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Authors: Hubert Lavrard and Florence Popowycz

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Harnessing cascade Suzuki-cyclization reactions of pyrazolo[3,4-*b*]pyridine for the synthesis of tetracyclic fused heteroaromatics

Hubert Lavrard,[a] Florence Popowycz*[a]

Abstract: Numerous procedures have been described for the functionalization of pyrazolo[3,4-*b*]pyridine, mainly nucleophilic substitutions on C-4 position and esterifications/amidations on C-5 position. Thus, we report herein a robust, easy to implement protocol for the Suzuki cross-coupling reaction of the chloroarene **2**, followed by *in situ* lactonisation to provide chromenopyrazolopyridines. The extension of the scope of the reaction to fused naphthyridinones is also reported. This strategy granted the access to ten original pyrazolopyridine-embedded tetracyclic compounds.

Introduction

Over the years, the pyrazolo[3,4-*b*]pyridine has emerged as a multivalent scaffold involved in numerous pharmaceutically active compounds. A broad range of medicinal compounds such as analgesics,[1] anti-inflammatories,[2] vasodilators,[3] anxiolytics,[4] anti-diabetics,[5] anti-tumoral agents,[6] anti-retroviral[7]or anti-leishmanial[8] molecules display this moiety, which is structurally related to purine bases[9] and allopurinol.[10] Such biological importance, along with the availability of pyrazolo[3,4-*b*]pyridines anxiolytic drugs like cartazolate, etazolate, tracazolate, BAY 41-2272 cardiovascular therapeutic[11] or GSK-3 inhibitor (Figure 1) make them desirable compounds for the screening of new biological activities.

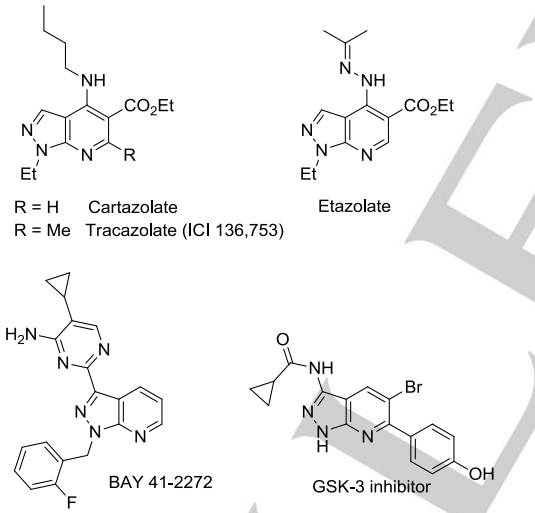
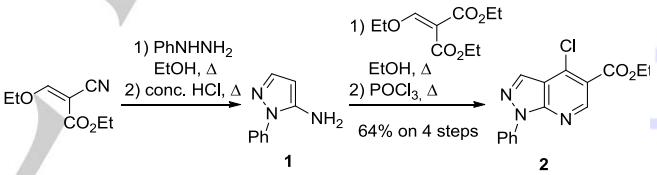


Figure 1. Biologically active pyrazolo[3,4-*b*]pyridines

In addition to their wide potential, synthesis of the pyrazolo[3,4-*b*]pyridine core is usually straightforward, relying on condensation reactions of either 1,3-dicarbonyl or α,β-unsaturated carbonyl compounds with 5-aminopyrazoles,[12] or cyclization of hydrazines with properly-substituted derivatives of nicotinic acid.[13] Some noteworthy improvements to these syntheses have been attained in this field, namely with the use of chromenones or isoflavones as Michael acceptors,[14] multicomponent reactions,[15] or hetero-Diels-Alder/microwave induced reactions.[16] In specific cases, the pyrazolo[3,4-*b*]pyridine pattern is inserted in more complex polycyclic molecular systems.[14a,15a] Among them, the Gould-Jacobs reaction[17] represents a high-yielding, easily scalable, user-friendly synthesis starting from inexpensive materials, which gives access to the 4-chloro-pyrazolo[3,4-*b*]pyridine **2**. A four step synthesis (Scheme 1) starting from the condensation of phenylhydrazine with ethyl 2-cyano-3-ethoxyacrylate, followed by an acidic mediated decarboxylation afforded 5-aminopyrazole **1**. Subsequent addition on diethyl ethoxymethylenemalonate followed by chlorinative cyclization in $POCl_3$ afforded 4-chloro-pyrazolo[3,4-*b*]pyridine **2** in 64% for 4 steps.



Scheme 1. Gould-Jacobs synthesis of pyrazolo[3,4-*b*]pyridine.

Despite the already proven prevalence of the pyrazolo[3,4-*b*]pyridine scaffold, very few synthetic methods have been reported for the introduction of molecular diversity at the C-4 position on derivative **2**. The only published examples being classical nucleophilic substitutions with a broad range of alcohols, amines, anilines, or hydrazines[18] apart from one patent by Jablonski which describes the sole example of a Suzuki cross-coupling reaction on a similar substrate.[19] Due to the cooperative electron-withdrawing effects of the intracyclic nitrogen and the ester moiety, the C-Cl bond is weakened, and prone to oxidative addition on transition metal complexes, which usually needs electron-rich ligands or harsh reaction conditions.[20] Therefore, application of the Suzuki cross-coupling reaction[21] with this chloropyridine moiety would afford an interesting functionalization method.

[a] H. Lavrard, F. Popowycz
Université Lyon, Institut National des Sciences Appliquées, Université Claude BernardLyon1, CNRS, ICBMS, UMR 5246, 20, Avenue Albert Einstein, F-69621, Villeurbanne, France.
E-mail: florence.popowycz@insa-lyon.fr

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Results and Discussion

Some cross-coupling reactions on activated chloroheteroarenes have been already successful.[22] Our preliminary experiments focused on three sets of cross-coupling conditions (Table 1) which were already described. The medium yields (77-84%) obtained by Jablonski[19] under standard conditions (toluene, EtOH, 5 mol% $Pd(PPh_3)_4$) seemed surprisingly low. When these conditions were re-evaluated on the simple phenylboronic acid (Table 1, entry 1), the reactions were unreproducible, and yields down to 70%. Although no dehalogenation product **5** was observed, the main impurity was the ether product **6** coming from nucleophilic substitution on C-4 position by ethanol. Since the lability of the chlorine atom was hampering the coupling reaction, replacement of EtOH by less nucleophilic ^{t}BuOH increased the yield up to 97% (Table1, entry 4), without any trace of ether side product **6**.

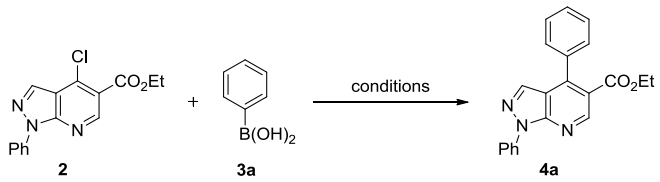
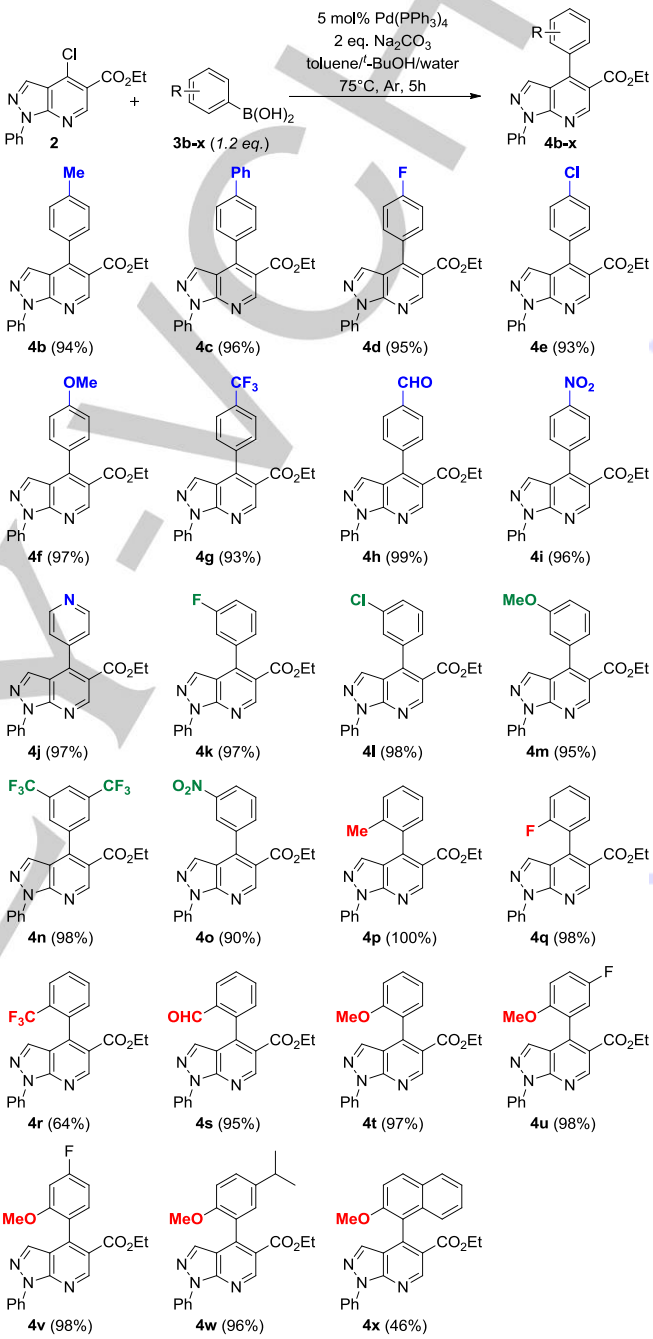


Table 1. Pyrazolo[3,4-*b*]pyridines in Suzuki cross-coupling

Entry	**3a**	Catalyst	Base	Solvent	Temp	Yield
1	1.2 eq.	5 mol% $Pd(PPh_3)_4$	Na_2CO_3	Toluene EtOH/water	75°C	70%
2	1.2 eq.	2 mol% $Pd(PPh_3)_4$	Na_2CO_3	Toluene EtOH/water	75°C	63%
3	1.2 eq.	1 mol% $Pd(PPh_3)_4$	Na_2CO_3	Toluene EtOH/water	75°C	57%
4	1.2 eq.	5 mol% $Pd(PPh_3)_4$	Na_2CO_3	Toluene ^{t}BuOH/water	75°C	97%
5	1.2 eq.	5 mol% $Pd(PPh_3)_4$	K_2CO_3	DME/water	100°C	**5** (86%)
6	1.5 eq.	5 mol% DAPCy	Cs_2CO_3	Dioxane	100°C	97%

Side products observed under some conditions:

The Gronowitz conditions,[23] which were successful with electron deficient chloropyridine[22a-b] and with hindered boronic acids[24] were also tested (Table 1, entry 5), affording dehalogenated compound **5** (86%) as the sole product. Intending to perform a mild and phosphine-free Suzuki reaction, bis(dicyclohexylamine) palladium diacetate[25] (DAPCy) was tried as a catalyst, affording excellent yields (Table 1, entry 6).



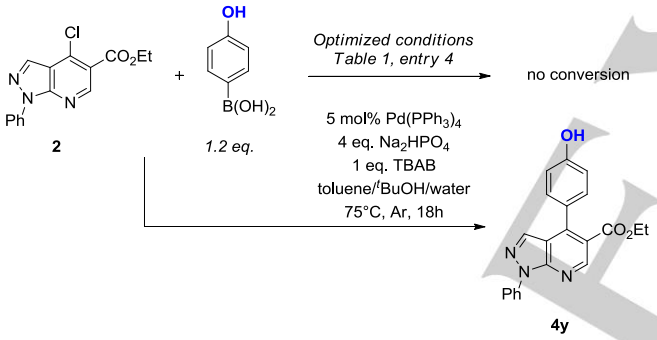
Scheme 2. Extension of the Suzuki reaction with substituted boronic acids

With those two sets of conditions in hand, we tried to further expand the scope of this reaction. Unfortunately, while expanding our scope, the DAPCy catalyst proved to be less versatile than $Pd(PPh_3)_4$ under the studied conditions. No

conversion was observed with electron-deficient or sterically hindered boronic acid, like **3h**, **3j** and **3p**. Therefore, the modified Jablonski's conditions were retained for the scope (Table 1, entry 4).

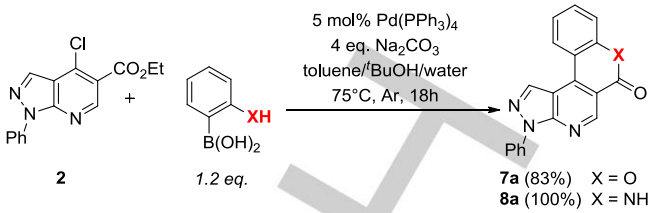
Almost all ***para***-substituted boronic acids (Scheme 2) could be smoothly coupled to the pyrazolopyridine moiety, with excellent yields. The ***meta***-substituted compounds furnished also satisfying yields. Challenging ***ortho***-substituted boronic acids afforded good yields, with the only exception of much hindered **3r** and **3x**. Despite these excellent results, limitations were observed in the case of 4-bromophenylboronic acid which resulted in an intractable mixture of products – probably due to oligomerization of the reagent under these conditions – and the mesitylboronic acid, indisputably predictable due to high steric hindrance.

Surprisingly, no conversion was detected with 4-hydroxyphenylboronic acid under the optimized conditions (Scheme 3). We assumed that the use of sodium carbonate resulted in the formation of the dianionic conjugated base of 4-hydroxyphenylboronic acid, which low solubility in toluene inhibited the reaction. Changing Na_2CO_3 by Na_2HPO_4 and adding 1 equivalent of ^{tert}butylammonium bromide provided the expected product in 46% yield with a partial conversion of 50%.



Scheme 3. Suzuki coupling of **2** with 4-hydroxyphenyl boronic acid

When using boronic acid ***ortho***-substituted with a nucleophilic moiety, like 2-hydroxyphenylboronic acid or 2-aminophenylboronic acid, a tandem Suzuki cross-coupling / cyclization occurred leading to tetracyclic derivatives **7a** and **8a** with good to excellent yields (Scheme 4). There is a noteworthy difference between the reactivity of 2- and 4-hydroxyphenylboronic acid. The ***ortho***-substituted reagent behaves classically under our standard conditions without the need of additional weaker base or TBAB. This could be explained by the existence of an intramolecular hydrogen bond between the phenol and the acid moiety. Second deprotonation of the stabilized 2-hydroxyphenylboronate is disfavoured leading to a monoanionic species displaying much more affinity with the organic phase, allowing thus the cross-coupling reaction.



Scheme 4. Domino Suzuki – cyclization

In addition to the good yields furnished by this domino reaction, no intermediate or by-product could be detected within the reaction medium.

However, owing to the limited availability of substituted 2-hydroxyphenylboronic acids, the polycyclic compounds were prepared from the Suzuki products **4t-x**, which were demethylated with BBr_3 according to standard procedures.[26] Therefore, intramolecular transesterification occurred more or less smoothly and, in certain cases, might need the use of azeotropic distillation of water (Table 2).

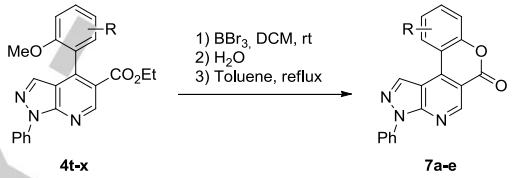


Table 2. Cyclization of Suzuki adducts

Entry	Starting material (R =)	Third step[a]	Product (yield[b], %)
1	**4t** (H)	no	**7a** (86)
2	**4u** (5-F)	no	**7b** (94)
3	**4v** (4-F)	yes	**7c** (53)
4	**4w** (5-^{i}Pr)	no	**7d** (83)
5	**4x** (2-methoxynaphtalen-1-yl)	yes	**7e** (64)

[a] Azeotropic distillation of water using a Dean-Stark apparatus. [b]Yields calculated on the pure isolated products.

The same difficulties were addressed for the preparation of derivatives of **8a**. A family of compound **8a** has been patented by Pierre Fabre in 2012 as antineoplastic agent, with a completely different methodology.[27] Since substituted 2-aminophenylboronic acids are not available, an alternate synthesis was considered. *N*-Boc protected boronic acids were prepared through *ortho*-lithiation of protected anilines. Investigation of the Suzuki coupling directly on *N*-Boc protected boronic acid **11a** was first investigated (Table 3). Optimized conditions used on 2-*N*-Boc-aminophenylboronic acid led to a mixture of three products: starting material **2** (22%), Suzuki adduct **9a** (33%), Suzuki / cyclization product **10a** (45%) (Table 3, entry 1). Increasing the load of Pd to 7 or 10 mol% did not affect the conversion but compound **9a** was always the major product (Table 3, entries 2 and 3). Total conversion was observed with 1.5 equivalent of boronic acid instead of 1.2 equivalents (Table 3, entries 4-6) and the best conditions (Table

3, entry 4) were retained for the coupling step. Unfortunately, isolation of the three different products was difficult in most of the cases due to solubility or separation issues. Since **8a** was the only compound of interest, the crude mixture obtained after the cross-coupling step was simply treated with TFA, converting simultaneously **9a** and **10a** to **8a**. Tetracyclic derivative **8a** was finally isolated in yields ranging from 71% to 78% in two steps (Scheme 5).

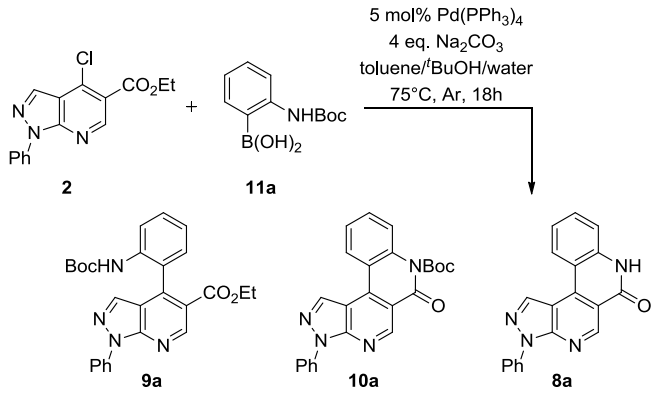
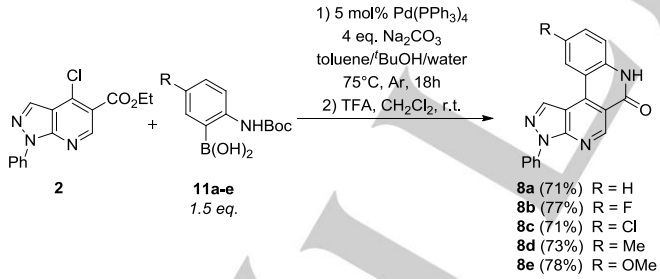


Table 3. Optimization of coupling with *ortho*-NHBoc boronic acid

Entry	Boronic acid	$Pd(PPh_3)_4$	Conversion[a]	**9a**[a]	**10a**[a]	**8a**[a]
1	1.2 eq.	5 mol%	78%	33%	45%	0%
2	1.2 eq.	7 mol%	80%	60%	20%	0%
3	1.2 eq.	10 mol%	82%	53%	29%	0%
4	1.5 eq.	5 mol%	100%	58%	36%	6%
5	1.5 eq.	7 mol%	100%	66%	28%	6%
6	1.5 eq.	10 mol%	100%	80%	12%	8%

[a] NMR ratios



Scheme 5. Two-step Suzuki – cyclization

Conclusion

In conclusion, we have developed a robust practical protocol for the cross-coupling of 4-chloro-pyrazolo[3,4-*b*]pyridine, affording biphenyl products in excellent yields. Capitalizing on this methodology, a family of 10 tetracyclic fused products was obtained with satisfying yields in the presence of *ortho*-hydroxyl or *ortho*-amino substituted phenylboronic acids.

Experimental Section

Reagents and solvents were supplied by Aldrich, Acros, Lancaster, Alfa Aesar, Fluka or TCI and purchased at the highest commercial quality to be used without further purification. NMR spectra were recorded on a Brüker 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz; ^{19}F: 282 MHz), Bruker 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz; ^{19}F: 376 MHz) spectrometers at 298 K, using $CDCl_3$, DMSO-d_6, and TFA-*d* as solvents. The chemical shifts (δ, ppm) are referenced to the residual solvent peak and coupling constants (*J*) are reported in the standard fashion. Chemical shifts reference for ^{19}F was $CFCl_3$. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, hept. = heptuplet, m = multiplet, br = broad, app. = apparent. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on a Thermo Finnigan LCQ Advantage mass spectrometer. High-resolution mass spectra (HRMS) were recorded on a Finnigan Mat 95xL mass spectrometer using either the electrospray (ESI) or atmospheric pressure chemical ionization (APCI) technique. Analytical thin-layer chromatography was carried out on silica gel Merck 60 D254 (0.25 mm). Flash chromatography was performed on Merck Si 60 silica gel (40–63 µm). Infra-red (IR) spectra were recorded with an IRAffinity-1 Shimadzu spectrometer using attenuated total reflectance (ATRMiracle), and the wavenumbers were expressed in cm^{-1}. Melting points were measured using Büchi apparatus B-540.

Preparations of products 4a-x: In a round-bottom flask, compound **2** (150 mg, 0.497 mmol, 1 eq.), $Pd(PPh_3)_4$ (29 mg, 5 mol%), boronic acid **3a-x** (0.596 mmol, 1.2 eq.), and Na_2CO_3 (105 mg, 0.998 mmol, 2 eq.) were weighed, and carefully purged with Ar. Degassed toluene (3 mL), ^{t}BuOH (1.5 mL), and water (0.5 mL) were added, and the solution was heated at 75°C for 5-18 hours. The crude mixture was cooled down to room temperature, diluted with a saturated aqueous solution of Na_2CO_3 (10 mL), and extracted with CH_2Cl_2 (3x20 mL). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, and evaporated under reduced pressure. Flash chromatography on silica gel (pentane/EtOAc 95:5 to 80:20) afforded pure products.

Ethyl 1,4-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4a): white powder, 97%, m.p.: 91°C. IR: 1701, 1587, 1502, 1369, 1307, 1257, 1153. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.16 (s, 1H), 8.26 (dd, 2H, *J* = 8.7 Hz, *J* = 1.1 Hz), 8.05 (s, 1H), 7.59-7.51 (m, 5H), 7.47-7.44 (m, 2H), 7.36 (tt, 1H, *J* = 7.4 Hz, *J* = 1.1 Hz), 4.18 (q, 2H, *J* = 7.1 Hz), 1.06 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.8 (C_q), 151.6 (CH), 150.8 (C_q), 146.8 (C_q), 139.2 (C_q), 136.3 (C_q), 135.2 (CH), 129.3 (2 CH), 129.0 (CH), 128.6 (2 CH), 128.5 (2 CH), 126.8 (CH), 121.8 (2 CH), 120.1 (C_q), 117.5 (C_q), 61.3 (CH_2), 13.8 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{21}H_{18}N_3O_2$: 344.1394; found: 344.1390.

Ethyl 4-(4-methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4b): white crystals, 94%, m.p.: 100°C. IR: 2912, 1701, 1583, 1504, 1421, 1365, 1313, 1259, 1151, 1020, 983, 798, 754, 736. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.97 (s, 1H), 8.25 (s, 1H), 8.22 (dd, 2H, *J* = 8.0 Hz, *J* = 1.1 Hz), 7.58 (t, 2H, *J* = 8.0 Hz), 7.41-7.34 (m, 5H), 4.11 (q, 2H, *J* = 7.1 Hz), 2.41 (s, 3H), 1.01 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 166.3 (C_q), 150.6 (CH), 150.1 (C_q), 145.7 (C_q), 138.7 (C_q), 138.6 (C_q), 135.3 (CH), 132.3 (C_q), 129.3 (2 CH), 129.1 (2 CH), 128.6 (2 CH), 126.6 (CH), 121.0 (2 CH), 120.3 (C_q), 116.5 (C_q), 61.0 (CH_2), 20.9 (CH_3), 13.5 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{22}H_{20}N_3O_2$: 358.1550; found: 358.1554.

Ethyl 4-([1,1'-biphenyl]-4-yl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4c): white powder, 96%, m.p.: 131°C. IR: 2993, 1697, 1573, 1502, 1313, 1259, 1151, 756, 732. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.18

(s, 1H), 8.28 (dd, 2H, *J* = 8.6 Hz, *J* = 1.1 Hz), 8.13 (s, 1H), 7.77 (d, 2H, *J* = 8.4 Hz), 7.71 (d, 2H, *J* = 8.4 Hz), 7.60-7.48 (m, 6H), 7.44-7.35 (m, 2H), 4.22 (q, 2H, *J* = 7.1 Hz), 1.11 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.9 (C_q), 151.6 (CH), 150.8 (C_q), 146.5 (C_q), 141.9 (C_q), 140.4 (C_q), 139.2 (C_q), 135.2 (CH), 135.1 (C_q), 129.3 (2 CH), 129.2 (2 CH), 129.1 (2 CH), 127.9 (CH), 127.3 (2 CH), 127.2 (2 CH), 126.8 (CH), 121.8 (2 CH), 120.1 (C_q), 117.5 (C_q), 61.4 (CH_2), 13.9 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{27}H_{22}N_3O_2$: 420.1707; found: 420.1695.

Ethyl 4-(4-fluorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4d): white crystals, 95%, m.p.: 139°C. IR: 3068, 2978, 1707, 1581, 1500, 1317, 1232, 1161, 796, 758, 736. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.16 (s, 1H), 8.25 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 8.02 (s, 1H), 7.56 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.47-7.42 (m, 2H), 7.37 (tt, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 7.26-7.20 (m, 2H), 4.21 (q, 2H, *J* = 7.1 Hz), 1.13 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.5 (C_q), 163.3 (d, *J* = 249 Hz, C_q), 151.7 (CH), 150.7 (C_q), 145.8 (C_q), 139.1 (C_q), 134.9 (CH), 132.2 (d, *J* = 4 Hz, C_q), 130.5 (d, J = 8 Hz, 2 CH), 129.3 (2 CH), 126.9 (CH), 121.8 (2 CH), 120.0 (C_q), 117.6 (C_q), 115.7 (d, *J* = 22 Hz, 2 CH), 61.4 (CH_2), 14.0 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -112.79. HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{21}H_{16}FN_3NaO_2$: 384.1119; found: 384.1110.

Ethyl 4-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4e): white powder, 93%, m.p.: 109°C. IR: 2978, 1712, 1581, 1496, 1423, 1313, 1165, 1087, 829, 796, 723. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.18 (s, 1H), 8.24 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 8.00 (s, 1H), 7.56 (t, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.51 (dt, 2H, *J* = 8.5 Hz, *J* = 2.1 Hz), 7.40 (dt, 2H, *J* = 8.5 Hz, *J* = 2.1 Hz), 7.37 (tt, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 4.21 (q, 2H, *J* = 7.1 Hz), 1.14 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.4 (C_q), 151.7 (CH), 150.7 (C_q), 145.6 (C_q), 139.0 (C_q), 135.2 (C_q), 134.8 (CH), 134.7 (C_q), 129.9 (2 CH), 129.3 (2 CH), 128.8 (2 CH), 126.9 (CH), 121.8 (2 CH), 119.7 (C_q), 117.4 (C_q), 61.5 (CH_2), 14.0 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{21}H_{17}ClN_3O_2$: 378.1004; found: 378.0994.

Ethyl 4-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4f): white powder, 97%, m.p.: 80°C. IR: 2974, 1722, 1583, 1502, 1423, 1298, 1228, 1168, 1028, 827, 798, 750, 729. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.11 (s, 1H), 8.25 (dd, 2H, *J* = 8.5 Hz, *J* = 1.0 Hz), 8.09 (s, 1H), 7.55 (dd, 2H, *J* = 8.5 Hz, 7.5 Hz), 7.42 (d, 2H, *J* = 8.7 Hz), 7.35 (tt, 1H, *J* = 7.5 Hz, 1.1 Hz), 7.06 (d, 2H, *J* = 8.7 Hz), 4.22 (q, 2H, *J* = 7.1 Hz), 3.90 (s, 3H), 1.14 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.1 (C_q), 160.4 (C_q), 151.5 (CH), 150.8 (C_q), 146.5 (C_q), 139.2 (C_q), 135.2 (CH), 130.2 (2 CH), 129.3 (2 CH), 128.3 (C_q), 126.7 (CH), 121.7 (2 CH), 120.1 (C_q), 117.5 (C_q), 114.0 (2 CH), 61.3 (CH_2), 55.5 (CH_3), 14.0 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{22}H_{20}N_3O_3$: 374.1499; found: 374.1494.

Ethyl 1-phenyl-4-(4-(trifluoromethyl)phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4g): white powder, 93%, m.p.: 124°C. IR: 1693, 1583, 1502, 1319, 1263, 1161, 1134, 1066, 840, 800, 752, 734. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.23 (s, 1H), 8.25 (dd, 2H, *J* = 8.6 Hz, *J* = 1.1 Hz), 7.80 (d, 2H, *J* = 8.1 Hz), 7.59-7.54 (m, 4H), 7.38 (tt, 1H, *J* = 7.4 Hz, *J* = 1.1 Hz), 4.19 (q, 2H, *J* = 7.1 Hz), 1.09 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 166.1 (C_q), 151.8 (CH), 150.7 (C_q), 145.3 (C_q), 140.1 (C_q), 139.0 (C_q), 134.7 (CH), 131.1 (q, *J* = 33 Hz, C_q), 129.4 (2 CH), 128.9 (2 CH), 127.0 (CH), 125.5 (q, *J* = 4 Hz, 2 CH), 124.1 (q, *J* = 272 Hz, CF_3), 121.8 (2 CH), 119.6 (C_q), 117.4 (C_q), 61.5 (CH_2), 13.8 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -63.12. HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{22}H_{17}F_3N_3O_2$: 412.1267; found: 412.1260.

Ethyl 4-(4-formylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4h): white powder, 99%, m.p.: 122°C. IR: 1693, 1581, 1502, 1309, 1261, 1168, 798, 752, 740. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.14 (s, 1H), 9.23 (s, 1H), 8.24 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 8.05 (d, 2H, *J* = 8.2 Hz), 7.96 (s, 1H), 7.62 (d, 2H, *J* = 8.2 Hz), 7.56 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.37 (tt, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 4.19 (q, 2H, *J* = 7.1 Hz), 1.09 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 191.8 (CH), 166.0 (C_q), 151.8 (CH), 150.7 (C_q), 145.5 (C_q), 142.5 (C_q), 138.9 (C_q), 136.4 (C_q), 134.7 (CH), 129.7 (2 CH), 129.4 (2 CH), 129.3 (2 CH), 127.0 (CH), 121.8 (2 CH), 119.4 (C_q), 117.2 (C_q), 61.5 (CH_2), 13.9 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{22}H_{18}N_3O_3$: 372.1343; found: 372.1324.

Ethyl 4-(4-nitrophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4i): white crystals, 96%, m.p.: 155°C. IR: 1710, 1577, 1516 1500, 1348, 1336, 1307, 1259, 1151, 1134, 983, 852, 800, 756, 738. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.26 (s, 1H), 8.40 (dt, 2H, *J* = 8.8 Hz, *J* = 2.2 Hz), 8.24 (dd, 2H, *J* = 8.6 Hz, *J* = 1.1 Hz), 7.93 (s, 1H), 7.62 (dt, 2H, *J* = 8.8 Hz, *J* = 2.2 Hz), 7.56 (dd, 2H, *J* = 8.6 Hz, *J* = 7.5 Hz), 7.38 (tt, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 4.22 (q, 2H, *J* = 7.1 Hz), 1.15 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.6 (C_q), 151.9 (CH), 150.7 (C_q), 148.1 (C_q), 144.5 (C_q), 143.0 (C_q), 138.9 (C_q), 134.4 (CH), 129.5 (2 CH), 129.4 (2 CH), 127.1 (CH), 123.7 (2 CH), 121.8 (2 CH), 119.1 (C_q), 117.1 (C_q), 61.6 (CH_2), 14.0 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{21}H_{17}N_4O_4$: 389.1244; found: 389.1242.

Ethyl 1-phenyl-4-(4-pyridinyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4j): white powder, 97%, m.p.: 178°C. IR: 1708, 1581, 1494, 1315, 1261, 1166, 985, 752. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.23 (s, 1H) 8.79 (bs, 2H), 8.23 (dd, 2H, *J* = 8.0 Hz, *J* = 1.0 Hz), 7.94 (s, 1H), 7.55 (t, 2H, *J* = 8.0 Hz), 7.38-7.34 (m, 3H), 4.19 (q, 2H, *J* = 7.1 Hz), 1.09 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.7 (C_q), 151.8 (CH), 150.7 (C_q), 149.9 (2 CH), 144.5 (C_q), 143.8 (C_q), 138.9 (C_q), 134.4 (CH), 129.3 (2 CH), 127.0 (CH), 123.1 (2 CH), 121.7 (2 CH), 119.0 (C_q), 116.8 (C_q), 61.6 (CH_2), 13.8 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{20}H_{17}N_4O_2$: 345.1346; found: 345.1344.

Ethyl 4-(3-fluorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4k): white powder, 97%, m.p.: 125°C. IR: 1695, 1575, 1498 1311, 1163, 1016, 756. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.18 (s, 1H), 8.24 (dd, 2H, *J* = 8.5 Hz, *J* = 1.5 Hz), 8.02 (s, 1H), 7.55 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.48 (td, 1H, *J* = 8.0 Hz, *J* = 5.8 Hz), 7.36 (t, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 7.24-7.16 (m, 3H), 4.20 (q, 2H, *J* = 7.1 Hz), 1.10 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.3 (C_q), 162.6 (d, *J* = 247 Hz, CF), 151.6 (CH), 150.7 (C_q), 145.2 (d, *J* = 2 Hz, C_q), 139.0 (C_q), 138.3 (d, *J* = 8 Hz, C_q), 134.8 (CH), 130.2 (d, *J* = 9 Hz, CH), 129.3 (2 CH), 126.9 (CH), 124.3 (d, *J* = 3 Hz, CH), 121.7 (2 CH), 119.8 (C_q), 117.3 (C_q), 115.9 (d, *J* = 21 Hz, CH), 115.8 (d, *J* = 23 Hz, CH), 61.4 (CH_2), 13.8 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -113.06. HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{21}H_{17}FN_3O_2$: 362.1299; found: 362.1311.

Ethyl 4-(3-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4l): white powder, 98%, m.p.: 133°C. IR: 1708, 1581, 1497, 1368, 1308, 1258, 1164, 983, 786. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.19 (s, 1H), 8.25 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 8.01 (s, 1H), 7.55 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.51-7.44 (m, 3H), 7.36 (tt, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 7.33 (dt, 1H, *J* = 7.1 Hz, *J* = 1.6 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 1.11 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.3 (C_q), 151.7 (CH), 150.7 (C_q), 145.1 (C_q), 139.0 (C_q), 138.0 (C_q), 134.8 (CH), 134.4 (C_q), 129.8 (CH), 129.3 (2 CH), 129.0 (CH), 128.6 (CH), 126.9 (CH), 126.7 (CH), 121.7 (2 CH), 119.7 (C_q), 117.3 (C_q), 61.4 (CH_2), 13.9 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{21}H_{17}ClN_3O_2$: 378.1004; found: 378.1004.

Ethyl 4-(3-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4m): white powder, 95%, m.p.: 95°C. IR: 1697, 1577, 1315,

1244, 1159, 1018, 785, 754, 690. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 1H), 8.25 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 8.07 (s, 1H), 7.55 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.43 (t, 1H, *J* = 7.9 Hz), 7.36 (tt, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 7.06-7.02 (m, 2H), 7.00-6.99 (m, 1H), 4.19 (q, 2H, *J* = 7.1 Hz), 3.86 (s, 3H), 1.09 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.8 (C_q), 159.6 (C_q), 151.4 (CH), 150.7 (C_q), 146.5 (C_q), 139.1 (C_q), 137.5 (C_q), 135.2 (CH), 129.6 (CH), 129.3 (2 CH), 126.8 (CH), 121.7 (2 CH), 121.0 (CH), 120.2 (C_q), 117.4 (C_q), 114.4 (CH), 114.2 (CH), 61.3 (CH_2), 55.5 (CH_3), 13.9 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{22}H_{20}N_3O_3$: 374.1499; found: 374.1501.

Ethyl 4-(3,5-bis(trifluoromethyl)phenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4n): white crystals, 98%, m.p.: 128°C. IR: 1698, 1576, 1314, 1273, 1190, 1162, 1125, 1108, 896, 799, 706. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 1H), 8.24 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 8.05 (bs, 1H), 7.94 (s, 1H), 7.91 (bs, 2H), 7.57 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.40 (tt, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 1.09 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.5 (C_q), 152.2 (CH), 150.8 (C_q), 143.3 (C_q), 138.8 (C_q), 138.6 (C_q), 134.2 (CH), 132.0 (q, *J* = 34 Hz, 2 C_q), 129.4 (2 CH), 128.9 (q, *J* = 3 Hz, 2 CH), 127.2 (CH), 123.2 (q, *J* = 273 Hz, 2 CF_3), 122.7 (vquint., *J* = 4 Hz, CH), 121.9 (2 CH), 119.3 (C_q), 117.2 (C_q), 61.7 (CH_2), 13.8 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -63.28. HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{23}H_{16}F_6N_3O_2$: 480.1141; found: 480.1128.

Ethyl 4-(3-nitrophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4o): purified on flash column chromatography with pure CH_2Cl_2 as the eluent, white powder, 90%, m.p.: 152°C. IR: 1709, 1579, 1529, 1500, 1348, 1315, 1262, 1143, 797. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.27 (s, 1H), 8.38 (ddd, 1H, *J* = 7.9 Hz, *J* = 2.3 Hz, *J* = 1.4 Hz), 8.33 (dd, 1H, *J* = 2.3 Hz, *J* = 1.4 Hz), 8.24 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 7.95 (s, 1H), 7.78 (dt, 1H, *J* = 7.9 Hz, *J* = 1.4 Hz), 7.72 (t, 1H, *J* = 7.9 Hz), 7.56 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.37 (tt, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 4.22 (q, 2H, *J* = 7.1 Hz), 1.14 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.6 (C_q), 152.0 (CH), 150.7 (C_q), 148.2 (C_q), 144.2 (C_q), 138.9 (C_q), 137.9 (C_q), 134.5 (CH), 134.4 (CH), 129.5 (CH), 129.3 (2 CH), 127.1 (CH), 123.73 (CH), 123.69 (CH), 121.8 (2 CH), 119.2 (C_q), 117.3 (C_q), 61.6 (CH_2), 14.0 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{21}H_{17}N_4O_4$: 389.1244; found: 389.1240.

Ethyl 4-(2-methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4p): colorless oil, 100%. IR: 1708, 1583, 1500, 1311, 1155, 891, 754, 729. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.28 (s, 1H), 8.28 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 7.86 (s, 1H), 7.56 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.41-7.29 (m, 4H), 7.17 (dd, 1H, *J* = 7.5 Hz, *J* = 1.2 Hz), 4.14 (q, 2H, *J* = 7.1 Hz), 1.02 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.1 (C_q), 151.8 (CH), 150.7 (C_q), 147.1 (C_q), 139.1 (C_q), 136.2 (C_q), 135.3 (CH), 135.0 (C_q), 130.0 (CH), 129.3 (2 CH), 128.6 (CH), 127.8 (CH), 126.7 (CH), 125.6 (CH), 121.6 (2 CH), 120.0 (C_q), 117.8 (C_q), 61.1 (CH_2), 19.9 (CH_3), 13.7 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{22}H_{20}N_3O_2$: 358.1550; found: 358.1555.

Ethyl 4-(2-fluorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4q): white powder, 98%, m.p.: 92°C. IR: 1709, 1585, 1504, 1313, 1255, 1149, 1016, 987, 894, 756, 534. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.27 (s, 1H), 8.26 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 8.01 (s, 1H), 7.56 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.52-7.50 (m, 1H), 7.45 (td, 1H, *J* = 7.4 Hz, *J* = 1.7 Hz), 7.39-7.31 (m, 2H), 7.23 (t, 1H, *J* = 9.1 Hz), 4.23 (qd, 2H, *J* = 7.1 Hz, *J* = 3.7 Hz), 1.13 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.0 (C_q), 159.4 (d, *J* = 248 Hz, CF), 151.8 (CH), 151.0 (C_q), 140.6 (C_q), 139.1 (C_q), 135.0 (CH), 131.0 (d, *J* = 8 Hz, CH), 130.3 (d, *J* = 3 Hz, CH), 129.4 (2 CH), 126.9 (CH), 124.3 (d, *J* = 3 Hz, CH), 124.2 (C_q), 121.8 (2 CH), 120.3 (C_q), 117.7 (C_q), 115.9 (d, *J* = 21 Hz, CH), 61.4 (CH_2), 13.9 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -115.01. HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{21}H_{17}FN_3O_2$: 362.1299; found: 362.1295.

Ethyl 1-phenyl-4-(2-(trifluoromethyl)phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4r): white crystals, 64%, m.p.: 90°C. IR: 1726, 1498, 1311, 1168, 1103, 1031. 898, 754, 534, ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.34 (s, 1H), 8.27 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 7.85 (d, 1H, *J* = 7.4 Hz), 7.79 (s, 1H), 7.70-7.61 (m, 2H), 7.56 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.37 (tt, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 7.32 (d, 1H, *J* = 7.0 Hz), 4.12 (q, 2H, *J* = 7.1 Hz), 1.00 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.4 (C_q), 151.9 (CH), 150.5 (C_q), 144.4 (C_q), 139.0 (C_q), 135.3 (q, *J* = 2.1 Hz, C_q), 135.0 (CH), 131.6 (CH), 129.7 (CH), 129.4 (2 CH), 128.7 (CH), 128.0 (q, *J* = 31 Hz, C_q), 126.9 (CH), 126.3 (q, *J* = 4.9 Hz, CH), 123.9 (q, *J* = 274 Hz, CF_3), 121.7 (2 CH), 119.6 (C_q), 118.1 (C_q), 61.1 (CH_2), 13.7 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -59.61. HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{22}H_{17}F_3N_3O_2$: 412.1267; found: 412.1262.

Ethyl 4-(2-formylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4s): white powder, 95%, m.p.: 105°C. IR: 1689, 1583, 1311 1153, 985, 758, 638. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.81 (s, 1H), 9.33 (s, 1H), 8.25 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 8.10 (dd, 1H, *J* = 7.5 Hz, *J* = 1.3 Hz), 7.79 (s, 1H), 7.74 (td, 1H, *J* = 7.5 Hz, *J* = 1.5 Hz), 7.68 (td, 1H, *J* = 7.5 Hz, *J* = 1.3 Hz), 7.56 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.40-7.33 (m, 2H), 4.13 (q, 2H, *J* = 7.1 Hz), 1.05 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 190.6 (CH), 165.4 (C_q), 151.9 (CH), 150.6 (C_q), 144.4 (C_q), 138.91 (C_q), 138.86 (C_q), 134.8 (CH), 133.8 (C_q), 133.7 (CH), 129.54 (CH), 129.45 (CH), 129.4 (2 CH), 129.3 (CH), 127.0 (CH), 121.8 (2 CH), 119.8 (C_q), 118.3 (C_q), 61.4 (CH_2), 13.8 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{22}H_{18}N_3O_3$: 372.1343; found: 372.1341.

Ethyl 4-(2-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4t): off-white powder, 97%, m.p.: 110°C. IR: 1720, 1585, 1490, 1417, 1288, 1242, 1157, 1028, 889, 800, 744. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.16 (s, 1H), 8.25 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 8.02 (s, 1H), 7.55 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.48 (ddd, 1H, *J* = 8.3 Hz, *J* = 7.5 Hz, *J* = 1.7 Hz), 7.39-7.33 (m, 2H), 7.14 (td, 1H, *J* = 7.5 Hz, *J* = 0.9 Hz), 7.03 (d, 1H, *J* = 8.3 Hz), 4.17 (q, 2H, *J* = 7.1 Hz), 3.75 (s, 3H) 1.08 (t 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.7 (C_q), 156.3 (C_q), 151.2 (CH), 151.1 (C_q), 143.3 (C_q), 139.2 (C_q), 135.4 (CH), 130.5 (CH), 129.9 (CH), 129.3 (2 CH), 126.7 (CH), 125.3 (C_q), 121.7 (2 CH), 121.1 (C_q), 120.8 (CH), 117.8 (C_q), 110.8 (CH), 61.0 (CH_2), 55.5 (CH_3), 13.9 (CH_3). HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{22}H_{19}NaN_3O_3$: 396.1319; found: 396.1304.

Ethyl 4-(5-fluoro-2-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4u): white powder, 98%, m.p.: 116°C. IR: 1718, 1498, 1244, 1157, 1029, 922, 744. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.19 (s, 1H), 8.26 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 8.01 (s, 1H), 7.55 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.36 (tt, 1H, *J* = 7.5 Hz, *J* = 1.1 Hz), 7.17 (ddd, 1H, *J* = 9.0 Hz, *J* = 8.0 Hz, *J* = 3.1 Hz), 7.11 (dd, 1H, *J* = 8.3 Hz, *J* = 3.1 Hz), 6.95 (dd, 1H, *J* = 9.0 Hz, *J* = 4.3 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 3.71 (s, 3H), 1.13 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.4 (C_q), 157.0 (d, *J* = 240 Hz, CF), 152.5 (d, *J* = 2 Hz, C_q), 151.3 (CH) 151.1 (C_q), 141.9 (d, *J* = 2 Hz, C_q), 139.2 (C_q), 135.0 (CH), 129.3 (2 CH), 126.8 (CH), 126.6 (d, *J* = 8 Hz, C_q), 121.8 (2 CH), 120.9 (C_q), 117.5 (C_q), 116.8 (d, *J* = 25 Hz, CH), 116.3 (d, *J* = 23 Hz, CH), 111.8 (d, *J* = 8 Hz, CH), 61.2 (CH_2), 56.1 (CH_3), 14.0 (CH_3). ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -123.97. HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{22}H_{18}FN_3NaO_3$: 414.1224; found: 414.1218.

Ethyl 4-(4-fluoro-2-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4v): white powder, 98%, m.p.: 109°C. IR: 1724, 1500, 1276, 1176, 1026, 948, 842, 767, 694. ^{1}H-NMR (400 MHz,

$CDCl_3$): δ = 9.16 (s, 1H), 8.25 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 7.99 (s, 1H), 7.55 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.37-7.31 (m, 2H), 6.85 (vtd, 1H, *J* = 8.2 Hz, *J* = 2.4 Hz), 6.76 (dd, 1H, *J* = 11 Hz, *J* = 2.3 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 3.73 (s, 3H), 1.14 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.6 (C_q), 164.4 (d, *J* = 249 Hz, CF), 157.7 (d, *J* = 10 Hz, C_q), 151.3 (CH), 151.1 (C_q), 142.4 (C_q), 139.2 (C_q), 135.1 (CH), 130.7 (d, *J* = 10 Hz, CH), 129.3 (2 CH), 126.7 (CH), 121.7 (2 CH), 121.2 (d, *J* = 3 Hz, C_q), 121.0 (C_q), 117.8 (C_q), 107.4 (d, *J* = 22 Hz, CH), 99.5 (d, *J* = 26 Hz, CH), 61.1 (CH_2), 55.8 (CH_3), 14.0 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -109.67. HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{22}H_{19}FN_3O_3$: 392.1405; found: 392.1405.

Ethyl 4-(5-isopropyl-2-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4w): colorless oil, 96%. IR: 2956, 1712, 1500, 1244, 1159, 1206, 754, 690. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.14 (s, 1H), 8.26 (dd, 2H, *J* = 8.5 Hz, *J* = 1.5 Hz), 8.04 (s, 1H), 7.55 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.37-7.31 (m, 2H), 7.24 (d, 1H, *J* = 2.3 Hz), 6.94 (d, 1H, *J* = 8.5 Hz), 4.17 (q, 2H, *J* = 7.1 Hz), 3.73 (s, 3H), 2.96 (hept., 1H, *J* = 6.9 Hz), 1.30 (d, 3H, *J* = 6.9 Hz), 1.29 (d, 3H, *J* = 6.9 Hz), 1.06 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.9 (C_q), 154.3 (C_q), 151.1 (C_q), 151.0 (CH), 143.5 (C_q), 141.2 (C_q), 139.2 (C_q), 135.5 (CH), 129.3 (2 CH), 128.2 (CH), 128.0 (CH), 126.6 (CH), 124.9 (C_q), 121.7 (2 CH), 121.3 (C_q), 117.7 (C_q), 110.7 (CH), 61.0 (CH_2), 55.6 (CH_3), 33.4 (CH), 24.4 (CH_3), 24.2 (CH_3), 13.8 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{25}H_{26}N_3O_3$: 416.1969; found: 416.1962.

Ethyl 4-(2-methoxynaphthalen-1-yl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4x): white powder, 46%, m.p.: 147°C. IR: 1720, 1587, 1498, 1417, 1238, 1170, 889, 806, 750, 534. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.38 (s, 1H), 8.30 (dd, 2H, *J* = 8.5 Hz, *J* = 1.1 Hz), 8.02 (d, 1H, *J* = 9.0 Hz), 7.88 (d, 1H, *J* = 7.5 Hz), 7.71 (s, 1H), 7.57 (dd, 2H, *J* = 8.5 Hz, *J* = 7.5 Hz), 7.43 (d, 1H, *J* = 9.0 Hz), 7.39-7.34 (m, 2H), 7.31 (ddd, 1H, *J* = 8.3 Hz, *J* = 6.8 Hz, *J* = 1.5 H), 7.16 (d, 1H, *J* = 8.3 Hz), 3.96 (q, 2H, *J* = 7.1 Hz), 3.82 (s, 3H), 0.72 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.1 (C_q), 153.3 (C_q), 152.1 (CH), 151.0 (C_q), 142.8 (C_q), 139.3 (C_q), 135.7 (CH), 132.4 (C_q), 130.6 (CH), 129.3 (2 CH), 128.9 (C_q), 128.3 (CH), 127.2 (CH), 126.7 (CH), 124.2 (CH), 124.0 (CH), 121.73 (C_q), 121.68 (2 CH), 119.2 (C_q), 118.7 (C_q), 113.1 (CH), 60.8 (CH_2), 56.6 (CH_3), 13.5 (CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{26}H_{22}N_3O_3$: 424.1656; found: 424.1640.

Domino preparation of tetracyclic compound 7a and 8a: In a round-bottom flask, compound **2** (150 mg, 0.497 mmol, 1 eq.), $Pd(PPh_3)_4$ (29 mg, 5 mol%), boronic acid **3a-x** (0.596 mmol, 1.2 eq.), and Na_2CO_3 (105 mg, 0.998 mmol, 2 eq.) were weighed, and carefully purged with Ar. Degassed toluene (3 mL), ^{t}BuOH (1.5 mL), and water (0.5 mL) were added, and the solution was heated at 75°C for 18 hours. The crude mixture was cooled to room temperature, diluted with water (10 mL) and CH_2Cl_2 (10 mL), and filtered to afford the product with satisfying purity.

3-Phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one (7a): purple powder, 83%, m.p.: 250°C (dec.). IR: 1720, 1593, 1571, 1548, 1502, 1448, 1425, 1328, 1261, 1207, 1151, 981, 840, 752. ^{1}H-NMR (400 MHz, TFA-*d*): δ = 9.85 (s, 1H), 9.58 (s, 1H), 8.90 (d, 1H, *J* = 7.8 Hz), 8.13 (t, 1H, *J* = 7.8 Hz), 7.88 (t, 1H, *J* = 7.8 Hz), 7.85-7.78 (m, 5H), 7.76 (d, 1H, *J* = 7.8 Hz). ^{13}C-NMR (100 MHz, TFA-*d*): δ = 163.4 (C_q), 156.5 (C_q), 149.7 (CH), 149.3 (C_q), 145.3 (C_q), 140.6 (CH), 139.4 (CH), 136.0 (C_q), 134.2 (CH), 132.7 (2 CH), 130.4 (CH), 129.6 (CH), 127.4 (2 CH), 121.1 (CH), 116.8 (C_q), 116.1 (C_q), 114.0 (C_q). HRMS-APCI: *m/z* $[M+H]^+$ calcd. for $C_{19}H_{13}N_3O_2$: 314.0924; found: 314.0919.

3-Phenyl-3*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridin-6(7*H*)-one (8a): purple powder, 100%, m.p.: > 365°C (dec). IR: 2879, 1680, 1595, 1575, 1504, 1421, 1342, 1292, 987, 927, 804, 742. ^{1}H-NMR (400 MHz, TFA-*d*): δ = 9.93 (s, 1H), 9.56 (s, 1H), 8.93 (d, 1H, *J* = 8.0 Hz), 8.04 (t, 1H, *J* = 8.0 Hz), 7.78 (t, 1H, *J* = 8.0 Hz), 7.75-7.69 (m, 5H), 7.67 (d, 1H, *J* = 8.0 Hz). ^{13}C-NMR (100 MHz, TFA-*d*): δ = 163.5 (C_q), 149.1 (C_q), 147.8 (CH), 143.0 (C_q), 141.8 (C_q), 140.2 (CH), 139.6 (CH), 135.8 (C_q), 134.4 (CH), 132.9 (2 CH), 130.7 (CH), 128.9 (CH), 127.4 (2 CH), 120.6 (CH), 117.9 (C_q), 117.8 (C_q), 117.0 (C_q). HRMS-APCI: *m/z* $[M+H]^+$ calcd. for $C_{19}H_{13}N_4O$: 313.1084; found: 313.1084.

Preparation of chromenone derivatives 7a-7e through BBr_3 cyclization: To a solution of **4t-4x** (0.14 mmol) in CH_2Cl_2 (0.8 mL) was added BBr_3 (4 eq., 560 µL, 1M solution in CH_2Cl_2). After stirring at room temperature for 18 hours, a KOH solution (20 eq., 2M in water) was added, and stirred for 15 minutes. The organic and aqueous layers were separated, and the latter was extracted with CH_2Cl_2 (3 x 50mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, pure EtOAc or CH_2Cl_2/MeOH 9:1).
In the case of compounds **7c** and **7e**, the same procedure was followed at the beginning. After stirring at room temperature for 18 hours, water (2 mL) and toluene (10 mL) were added, and heated at reflux with a Dean-Stark apparatus for 18 h. Concentration of the crude mixture, followed by purification by flash column chromatography (SiO_2, pure EtOAc or CH_2Cl_2/MeOH 9:1) afforded the expected compounds.

3-Phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one (7a): white powder, 86%.

10-Fluoro-3-phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one (7b): white powder, 94%, m.p.: 360°C (dec.). IR: 1730, 1575, 1552, 1500 1448, 1259, 1182, 1122, 1008, 839, 750. ^{1}H-NMR (400 MHz, TFA-*d*): δ = 9.68 (s, 1H), 9.33 (s, 1H), 8.32 (dd, 1H, *J* = 7.9 Hz, *J* = 2.2 Hz), 7.74-7.66 (m, 7H). ^{13}C-NMR (100 MHz, TFA-*d*): δ = 163.7 (C_q), 162.7 (d, *J* = 250 Hz, CF), 152.4 (d, *J* = 1.6 Hz, C_q), 151.5 (CH), 147.5 (C_q), 147.0 (C_q), 138.4 (CH), 136.4 (C_q), 133.9 (CH), 132.6 (2 CH), 127.6 (2 CH), 127.1 (d, *J* = 25 Hz, CH), 122.9 (d, *J* = 8.6 Hz, CH), 117.9 (C_q), 115.5 (d, *J* = 26 Hz, CH), 115.1 (C_q), 113.9 (C_q). ^{19}F-NMR (282 MHz, DMSO-d_6): δ = -115.51. HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{19}H_{11}FN_3O_2$: 332.0830; found: 332.0832.

9-Fluoro-3-phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one (7c): yellow powder, 53%, m.p.: 197°C. IR: 1741, 1727, 1602, 1503, 1333, 1271, 1153, 759. ^{1}H-NMR (400 MHz, TFA-*d*): δ = 9.62 (s, 1H), 9.34 (s, 1H), 8.75 (dd, 1H, *J* = 9.0 Hz, *J* = 5.4 Hz), 7.62-7.57 (m, 5H), 7.39 (dd, 1H, *J* = 9.0 Hz, *J* = 6.7 Hz), 7.24 (dd, 1H, *J* = 8.3 Hz, *J* = 2.1 Hz). ^{13}C-NMR (100 MHz, TFA-*d*): δ = 170.9 (d, *J* = 266 Hz, CF), 163.1 (C_q), 158.3 (d, *J* = 14 Hz, C_q), 150.5 (CH), 148.3 (C_q), 146.0 (C_q), 139.1 (CH), 136.1 (C_q), 134.2 (CH), 133.1 (d, *J* = 12 Hz, CH), 132.7 (2 CH), 127.6 (2 CH), 118.1 (d, *J* = 24 Hz, CH), 115.4 (C_q), 113.8 (d, *J* = 3 Hz, C_q), 113.3 (C_q), 108.6 (d, *J* = 26 Hz, CH). ^{19}F-NMR (282 MHz, TFA-*d*): δ = -99.13. HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{19}H_{11}FN_3O_2$: 332.0830; found: 332.0828.

10-Isopropyl-3-phenylchromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-6(3*H*)-one (7d): white powder, 83%, m.p.: 217°C (dec). IR: 1718, 1595, 1502, 1219, 1112, 979, 815, 750, 671. ^{1}H-NMR (400 MHz, TFA-*d*): δ = 9.62 (s, 1H), 9.31 (s, 1H), 8.42 (d, 1H, *J* = 1.8 Hz), 7.83 (dd, 1H, *J* = 8.7 Hz, *J* = 1.8 Hz), 7.61-7.56 (m, 5H), 7.46 (d, 1H, *J* = 8.7 Hz), 3.11 (hept., 1H, *J* = 6.9 Hz), 1.31 (d, 6H, *J* = 6.9 Hz). ^{13}C-NMR (100 MHz, TFA-*d*): δ = 163.7 (C_q), 154.9 (C_q), 152.0 (C_q), 149.8 (CH), 149.6 (C_q), 145.1 (C_q), 139.6 (CH), 139.4 (CH), 136.1 (C_q), 134.2 (CH), 132.8 (2 CH), 127.5 (2 CH), 127.5 (CH), 121.1 (CH), 116.7 (C_q), 116.2 (C_q), 114.0 (C_q), 36.1 (CH), 24.5 (2 CH_3). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{22}H_{18}N_3O_2$: 356.1394; found: 356.1395.

13-Phenylbenzo[5,6]chromeno[4,3-*d*]pyrazolo[3,4-*b*]pyridin-3(13*H*)-one (7e): yellow powder, 64%, m.p.: 205°C (dec). IR: 2922, 1735, 1560, 1506, 1311, 1220, 1112, 1018, 979, 750, 692, 680. ^{1}H-NMR (400 MHz, TFA-*d*): δ = 9.68 (s, 1H), 9.16 (s, 1H), 8.72 (d, 1H, *J* = 8.4 Hz), 8.36 (d, 1H, *J* = 9.0 Hz), 8.06 (d, 1H, *J* = 8.0 Hz), 7.81 (dd, 1H, *J* = 8.4 Hz, *J* = 7.2 Hz), 7.73 (dd, 1H, *J* = 8.0 Hz, *J* = 7.2 Hz), 7.67-7.61 (m, 5H), 7.55 (d, 1H, *J* = 9.0 Hz). ^{13}C-NMR (100 MHz, TFA-*d*): δ = 163.4 (C_q), 158.4 (C_q), 148.9 (C_q), 148.8 (CH), 144.5 (C_q), 143.4 (CH), 141.2 (CH), 136.0 (C_q), 134.6 (C_q), 134.3 (CH), 132.9 (2 CH), 132.11 (CH), 132.06 (CH), 131.3 (C_q), 130.6 (CH), 127.4 (2 CH), 126.9 (CH), 118.7 (CH), 117.5 (C_q), 114.3 (C_q), 112.6 (C_q). HRMS-ESI: m/z $[M+H]^+$ calcd. for $C_{23}H_{14}N_3O_2$: 364.1081; found: 364.1068.

Preparation of naphthyridinones-derivatives 8a-e: In a round-bottom flask, compound **2** (150 mg, 0.497 mmol, 1 eq.), $Pd(PPh_3)_4$ (29 mg, 5 mol%), boronic acid **11a-e** (0.746 mmol, 1.5 eq.), and Na_2CO_3 (210 mg, 1.966 mmol, 4 eq.) were weighed, and carefully purged with Ar. Degassed toluene (3 mL), ^{t}BuOH (1.5 mL), and water (0.5 mL) were added, and the solution was heated at 75°C for 5-18 hours. The crude mixture was cooled down to room temperature, diluted with a saturated aqueous solution of Na_2CO_3 (10 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude mixture was filtered on silica gel (pentane/EtOAc 80:20), evaporated, and the crude mixture was stirred with TFA (0.2 mL) in CH_2Cl_2 (0.8 mL) at room temperature for 18h. Evaporation under reduced pressure followed by trituration in CH_2Cl_2 afforded the product with satisfying purity.

3-Phenyl-3*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridin-6(7*H*)-one (8a): white powder, 71%.

10-Fluoro-3-phenyl-3*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridin-6(7*H*)-one (8b): white powder, 77%, m.p.: > 360°C. IR: 1685, 1577, 1446, 1337, 1281, 1197, 951, 868, 816, 754. ^{1}H-NMR (400 MHz, TFA-*d*): δ = 9.78 (s, 1H), 9.35 (s, 1H), 8.37 (dd, 1H, *J* = 8.4 Hz, *J* = 1.6 Hz), 7.61-7.54 (m, 7H). ^{13}C-NMR (100 MHz, TFA-*d*): δ = 163.5 (C_q), 162.6 (d, *J* = 250 Hz, CF), 148.7 (CH), 147.6 (d, *J* = 4 Hz, C_q), 143.9 (C_q), 138.9 (CH), 138.1 (d, *J* = 2 Hz, C_q), 136.0 (C_q), 134.3 (CH), 132.8 (2 CH), 128.1 (d, *J* = 25 Hz, CH), 127.5 (2 CH), 122.7 (d, *J* = 9 Hz, CH), 118.6 (d, *J* = 9 Hz, C_q), 118.1 (C_q), 116.7 (C_q), 115.7 (d, *J* = 25 Hz, CH). ^{19}F-NMR (282 MHz, DMSO-d_6): δ = -118.60. HRMS-APCI: *m/z* $[M+H]^+$ calcd. for $C_{19}H_{12}FN_4O$: 331.0990; found: 331.0986.

10-Chloro-3-phenyl-3*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridin-6(7*H*)-one (8c): white powder, 71%, m.p.: > 360°C. IR: 2867, 1677, 1592, 1573, 1501, 1424, 1332, 1007, 932, 800, 756. ^{1}H-NMR (400 MHz, TFA-*d*): δ = 9.69 (s, 1H), 9.29 (s, 1H), 8.58 (d, 1H, *J* = 2.0 Hz), 7.70 (dd, 1H, *J* = 8.9 Hz, *J* = 2.0 Hz), 7.51-7.46 (m, 5H), 7.39 (d, 1H, *J* = 8.9 Hz). ^{13}C-NMR (100 MHz, TFA-*d*): δ = 163.5 (C_q), 148.6 (CH), 147.2 (C_q), 143.9 (C_q), 140.0 (C_q), 139.7 (CH), 139.0 (CH), 136.0 (C_q), 135.0 (C_q), 134.3 (CH), 132.8 (2 CH), 129.5 (CH), 127.5 (2 CH), 121.9 (CH), 118.7 (C_q), 118.1 (C_q), 116.6 (C_q). HRMS-APCI: *m/z* $[M+H]^+$ calcd. for $C_{19}H_{12}ClN_4O$: 347.0694; found: 347.0697.

10-Methyl-3-phenyl-3*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridin-6(7*H*)-one (8d): white powder, 73%, m.p.: 358°C (dec.). IR: 2862, 1661, 1594, 1577, 1499, 1420, 1333, 985, 942, 800. ^{1}H-NMR (400 MHz, TFA-*d*): δ = 9.73 (s, 1H), 9.36 (s, 1H), 8.49 (s, 1H), 7.70 (d, 1H, *J* = 8.4 Hz), 7.54-7.52 (m, 5H), 7.39 (d, 1H, *J* = 8.4 Hz), 2.47 (s, 3H). ^{13}C-NMR (100 MHz, TFA-*d*): δ = 163.5 (C_q), 148.8 (C_q), 147.9 (CH), 142.9 (C_q), 141.9 (CH), 140.4 (C_q), 139.8 (C_q), 139.6 (CH), 135.8 (C_q), 134.3 (CH), 132.9 (2 CH), 129.8 (CH), 127.4 (2 CH), 120.6 (CH), 117.9 (C_q), 117.8 (C_q), 116.9 (C_q), 21.8 (CH_3). HRMS-APCI: *m/z* $[M+H]^+$ calcd. for $C_{20}H_{15}N_4O$: 327.1240; found: 327.1231.

10-Methoxy-3-phenyl-3*H*-benzo[*c*]pyrazolo[4,3-*f*][2,7]naphthyridin-6(7*H*)-one (8e): yellow powder, 78%, m.p.: 332°C. IR: 1667, 1578, 1504, 1231, 1100, 1036, 991, 815, 750. ^{1}H-NMR (400 MHz, TFA-*d*): δ = 9.90 (s, 1H), 9.51 (s, 1H), 8.28 (d, 1H, *J* = 1.7 Hz), 7.70-7.64 (m, 7H), 4.08 (s, 3H). ^{13}C-NMR (100 MHz, TFA-*d*): δ = 163.2 (C_q), 159.9 (C_q), 148.3 (CH), 148.0 (C_q), 143.2 (C_q), 139.3 (CH), 136.3 (C_q), 135.9 (C_q), 134.3 (CH), 132.9 (2 CH), 128.1 (CH), 127.4 (2 CH), 122.2 (CH), 118.8 (C_q), 117.9 (C_q), 116.8 (C_q), 113.4 (CH), 57.8 (CH_3). HRMS-APCI: *m/z* $[M+H]^+$ calcd for $C_{20}H_{15}N_4O_2$: 343.1190; found: 343.1184.

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Keywords: pyrazolo[3,4-*b*]pyridine • Suzuki • tandem reaction • chromenopyrazolopyridine • naphthyridinones

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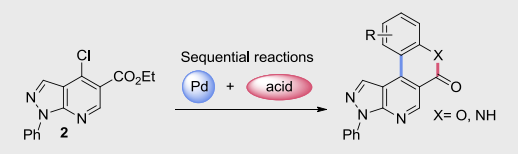

Preparation of chromenopyrazolopyridine and naphthyridinone families is described from well-known intermediate **2** *via* a sequential Suzuki cross-coupling reaction / acidic cyclization.

Heterocycles*

*H. Lavrard, F. Popowycz**

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Harnessing cascade Suzuki-cyclization reactions of pyrazolo[3,4-*b*]pyridine for the synthesis of tetracyclic fused heteroaromatics