i. Triturating of the crude product in EtOAc−AcOH (5:1) gave 80 mg (36%) of **6i**, R_f = 0.4 (DCM−EtOAc−AcOH 90:10:1), mp 290−291 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.5−12.8 (broad s, 1H), 8.53 (d, J = 8.7 Hz, 1H), 8.47 (s, 1H), 8.03−8.08 (two overlapping doublets, J = 6.3−8.7 Hz, 2H), 7.96 (d, J = 9.3 Hz, 1H), 7.84 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.1, 143.6, 138.5, 133.6, 130.7, 129.0, 128.5, 126.0, 123.2, 116.2, 115.3, 106.7. FT-IR (KBr, cm^{-1}): 1659, 1614, 1552, 1271, 812. LC−MS: [M + H]$^+$, *m*/*z* 213 (t_r = 5.5 min). Calcd for $C_{12}H_8N_2O_2$: C, 67.92%; H, 3.80%; N, 13.20%. Found: C, 67.24%; H, 3.57%; N, 12.76%.

2-Methylpyrazolo[1,5-*a*]pyridine-3-carboxylic Acid 6j. Recrystallization of the crude product from EtOAc gave 92 mg (74%) of **6j**, R_f = 0.4 (DCM−EtOAc−AcOH 90:10:1), mp 224−225 °C (lit. 243−245 °C[16b]). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.3 (s, 1H), 8.70 (d, J = 7.2 Hz, 1H), 8.00 (dd, J = 8.7 and 0.9 Hz, 1H), 7.48 (td, J = 6.9−8.7 and 0.9 Hz, 1H), 7.04 (td, J = 6.9−8.7 Hz and 1.5 Hz, 1H), 2.55 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.8, 154.6, 141.5, 129.1, 127.7, 118.1, 113.6, 100.8, 13.9. FT-IR (KBr, cm^{-1}): 1661, 1520, 1300, 1254, 750. LC−MS: [M + H]$^+$, *m*/*z* 177 (t_r = 4.1 min). Calcd for $C_9H_8N_2O_2$: C, 61.36%; H, 4.58%; N, 15.90%. Found: C, 61.20%; H, 4.08%; N, 15.52%.

2,7-Dimethylpyrazolo[1,5-*a*]pyridine-3-carboxylic Acid 6k.[22] Recrystallization of the crude product from EtOAc gave 77 mg (52%, purity >90%) of **6k**, R_f = 0.4 (DCM−EtOAc−AcOH 90:10:1), mp 212−213 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 12.3 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.44 (dd, J = 8.7 and 7.2 Hz, 1H), 6.97 (d, J = 6.9 Hz, 1H), 2.69 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.9, 154.0, 141.9, 138.4, 127.6, 115.8, 112.9, 101.0, 17.3, 14.2. FT-IR (KBr, cm^{-1}): 1667, 1530, 1286, 1131, 796. LC−MS: [M + H]$^+$, *m*/*z* 191 (t_r = 4.9 min). Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15%; H, 5.30%; N, 14.73%. Found: C, 62.87%; H, 5.02%; N, 14.47%.

2-Phenylpyrazolo[1,5-*a*]pyridine 6o. Yield 120 mg (79%), R_f = 0.9 (DCM−EtOAc−AcOH 90:10:1), mp 110 °C (lit. 111−112 °C[23]). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.7 (d, J = 7.2 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 9 Hz, 1H), 7.47 (t, J = 6.9−8.1 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.21 (dd, J = 8.7 and 6.6 Hz, 1H), 7.05 (s, 1H), 6.88 (td, J = 6.6 and 1.2 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 152.3, 141.1, 132.9, 128.8, 128.7, 128.4, 126.0, 123.9, 117.9, 112.3, 93.6. FT-IR (KBr, cm^{-1}): 1633, 1470, 1347, 783, 683. LC−MS: [M + H]$^+$, *m*/*z* 195 (t_r = 7.8 min). Calcd for $C_{13}H_{10}N_2$: C, 80.39%; H, 5.19%; N, 14.42%. Found: C, 80.24%; H, 5.05%; N, 14.34%.

7-Methyl-2-phenylpyrazolo[1,5-*a*]pyridine 6p.[24] Yield 88 mg (52%), R_f = 0.9 (DCM−EtOAc−AcOH 90:10:1), mp 55 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.02 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 9.0 Hz, 1H), 7.47 (t, J = 8.1 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.16 (dd, J = 8.7 and 6.6 Hz, 1H) 7.08 (s, 1H), 6.80 (d, J = 6.6 Hz, 1H), 2.72 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 151.8, 141.5, 137.6, 133.1, 128.7, 128.3, 126.1, 123.8, 115.5, 111.3, 94.0, 17.4. FT-IR (KBr, cm^{-1}): 1635, 1547, 1306, 798, 691. LC−MS: [M + H]$^+$, *m*/*z* 209 (t_r = 9.0 min). Calcd for $C_{14}H_{12}N_2$: C, 80.74%; H, 5.81%; N, 13.45%. Found: C, 80.48%; H, 5.53%; N, 12.78%.

4-Methyl-2-phenylpyrazolo[1,5-*a*]pyridine 6q[25] **and 6-Methyl-2-phenylpyrazolo[1,5-*a*]pyridine 6r.** Yield 34 mg (32%, 2:1 mixture of regioisomers **6q** and **6r**), **6q** (purity 85%): R_f = 0.9 (DCM−EtOAc−AcOH 90:10:1). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.54 (d, J = 6.9 Hz, 1H), 8.01 (dd, J = 6.9 and 1.5 Hz, 2H), 7.36−7.50 (m, 3H), 7.10 (s, 1H), 7.01 (d, J = 6.9 Hz, 1H), 6.81 (t, J = 7.2 Hz, 1H), 2.47 (s, 3H). FT-IR (KBr, cm^{-1}): 1507, 1463, 1322, 775, 694. LC−MS: [M + H]$^+$, *m*/*z* 209 (t_r = 8.4 min). Calcd for $C_{14}H_{12}N_2$: C, 80.74%; H, 5.81%; N, 13.45%. Found: C,

80.54%; H, 5.86%; N, 13.19%. **6r:** Sample for X-ray crystal structure analysis, recrystallized from EtOAc−*n*-hexane, mp 149−150 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.53 (s, 1H), 7.96 (dd, J = 8.4 and 1.5 Hz, 2H), 7.59 (d, J = 9.3 Hz, 1H), 7.33−7.49 (m, 3 H), 7.09 (dd, J = 9 and 1.2 Hz, 1H), 6.98 (s, 1H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 17.6, 93.2, 117.3, 121.7, 125.9, 126.3, 126.6, 128.4, 128.9, 133.0, 139.6, 151.7.

Pyrazolo[1,5-*a*]pyridine-3-carboxylic Acid Methyl Ester 7a. Yield 53 mg (40%), R_f = 0.7 (*n*-hexane−EtOAc 1:1), mp 88 °C (lit. 88 °C[26]). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.86 (dd, J = 6.9 and 1.2 Hz, 1H), 8.44 (s, 1H), 8.06 (dd, J = 9 and 1.2 Hz, 1H), 7.59 (ddd, J = 7.8, 6.9 and 1.2 Hz, 1H), 7.15 (td, J = 8.4 and 1.5 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 162.9, 144.3, 140.1, 130.0, 128.4, 118.0, 114.4, 102.5, 51.0. FT-IR (KBr, cm^{-1}): 1694, 1384, 1237, 1063, 779. LC−MS: $[M + H]^+$, m/z 177 (t_r = 5.3 min). Calcd for $C_9H_8N_2O_2$: C, 61.36%; H, 4.58%; N, 15.90%. Found: C, 61.18%; H, 4.36%; N, 15.66%. HRMS $[M + H]^+$ calcd 177.0664, found 177.0660.

7-Methylpyrazolo[1,5-*a*]pyridine-3-carboxylic Acid Methyl Ester 7b. Yield 30 mg (31%), R_f = 0.6 (*n*-hexane−EtOAc 2:1), mp 101 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 8.49 (s, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.55 (dd, J = 8.7 and 6.9 Hz, 1H), 7.09 (d, J = 6.9 Hz, 1H), 3.83 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 163.0, 143.8, 140.4, 139.3, 128.4, 115.7, 113.7, 102.7, 51.0, 17.3. FT-IR (KBr, cm^{-1}): 1707, 1541, 1254, 1110, 786. LC−MS: $[M + H]^+$, m/z 191 (t_r = 6.4 min). Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15%; H, 5.30%; N, 14.73%. Found: C, 63.72%; H, 4.99%; N, 14.46%. HRMS $[M + H]^+$ calcd 191.0821, found 191.0824.

Abbreviations. Ac, acetyl; DCM, dichloromethane; DIPEA, *N*-ethyldiisopropylamine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; rt, room temperature; NOESY, nuclear Overhauser effect spectroscopy; TFA, trifluoroacetic acid; THF, tetrahydrofuran.

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Supporting Information Available. Crystallographic information files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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