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An Expedient Approach to Pyrazolo[3,4-*b*]pyridine-3-carboxamides via Palladium-Catalyzed Aminocarbonylation

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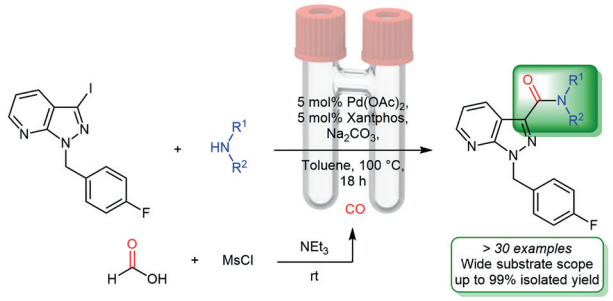

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Abstract Pyrazolo[3,4-*b*]pyridine is a privileged scaffold found in many small drug molecules that possess a wide range of pharmacological properties. Efforts to further develop and exploit synthetic methodologies that permit the functionalization of this heterocyclic moiety warrant investigation. To this end, a series of novel 1,3-disubstituted pyrazolo[3,4-*b*]pyridine-3-carboxamide derivatives have been prepared by introducing the 3-carboxamide moiety using palladium-catalyzed aminocarbonylation methodology and employing CO gas generated ex situ using a two-chamber reactor (COware®). The functional group tolerance of this optimized aminocarbonylation protocol is highlighted through the synthesis of a range of diversely substituted C-3 carboxamide pyrazolo[3,4-*b*]pyridines in excellent yields of up to 99%.

Key words pyrazolo[3,4-*b*]pyridine, 7-azaindazole, palladium, aminocarbonylation, carboxamide

From a pharmaceutical perspective, the development of synthetic strategies affording pyrazolo[3,4-*b*]pyridine derivatives is of significant interest. The pyrazolo[3,4-*b*]pyridine heterocyclic motif is a privileged scaffold, present in a large number of biologically active small molecules. For example, 1,3-disubstituted pyrazolo[3,4-*b*]pyridines, **1** [riociguat, Adempas® (Bayer)] and **2** [vericiguat, Verquvo® (Merck)] both possess vasodilatory properties (Figure 1).[1] Moreover, pyrazolo[3,4-*b*]pyridine derivatives, including **3**–**6** and **7**, have been shown to possess anticancer[2–5] and antiviral activity,[6] respectively. Several examples of central nervous system (CNS) active agents also contain a pyrazolo[3,4-*b*]pyridine heterocyclic core and have been investigated for their potential use in the treatment of neurological disorders, such as multiple sclerosis (**8**),[7] Parkinson's disease (**9**),[8] and Alzheimer's disease (**10**).[9] Furthermore, recent literature has highlighted that certain 1,3-disubstituted pyrazolo[3,4-*b*]pyridines, such as **11**, possess high affinity and efficacy at both the cannabinoid receptor subtypes 1 and 2.[10]

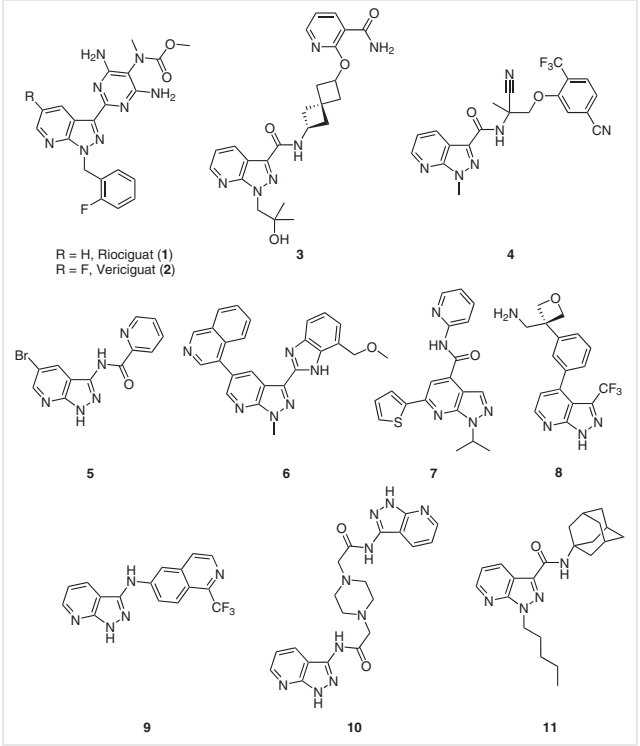
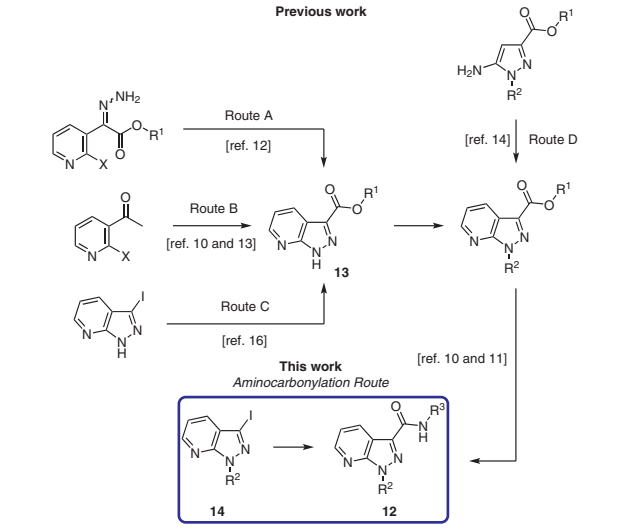


Figure 1 Examples of biologically active pyrazolo[3,4-*b*]pyridine derivatives **1**–**11**[1–10]

As part of ongoing work in our laboratory, we became interested in accessing a series of *N*-1-substituted pyrazolo[3,4-*b*]pyridine-3-carboxamide derivatives **12** (Scheme 1). Pyrazolo[3,4-*b*]pyridine **13** represents a pivotal intermediate in the synthesis of carboxamide **12**. However, several previous reports[10–14] outlining the preparation of *N*-1-

substituted pyrazolo[3,4-*b*]pyridine **12** often require multistep routes (Scheme 1, Routes A–D). Palladium-catalyzed alkoxycarbonylation has previously been employed to great effect to furnish C-3 carboxylate esters of indazole[15] and pyrazolo[3,4-*b*]pyridine.[16] Blake and co-workers have prepared pyrazolo[3,4-*b*]pyridine-3-carboxamide derivatives under Pd-catalyzed aminocarbonylative conditions, using a balloon of CO, albeit in poor yield.[17] Similarly, Kannaboina et al. have demonstrated the Pd-catalyzed aminocarbonylation of a limited number (n = 3) of 3-iodo-1*H*-pyrazolo[3,4-*b*]-pyridines in fair yield (57–70%) using CO generated in situ.[18] Thus, considering these suboptimal yields and tedious purification steps associated with routes A–D, we aimed to explore and develop an efficient aminocarbonylation strategy that would permit rapid and direct access to a wide range of functionally diverse pyrazolo[3,4-*b*]pyridine-3-carboxamide derivatives **12** from aryl iodide **14** in high yield.



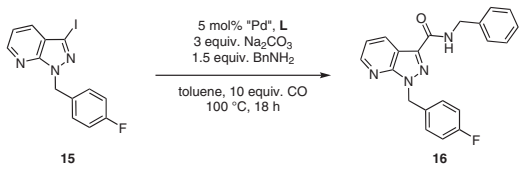
Scheme 1 Synthetic methods for the preparation of N-1-substituted pyrazolo[3,4-*b*]pyridine-3-carboxamides **12**

While carbon monoxide (CO) gas has been utilized for decades as part of many useful synthetic industrial processes,[19] the handling and manipulation of this toxic and flammable gas presents significant safety concerns. Prior to recent advances made by the Skrydstrup group,[20,21] transition-metal-catalyzed aminocarbonylative transformations were carried out using pressurized autoclave reactors[22] or performed at atmospheric pressure using a balloon of CO gas. Several aminocarbonylation procedures utilize CO generated in situ using liquid or solid CO surrogates, such as chloroform,[18,23] dimethylformamide,[24] and metal carbonyl derivatives.[25–27] Although the latter approach obviates the use of CO gas, the CO surrogate and/or by-products thereof may potentially hinder the desired aminocarbonylation reaction.[20] Alternatively, ex situ CO generation has been successfully applied in dual-chamber reaction vessels.[28–32] Verseyer et al. have generated CO ex situ, from formic acid, mesyl chloride, and triethylamine, facilitating aminocarbonylative transformations to great effect.[33] Comprehensive reviews[19,34–36] indicate that a wide array of palladium catalysts and ligands may be used to facilitate palladium-catalyzed aminocarbonylations. To this end, the initial investigation of our desired pyrazolo[3,4-*b*]pyridine-3-carboxamide **12** panel sought to examine the effect of varying the palladium catalyst precursor and ligand, whilst using a two-chamber reaction vessel (COware®)[20] and ex situ generated CO,[33] on the conversion of aryl iodide **15**[37] to exemplar pyrazolo[3,4-*b*]pyridine **16** (Table 1).

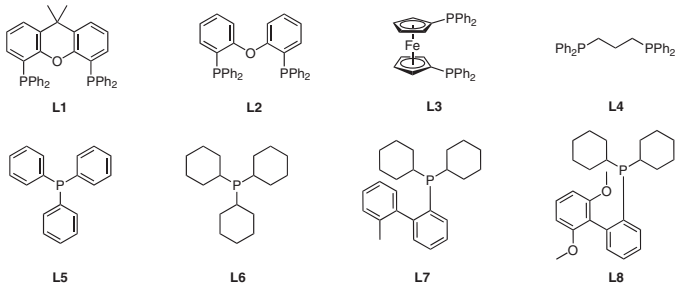
The reaction of aryl iodide **15** with our chosen amine nucleophile, benzylamine, proceeded smoothly to furnish the desired C-3 carboxamide **16** in good to excellent yield when employing several palladium catalyst precursors (5 mol%), including $PdCl_2$ (72%), $Pd(dba)_2$ (84%), and $Pd(OAc)_2$ (95%) (Table 1, entries 1–3), in the presence of Xantphos (**L1**) (5 mol%). Taking $Pd(OAc)_2$ as the optimal catalyst precursor, we then screened a range of mono- and bidentate phosphane ligands to determine the impact of ligand variation on the yield of carboxamide **16** (Table 1, entries 4–10). When compared with Xantphos (**L1**, bite angle 107°) (95% yield **16**; Table 1, entry 3), DPEphos (**L2**, bite angle 103°), dppf (**L3**, bite angle 96°), and dppp (**L4**, bite angle 91°) all gave **16** in significantly lower yields (16–46%, Table 1, entries 4–6).[38] Notably, employing DPEphos (**L2**) as ligand showed a greater than two-fold decrease in the yield of amide **16** (Table 1, entry 4), despite having similar electronic properties to Xantphos (**L1**). These latter results (Table 1, entries 1–10) suggest that optimal conversion of aryl iodide **15** to C-3 carboxamide **16** is achieved when a wide bite angle phosphane ligand, such as Xantphos (**L1**), is employed. Notably, while screening several bidentate phosphane ligands for the Pd-catalyzed carbonylation of aryl bromides, Buchwald and co-workers found that Xantphos (**L1**) gave superior results when compared with similar bidentate phosphane ligands that possess a similar bite angle, such as DPEphos and dppf.[39] This latter finding has been attributed to the flexibility of the backbone of **L1** (flexibility range 97–133°)[40] which may provide a dynamic coordination environment and facilitate distinct steps in the catalytic cycle.[39]

To probe the effect of monodentate phosphane ligands **L5**–**L8** on the formation of **16**, a series of electron-rich ligands possessing varying degrees of steric bulk, including PPh_3 (**L5**; Tolman cone angle Θ = 145°), PCy_3 (**L6**; Θ = 170°),[41] MePhos (**L7**; Θ = 190°), and SPhos (**L8**; Θ = 205°),[42] were investigated (Table 1, entries 7–10). While PPh_3 furnished amide **16** in very good yield (87%, Table 1, entry 7), the use of bulkier monodentate phosphane ligands with a larger Tolman cone angle (≥170°) only gave **16** in moderate yields (62–68%, Table 1, entries 8–10). Although bulkier ligands can facilitate the reductive elimination step of the catalytic cycle, CO coordination and/or acyl insertion into

Table 1 Effect of Pd Catalyst Precursor and Phosphine Ligand on the Yield of **16**[a,b,c]



15 16



L1 L2 L3 L4 L5 L6 L7 L8

Entry	Catalyst precursor	Ligand (mol%)	Yield of **16** (%)[d]
1	$PdCl_2$	**L1** (5)	72
2	$Pd(dba)_2$	**L1** (5)	84
3	$Pd(OAc)_2$	**L1** (5)	95
4	$Pd(OAc)_2$	**L2** (5)	46
5	$Pd(OAc)_2$	**L3** (5)	26
6	$Pd(OAc)_2$	**L4** (5)	16
7	$Pd(OAc)_2$	**L5** (10)	87
8	$Pd(OAc)_2$	**L6** (10)	62
9	$Pd(OAc)_2$	**L7** (10)	68
10	$Pd(OAc)_2$	**L8** (10)	64
11	$Pd(OAc)_2$	–	22
12	–	**L1** (5)	0

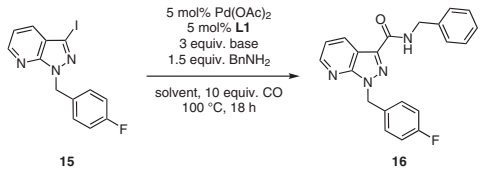
[a] Reaction scale: 0.14 mmol (with respect to aryl iodide **15**).
[b] Reaction concentration: 0.5 M (with respect to aryl iodide **15**).
[c] CO was generated ex situ.[33]
[d] Isolated yield following wet flash column chromatography.

the aryl carbon-palladium bond may be hindered by sterically demanding ligands.[43–45]

Following the identification of **L1** as the optimal ligand for the carbonylation of **15** to give amide **16**, control experiments to examine the necessity of the bidentate phosphane ligand revealed that, in the absence of Xantphos, the yield of **16** is significantly reduced (22% vs 95%, Table 1, entries 11 and 3, respectively). As expected, in the absence of $Pd(OAc)_2$, the formation of carboxamide **16** was not observed (Table 1, entry 12). These latter control experiments highlight the crucial role that both $Pd(OAc)_2$ and Xantphos play in the aminocarbonylation of aryl iodide **15** to afford **16**. Attempts to substitute sodium carbonate with other bases, such as potassium carbonate or triethylamine did not significantly impact the yield of **16** (Table 2, entries 1 and 2 vs Table 1, entry 3). However, replacing toluene with polar aprotic solvents, such as dimethylformamide (DMF) and dimethyl sulfoxide, (DMSO) caused a notable decline in the yield of carboxamide **16** from 95% (Table 1, entry 3) to 58% and 38%, respectively (Table 2, entries 3 and 4).

Numerous reports[23,33,46,47] outlining the aminocarbonylation of aryl (psuedo)halides typically describe the use of between 1 to 3 equivalents of CO surrogate. To determine if the transformation of **15** to carboxamide **16** could be achieved with less than 10 equivalents of CO, our attention turned to reducing the number of equivalents of our chosen CO surrogate (formic acid, mesyl chloride, and triethylamine)[33] with respect to aryl iodide **15** (Table 3), while keeping all other variables constant including the COware® apparatus volume (20 mL). Notably, lowering the CO

Table 2 Effect of Base and Solvent on the Yield of **16**[a,b,c]



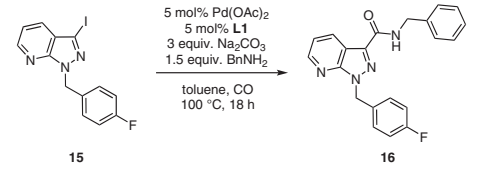
15 16

Entry	Base	Solvent	Yield of **16** (%)[d]
1	K_2CO_3	toluene	90
2	NEt_3	toluene	86
3	Na_2CO_3	DMF	58
4	Na_2CO_3	DMSO	38

[a] Reaction scale: 0.14 mmol (with respect to aryl iodide **15**).
[b] Reaction concentration: 0.5 M (with respect to aryl iodide **15**).
[c] CO was generated ex situ.[33]
[d] Isolated yield following wet flash column chromatography.

surrogate from 10 equivalents (Table 1, entry 3) to 5 equivalents (Table 3, entry 1), with respect to aryl iodide **15**, did not cause a significant decline in the yield of carboxamide **16** (95% vs 89%, respectively). However, a significant decrease in the yield of **16** was observed (50%, Table 3, entry 2), when employing only 2.5 equivalents of the CO surrogate. Interestingly, scaling the reaction up to 1 mmol **15** (Table 3, entry 3) from 0.14 mmol (Table 1, entry 3), while keeping the amount of CO surrogate constant (1.4 mmol) and COware® apparatus volume (20 mL) constant, permitted access to amide **16** in a comparably high yield (94%). The latter result indicates that **16** can be obtained in excellent yield under specific conditions using only 1.4 equivalents of CO surrogate, rather than a ten-fold excess.

Table 3 Effect of Variation of CO Equivalents on the Yield of **16**[a,b]



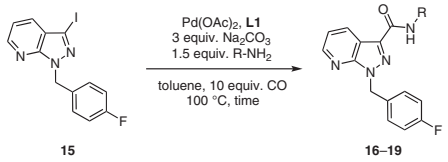
15 16

Entry	CO (equiv.)	Yield of **16** (%)[c]
1	5	89[d]
2	2.5	50[d]
3	1.4	94[e]

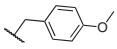
[a] Reaction concentration: 0.5 M (with respect to aryl iodide **15**).
[b] CO was generated ex situ.[33]
[c] Isolated yield following wet flash column chromatography.
[d] Reaction scale: 0.14 mmol (with respect to aryl iodide **15**).
[e] Reaction scale: 1 mmol (with respect to aryl iodide **15**).

Efforts to examine the effect of catalyst loading on the yield of **16** (Table 4, entries 1–3) from 5 mol% $Pd(OAc)_2$ and **L1** (Table 1, entry 3) revealed that the carboxamide could still be obtained in excellent yield (98%) using a 10-fold lower precatalyst and ligand load of 0.5 mol% $Pd(OAc)_2$ and **L1**, respectively (Table 4, entry 3). Furthermore, attempts to reduce the reaction time for the transformation of **15** to **16** (Table 4, entries 4–6) showed that the conversion of aryl iodide **15** proceeded to give the desired C-3 carboxamide **16** in near quantitative yield (99%, Table 4, entry 6) in only 15 minutes. To our knowledge, such comparable rapid aminocarbonylative transformations have only previously been reported under microwave-heating reaction conditions.[48,49] Using the latter 15-minute protocol, the *p*-methoxy congener of **17** was similarly obtained in excellent yield (93%, Table 4, entry 7).

Table 4 Optimization of Catalyst Loading and Reaction Time for Carboxamides **16–19**[a,b,c]



15 16–19

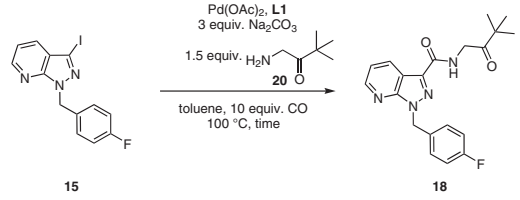
Entry	R	$Pd(OAc)_2$ (mol%)	**L1** (mol%)	Time (h)	Product	Yield (%)[d]
1	Bn	2.5	2.5	18	**16**	96
2	Bn	1	1	18	**16**	98
3	Bn	0.5	0.5	18	**16**	98
4	Bn	0.5	0.5	1	**16**	99
5	Bn	0.5	0.5	0.5	**16**	97
6	Bn	0.5	0.5	0.25	**16**	99
7		0.5	0.5	0.25	**17**	93
8		0.5	0.5	0.25	**18**	12
9		0.5	0.5	0.25	**19**	23

[a] Reaction scale: 0.14 mmol (with respect to aryl iodide **15**).
[b] Reaction concentration: 0.5 M (with respect to aryl iodide **15**).
[c] CO was generated ex situ.[33]
[d] Isolated yield following wet flash column chromatography.

However, further extension of these conditions to other intended amine nucleophile substrates (Table 4, entries 8 and 9) proved to be relatively unsuccessful, affording carboxamide derivatives **18** and **19** in poor yield (12% and 23%, respectively), and suggested that the 15-minute reaction time may only be applicable to a limited range of desirable targets.

Aiming to identify an adequately general set of reaction conditions that would provide access to a diverse range of pyrazolo[3,4-*b*]pyridine-3-carboxamide derivatives in excellent yield, α-keto amine nucleophile **20** (employed in Table 4, entry 8) was chosen for further investigation (Table 5). Initial attempts to improve the yield of carboxamide **18**, through increasing the reaction time from 15 minutes (Table 4, entry 8) to 1 hour (Table 5, entry 1) were met with disappointment (19%, yield **18**). Furthermore, increasing the Pd catalyst loading from 0.5 mol% to 1 mol% furnished **18** in similarly poor yield after 1 hour (24%, Table 5, entry 2) and 51% yield after 6 hours (Table 5, entry 3). Importantly, employing our initial reaction conditions, using 5 mol% catalyst loading and a prolonged reaction time (18 h) (see Table 1, entry 3), furnished the desired pyrazolo[3,4-*b*]pyridine **18** in excellent yield (93%, Table 5, entry 4). This result also suggests the Table 1, entry 3 protocol to be potentially generative towards the efficient synthesis of a disparate range of pyrazolo[3,4-*b*]pyridine-3-carboxamides.

Table 5 Effect of Catalyst Loading and Reaction Time on the Yield of **18**[a,b,c]



Entry	$Pd(OAc)_2$ (mol%)	**L1** (mol%)	Time (h)	Yield (%)[c]
1	0.5	0.5	1	19
2	1	1	1	24
3	1	1	6	51
4	5	5	18	93

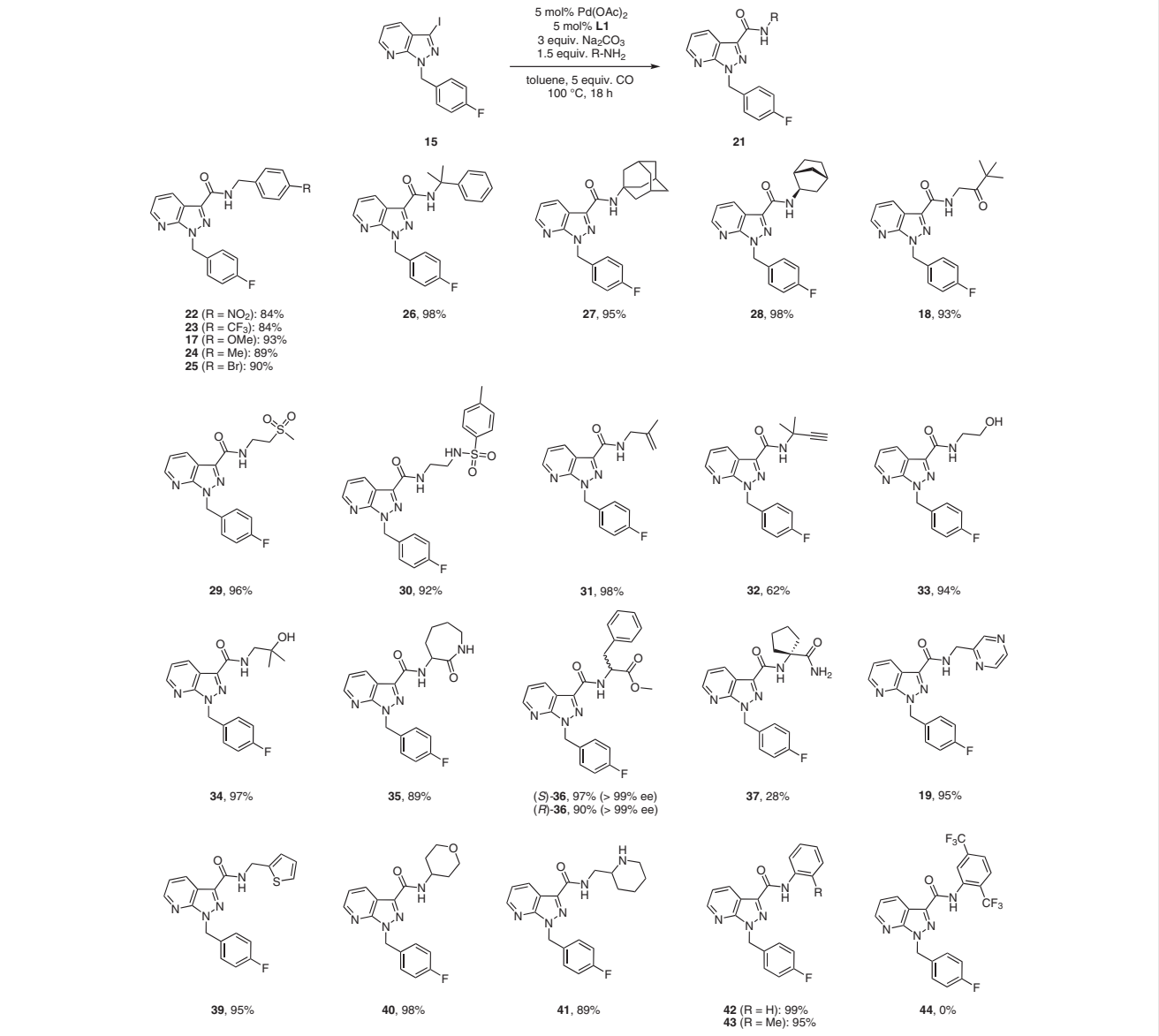
[a] Reaction scale: 0.14 mmol (with respect to aryl iodide **15**).
[b] Reaction concentration: 0.5 M (with respect to aryl iodide **15**).
[c] CO was generated ex situ.[33]
[d] Isolated yield following wet flash column chromatography.

To investigate further the generality of our initial aminocarbonylation protocol (Table 1, entry 3), we applied the methodology to the synthesis of a diverse range of pyrazolo[3,4-*b*]pyridine-3-carboxamides **21** employing a wide array of primary amine substrates (Scheme 2). Varying the electronic properties of benzylamine, our prototypical amine nucleophile, had little effect on the isolated yield of respective C-3 carboxamides **17** (*p*-OMe) and **22**–**25**. For example, the inclusion of electron-withdrawing substituents (*p*-NO_2 and *p*-CF_3) both gave carboxamides **22** and **23** in 84% yield. Notably, no evidence of palladium-catalyzed reduction of the nitro functionality of pyrazolo[3,4-*b*]pyridine **22** was observed under these investigated conditions. Similarly, the presence of electron-donating groups, including *p*-OMe and *p*-Me, gave the corresponding amides **17** and **24** in excellent yields of 93% and 89%, respectively.

The protocol tolerates the presence of a *p*-Br substituent (90%, yield **25**). While aryl iodides are more reactive than aryl bromides under typical aminocarbonylation conditions,[50] the latter result highlights both the chemoselectivity and utility of this transformation, offering a potential synthetic handle for subsequent functionalization of pyrazolo[3,4-*b*]pyridine **25**. Further incorporation of sterically hindered amine nucleophiles, including cumylamine and 1-adamantylamine, proceeded smoothly under the optimized conditions to give the desired amides **26** and **27** in excellent yield (98% and 95%, respectively). Similarly, inclusion of the bridged bicycloalkane, norbornylamine, furnished the corresponding product **28** in 98% yield.

The aminocarbonylation protocol demonstrated a high degree of tolerance for various functional groups, exemplified by sulfone (96% yield), sulfonamide (92%), and alkenyl (98%) derivatives, **29**, **30**, and **31**, respectively. However, terminal alkyne **32** was obtained in a comparatively lower yield (62% **32** vs >90% **29**–**31**). Evidence for the formation of several oligomeric by-products, likely arising from the uncontrolled aminocarbonylation of the reactive terminal alkynyl CH of **32**,[51–53] was observed using high-resolution mass spectrometry (HRMS) (see Supporting Information). Efforts to further probe the chemoselectivity of the catalyst system, using ethanolamine and the related *gem*-dimethyl congener as nucleophiles, revealed that, in both cases, carbonylation occurs via the N atom, rather than the O atom, to afford carboxamides **33** (94% yield) and **34** (97% yield), respectively, rather than their analogous carboxylate ester derivatives. Bisamide **35** and methyl esters (*S*)-**36** and (*R*)-**36** could be prepared in high yield (89%, 97%, and 90%, respectively), without any observable evidence of lactam or ester hydrolysis. Importantly, using chiral chromatography (see Supporting Information), it was possible to demonstrate that racemization of α-amino ester derivative enantiomers (*S*)-**36** and (*R*)-**36** does not occur under these aminocarbonylation conditions when their corresponding enantiopure phenylalanine methyl esters were used as the amine substrates [>99% ee, (*S*)-**36** and (*R*)-**36**, respectively].

Employing a conformationally rigid cyclic α-amino amide nucleophile gave the corresponding primary amide derivative **37** in significantly poor yield (28%), alongside the formation of by-product **38** (59% yield, Figure 2). The structural elucidation of **38** was accomplished using a combination of nuclear magnetic resonance (NMR) spectroscopy, including ^{1}H-^{15}N heteronuclear multiple bond correlation (HMBC), and HRMS. While aryl imide bond formation has previously been documented using Pd catalysis, in the presence of CO[54] it is reasonable that pyrazolo[3,4-*b*]pyridine dimer **38** may have similarly arisen from the carbonylative cross-coupling of amide **37** and aryl iodide **15**.



Scheme 2 Synthesis of *N*-1-substituted pyrazolo[3,4-*b*]pyridine-3-carboxamides **17**–**19**, **22**–**37**, and **39**–**44**. *Reagents and conditions*: aryl iodide **15** (0.28 mmol), amine (0.42 mmol), $Pd(OAc)_2$ (5 mol%), Xantphos (5 mol%), Na_2CO_3 (3 equiv.), toluene (0.56 mL), CO surrogate (5 equiv.), 100 °C, 18 h.

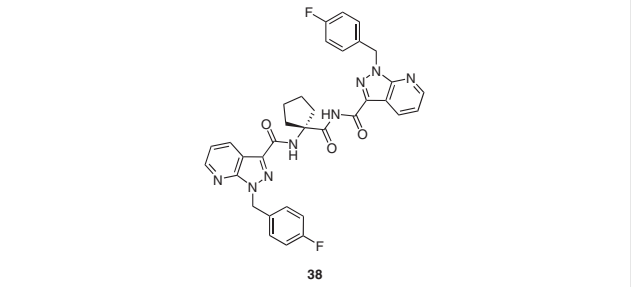
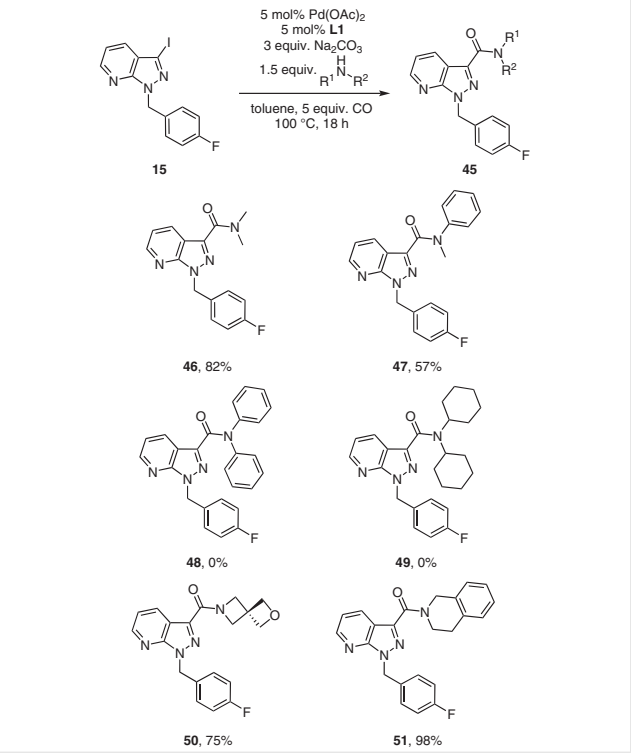


Figure 2 Dimeric by-product **38**

Utilizing heterocyclic amine nucleophiles afforded pyrazinyl **19**, thiophenyl **39**, tetrahydropyranyl **40**, and piperidinyl **41** derivatives in yields exceeding 95%, highlighting the significant tolerance of this aminocarbonylation protocol for diverse heterocyclic-containing amine nucleophiles. Also of note is the 95% yield of pyrazinyl carboxamide **19** relative to its much lower yield of 23% when a significantly shorter reaction time of 15 minutes and lower loadings of $Pd(OAc)_2$ precatalyst and Xanthphos (**L1**) ligand were employed (see Table 4, entry 9). Furthermore, no evidence for the formation of side products arising from the unwanted Buchwald–Hartwig cross coupling of aryl iodide **15** and amine nucleophiles were observed over the course of these

reactions. When using aniline as an example of an aromatic amine nucleophile, its pyrazolo[3,4-*b*]pyridine derivative **42** was obtained in excellent yield (99%). To demonstrate the tolerance of this catalyst system for sterically hindered anilines, *o*-methylaniline was employed to give the corresponding amide **43** in 95% yield. However, the use of 2,5-bis(trifluoromethyl)aniline failed to give the corresponding carboxamide **44**.

Following the identification of a reliable general method for the aminocarbonylation of aryl iodide **15** to give a wide range of secondary amides **17**–**19**, **22**–**37**, and **39**–**44** (see Scheme 2), we proceeded to extend this aminocarbonylation protocol to the preparation of pyrazolo[3,4-*b*]pyridine tertiary carboxamide derivatives of the general structure **45** (Scheme 3).



Scheme 3 Extension of general aminocarbonylation protocol to the synthesis of N-1-substituted pyrazolo[3,4-*b*]pyridine tertiary amide derivatives **46**–**51**. *Reagents and conditions*: aryl iodide **15** (0.28 mmol), amine (0.42 mmol), $Pd(OAc)_2$ (5 mol%), Xantphos (5 mol%), Na_2CO_3 (3 equiv.), toluene (0.56 mL), CO surrogate (5 equiv.), 100 °C, 18 h.

Employing dimethylamine HCl afforded the corresponding tertiary amide **46** in very good yield (82%). However, using the more sterically hindered secondary amine nucleophile, *N*-methylaniline, furnished the corresponding tertiary amide **47** in only fair yield (57%), when compared with aniline carboxamides **42** and **43** (99% and 95%, respectively). Unfortunately, employing diphenylamine or dicyclohexylamine HCl both failed to give the desired amides **48** and **49**, respectively. Notwithstanding the latter steric limitations exemplified through the attempted synthesis of **48** and **49**, other pharmaceutically relevant amines, such as 2-oxa-6-azaspiro[3.3]heptane and tetrahydroisoquinoline, could be utilized to afford the corresponding tertiary amides **50** and **51** in satisfactory yield (75% and 98%, respectively).

In summary, an expedient protocol for the synthesis of pyrazolo[3,4-*b*]-3-carboxamide derivatives, from commercially available 3-iodo-1*H*-pyrazolo[3,4-*b*]pyridine, has been developed. This method tolerates a wide range of primary amine nucleophiles, affording structurally diverse secondary and tertiary carboxamides in excellent yield (up to 99%). No evidence for the formation of the corresponding dicarbonylation or α-ketoamide products arising from aryl iodide **15** was observed.[55] Practically, these aminocarbonylative transformations do not require the handling of gaseous CO or pressurized autoclave reactors, as CO is generated ex situ from bench stable liquid reagents (formic acid, mesyl chloride, and triethylamine) in a conveniently sealed two-chamber reaction vessel (COware®). Given the current interest in the pharmacological potential of pyrazolo[3,4-*b*]-pyridine derivatives, this methodology would suitably facilitate the rapid synthesis of diverse structural analogues for biological assessment.

All reagents were obtained from commercial sources and were used without further purification, unless otherwise stated. Toluene was dried over 3 Å molecular sieves (which were dried prior to use, by heating to 175 °C for 48 h). Room temperature (rt) ranged between 16.5–24 °C with an average value of 20 °C. TLC was carried out on precoated Merck silica gel GF254 plates, using UV254 nm light detection. Wet flash column chromatography was performed using Merck Kieselgel 60 (particle size 0.040–0.063 mm, density 0.8 g/cm^3).

^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR spectra were obtained using a Bruker Avance III 600 MHz NMR spectrometer equipped with a dual CH cryoprobe. All spectra were recorded at 20 °C, using $CDCl_3$ (with TMS as internal standard, δ_H = 0.00) as sample solvent. Chemical shift values (δ_H and δ_C) are reported in ppm relative to TMS ($CDCl_3$) and coupling constants (*J*) are expressed in hertz (Hz), in the following format: chemical shift value (multiplicity, coupling constant, integration). ^{1}H NMR spectral data are described, using the standard abbreviations. ^{13}C NMR spectral data were calibrated using the solvent signal for $CDCl_3$ (δ_C = 77.0, t).

Melting points were obtained using a Unimelt Thomas–Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained using a PerkinElmer FTIR UATR2 spectrophotometer. Optical rotations were obtained using an Autopol® V Plus automatic polarimeter (Rudolph Research Analytical). High-resolution mass spectrometry (HRMS) experiments were performed on a Waters Micromass LCT Premier time-of-flight (TOF) mass spectrometer or a Waters Vion IMS QTOF mass spectrometer using electrospray ionization (ESI). The eluent system employed for MS analysis consisted of MeCN/H_2O (1:1) and contained 0.1% v/v formic acid. HRMS experiments were performed using leucine enkephalin as an internal calibrant.

1-(4-Fluorobenzyl)-3-iodo-1*H*-pyrazolo[3,4-*b*]pyridine (15)

To a 100 mL round-bottomed flask was added 3-iodo-1*H*-pyrazolo-[3,4-*b*]pyridine (1.8 g, 7.35 mmol) and DMF (7.5 mL). The resulting solution was treated with Cs_2CO_3 (2.633 g, 8.08 mmol) and allowed to stir at rt for a further 30 min. 4-Fluorobenzyl bromide (1 mL, 8.08 mmol) was added, and the resulting mixture was allowed to stir at rt for a further 16 h. The reaction mixture was diluted with sat. aq $Na_2S_2O_3$ (100 mL) and further stirred at rt for 1 h. The suspension was filtered under vacuum and the resulting solids were subsequently washed with H_2O (3 × 20 mL). Recrystallization from EtOH furnished title compound **15**; yield: 1.950 g (75%); fine colorless needles; mp 132–133 °C (EtOH); R_f = 0.67 (EtOAc/hexane 3:7).

IR (ATR): 3058, 3040, 3010, 2953, 1599, 1567, 1507, 1452, 1264, 1211, 1157, 1121, 970, 779, 765, 479 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.58 (dd, *J* = 4.5, 1.2 Hz, 1 H), 7.80 (dd, *J* = 8.1, 1.2 Hz, 1 H), 7.39–7.35 (m, 2 H), 7.18 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.01–6.95 (m, 2 H), 5.67 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.3 Hz), 150.3, 150.1, 132.4 (d, $J_{C,F}$ = 3.2 Hz), 130.6, 129.9 (d, $J_{C,F}$ = 8.2 Hz), 120.5, 117.7, 115.5 (d, $J_{C,F}$ = 21.6 Hz), 90.2, 50.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –114.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}FIN_3$: 353.9898; found: 353.9904.

Pyrazolo[3,4-*b*]pyridine-3-carboxamides 16–19, 22–43, 46, 47, 50, and 51; General Procedure

To Chamber A of an oven-dried 20 mL two-chamber reactor (SyTracks®) was added $Pd(OAc)_2$ (3.14 mg, 14 μmol) in anhyd toluene (0.2 mL), Xantphos (8.1 mg, 14 μmol) in anhyd toluene (0.3 mL), anhyd toluene (0.06 mL), Na_2CO_3 (90 mg, 0.42 mmol), 3-iodo-1*H*-pyrazolo[3,4-*b*]pyridine (100 mg, 0.28 mmol), and appropriate amine (0.42 mmol). To Chamber B of the two-chamber reactor was added formic acid (0.05 mL, 1.4 mmol) and MsCl (0.11 mL, 1.4 mmol). The vessel was then flushed with N_2 for 10 min (N_2 flow inlet through Chamber A and flow outlet through Chamber B). Chamber B was treated with NEt_3 (0.39 mL, 2.8 mmol) and the resulting Chamber B mixture allowed to stir at rt for a further 10 min. Both Chambers A and B were immersed in an oil bath set to 100 °C and allowed to stir rapidly (800 rpm) for 18 h. The vessel was then cooled to rt and reactor caps removed. The contents of Chamber A were transferred to a 50 mL round-bottomed flask using EtOAc (5 × 2 mL), mixed with Celite (ca. 200 mg), and concentrated in vacuo. The resulting crude mixture was subjected to gradient wet flash column chromatography using varying mixtures of EtOAc and hexane (unless specified otherwise) to yield the desired carboxamide.

***N*-Benzyl-1-(4-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (16)**

Yield: 96 mg (95%); pale yellow crystalline solid; mp 105 °C; R_f = 0.20 (EtOAc/hexane 1:3).

IR (ATR): 3291, 3030, 2940, 1638, 1542, 1510, 1391, 1222, 1165, 1138, 781, 737, 695, 525, 521, 423 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.70 (dd, *J* = 8.1, 1.6 Hz, 1 H), 8.60 (dd, *J* = 4.5, 1.6 Hz, 1 H), 7.40–7.26 (m, 9 H), 5.66 (s, 2 H), 4.68 (d, *J* = 6.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.7 Hz), 161.7, 149.6, 138.2, 136.9, 132.2, 132.0 (d, $J_{C,F}$ = 3.2 Hz), 129.7 (d, $J_{C,F}$ = 8.2 Hz), 128.7, 127.9, 127.5, 118.9, 115.6 (d, $J_{C,F}$ = 21.6 Hz), 114.9, 50.4, 43.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –114.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}FN_4O$: 361.1459; found: 361.1465.

1-(4-Fluorobenzyl)-*N*-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (17)

Yield: 102 mg (93%); colorless oil; R_f = 0.56 (EtOAc/hexane 1:1).

IR (ATR): 3415, 3320, 3068, 3006, 2934, 2836, 1659, 1534, 1510, 1245, 1223, 1172, 1033, 812, 782, 774, 520 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.70 (dd, *J* = 8.1, 1.6 Hz, 1 H), 8.59 (dd, *J* = 4.5, 1.6 Hz, 1 H), 7.33–7.25 (m, 6 H), 7.00–6.93 (m, 2 H), 6.91–6.86 (m, 2 H), 5.65 (s, 2 H), 4.61 (d, *J* = 6.0 Hz, 2 H), 3.80 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.6 Hz), 161.6, 159.0, 151.0, 149.6, 137.0, 132.1, 132.0 (d, $J_{C,F}$ = 3.2 Hz), 130.2, 129.7 (d, $J_{C,F}$ = 8.2 Hz), 129.2, 118.8, 115.5 (d, $J_{C,F}$ = 21.6 Hz), 114.8, 114.1, 55.2, 50.3, 42.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}FN_4O_2$: 391.1565; found: 391.1557.

***N*-(3,3-Dimethyl-2-oxobutyl)-1-(4-fluorobenzyl)-1*H*-pyrazolo-[3,4-*b*]pyridine-3-carboxamide (18)**

Yield: 96 mg (93%); colorless oil; R_f = 0.17 (EtOAc/hexane 3:7).

IR (ATR): 3398, 3312, 3064, 2970, 2936, 2872, 1717, 1661, 1531, 1510, 1493, 1222, 1158, 781, 755, 608, 562, 520, 483 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.63 (dd, *J* = 8.0, 1.6 Hz, 1 H), 8.59 (dd, *J* = 4.5, 1.6 Hz, 1 H), 7.75 (t, *J* = 4.5 Hz, 1 H), 7.40–7.35 (m, 2 H), 7.26 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.03–6.95 (m, 2 H), 5.70 (s, 2 H), 4.51 (d, *J* = 4.7 Hz, 2 H), 1.26 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.3, 162.5 (d, $J_{C,F}$ = 246.7 Hz), 161.9, 151.0, 149.6, 136.6, 132.0 (d, $J_{C,F}$ = 3.2 Hz), 131.9, 130.0 (d, $J_{C,F}$ = 8.2 Hz), 118.9, 115.6 (d, $J_{C,F}$ =21.5 Hz), 114.8, 50.5, 44.3, 43.2, 24.6.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.2.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}FN_4O_2$: 369.1721; found: 369.1723.

1-(4-Fluorobenzyl)-*N*-(pyrazin-2-ylmethyl)-1*H*-pyrazolo[3,4-*b*]-pyridine-3-carboxamide (19)

Yield: 96 mg (95%); yellow crystalline solid; mp 159 °C; R_f = 0.27 (EtOAc/hexane 3:1).

IR (ATR): 3539, 3411, 3314, 3061, 2936, 1660, 1536, 1510, 1493, 1392, 1272, 1222, 1158, 1018, 811, 773, 484 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 1.1 Hz, 1 H), 8.66 (dd, *J* = 8.1, 1.6 Hz, 1 H), 8.59 (dd, *J* = 4.5, 1.6 Hz, 1 H), 8.54 (dd, *J* = 2.4, 1.5 Hz, 1 H), 8.50 (d, *J* = 2.5 Hz, 1 H), 7.92 (t, *J* = 5.4 Hz, 1 H), 7.36–7.31 (m, 2 H), 7.27 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.01–6.94 (m, 2 H), 5.69 (s, 2 H), 4.85 (d, *J* = 5.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.7 Hz), 162.0, 152.8, 151.0, 149.6, 144.0, 143.9, 143.5, 136.6, 131.94 (d, $J_{C,F}$ = 2.8 Hz), 131.92, 129.7 (d, $J_{C,F}$ = 8.2 Hz), 118.9, 115.5 (d, $J_{C,F}$ = 21.7 Hz), 114.8, 50.4, 42.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}FN_6O$: 363.1364; found: 363.1358.

1-(4-Fluorobenzyl)-*N*-(4-nitrobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (22)

Yield: 95 mg (84%); pale yellow solid; mp 160 °C; R_f = 0.27 (EtOAc/hexane 2:3).

IR (ATR): 3411, 3312, 3073, 2937, 1662, 1510, 1499, 1343, 1222, 731 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (dd, J = 8.1, 1.5 Hz, 1 H), 8.62 (dd, J = 4.5, 1.5 Hz, 1 H), 8.18 (d, J = 8.7 Hz, 2 H), 7.53 (d, J = 8.7 Hz, 2 H), 7.35–7.27 (m, 4 H), 7.01–6.95 (m, 2 H), 5.68 (s, 2 H), 4.76 (d, J = 6.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5 (d, $J_{C,F}$ = 246.9 Hz), 162.1, 151.1, 149.9, 147.3, 145.9, 136.5, 132.00, 131.95 (d, $J_{C,F}$ = 3.5 Hz), 129.8 (d, $J_{C,F}$ = 8.2 Hz), 128.3, 123.9, 119.2, 115.7 (d, $J_{C,F}$ = 21.6 Hz), 114.8, 50.5, 42.4.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –113.9.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{21}H_{17}FN_5O_3$: 406.1310; found: 406.1308.

1-(4-Fluorobenzyl)-*N*-[4-(trifluoromethyl)benzyl]-1*H*-pyrazolo-[3,4-*b*]pyridine-3-carboxamide (23)

Yield: 101 mg (84%); beige crystalline solid; mp 138 °C; R_f = 0.23 (EtOAc/hexane 3:7).

IR (ATR): 3422, 3317, 3064, 2940, 1660, 1533, 1510, 1323, 1270, 1224, 1159, 1120, 1110, 1066, 837, 810, 782, 773 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (dd, J = 8.1, 1.6 Hz, 1 H), 8.60 (dd, J = 4.5, 1.6 Hz, 1 H), 7.59 (d, J = 8.2 Hz, 1 H), 7.50–7.44 (m, 3 H), 7.35–7.25 (m, 3 H), 7.01–6.93 (m, 2 H), 5.67 (s, 2 H), 4.72 (d, J = 6.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5 (d, $J_{C,F}$ = 246.8 Hz), 162.0, 151.1, 149.8, 142.4 (app d, $J_{C,F}$ = 0.9 Hz), 136.7, 132.1, 132.0 (d, $J_{C,F}$ = 3.3 Hz), 129.81 (d, $J_{C,F}$ = 8.2 Hz), 129.78 (q, $J_{C,F}$ = 32.4 Hz), 128.0, 125.7 (q, $J_{C,F}$ = 3.8 Hz), 124.1 (q, $J_{C,F}$ = 272.0 Hz), 119.1, 115.6 (q, $J_{C,F}$ = 21.6 Hz), 114.9, 50.5, 42.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.5, –114.0.

HRMS-ESI: m/z [M + H]+ calcd for $C_{22}H_{17}F_4N_4O$: 429.1333; found: 429.1326.

1-(4-Fluorobenzyl)-*N*-(4-methylbenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (24)

Yield: 93 mg (89%); pale yellow crystalline solid; mp 136 °C; R_f = 0.60 (EtOAc/hexane 1:1).

IR (ATR): 3419, 3316, 3064, 3023, 2924, 2859, 1658, 1531, 1509, 1498, 1390, 1269, 1222, 1158, 811, 781, 774, 483 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (dd, J = 8.1, 1.6 Hz, 1 H), 8.58 (dd, J = 4.5, 1.6 Hz, 1 H), 7.33–7.24 (m, 6 H), 7.15 (d, J = 7.9 Hz, 2 H), 7.00–6.92 (m, 2 H), 5.64 (s, 2 H), 4.63 (d, J = 6.1 Hz, 2 H), 2.33 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.6 Hz), 161.7, 151.0, 149.6, 137.2, 137.0, 135.1, 132.2, 132.0 (d, $J_{C,F}$ = 3.2 Hz), 129.7 (d, $J_{C,F}$ = 8.2 Hz), 129.4, 127.9, 118.9, 115.5 (d, $J_{C,F}$ = 21.7 Hz), 114.9, 50.4, 42.8, 21.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.1.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{22}H_{20}FN_4O$: 375.1616; found: 375.1607.

***N*-(4-Bromobenzyl)-1-(4-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (25)**

Yield: 111 mg (90%); colorless crystalline solid; mp 143–144 °C; R_f = 0.60 (EtOAc/hexane 1:1).

IR (ATR): 3413, 3316, 3064, 2936, 1548, 1531, 1509, 1488, 1269, 1222, 1158, 1011, 810, 775, 520, 483 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (dd, J = 8.1, 1.6 Hz, 1 H), 8.59 (dd, J = 4.5, 1.6 Hz, 1 H), 7.47–7.43 (m, 2 H), 7.38 (t, J = 5.6 Hz, 1 H), 7.34–7.23 (m, 5 H), 7.00–6.92 (m, 2 H), 5.65 (s, 2 H), 4.61 (d, J = 6.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.6 Hz), 161.8, 151.0, 149.7, 137.3, 136.7, 132.05, 131.96 (d, $J_{C,F}$ = 3.2 Hz), 131.7, 129.7 (d, $J_{C,F}$ = 8.2 Hz), 129.4, 121.4, 119.0, 115.6 (d, $J_{C,F}$ = 21.6 Hz), 114.8, 50.4, 42.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.0.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{21}H_{17}{}^{79}BrFN_4O$: 439.0564; found: 439.0549.

1-(4-Fluorobenzyl)-*N*-(2-phenylpropan-2-yl)-1*H*-pyrazolo[3,4-*b*]-pyridine-3-carboxamide (26)

Yield: 107 mg (98%); colorless oil; R_f = 0.17 (EtOAc/hexane 1:4).

IR (ATR): 3409, 3334, 3060, 2977, 2935, 1669, 1522, 1510, 1269, 1222, 1158, 849, 781, 762, 698, 563, 547, 520, 484 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (dd, J = 8.1, 1.6 Hz, 1 H), 8.56 (dd, J = 4.5, 1.6 Hz, 1 H), 7.51–7.48 (m, 2 H), 7.37–7.33 (m, 5 H), 7.26–7.19 (m, 2 H), 7.03–6.98 (m, 2 H), 5.70 (s, 2 H), 1.85 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.6 Hz), 160.9, 151.0, 149.5, 146.8, 137.6, 132.4, 132.1 (d, $J_{C,F}$ = 3.2 Hz), 129.7 (d, $J_{C,F}$ = 8.2 Hz), 128.4, 126.7, 124.7, 118.7, 115.6 (d, $J_{C,F}$ = 21.6 Hz), 114.8, 55.9, 50.4, 29.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –114.1.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{23}H_{21}FN_4ONa$: 411.1591; found: 411.1574.

***N*-[(3*s*,5*s*,7*s*)-Adamantan-1-yl]-1-(4-fluorobenzyl)-1*H*-pyrazolo-[3,4-*b*]pyridine-3-carboxamide (27)**

Yield: 108 mg (95%); colorless oil; R_f = 0.50 (EtOAc/hexane 3:7).

IR (ATR): 3402, 3312, 2907, 2850, 1665, 1529, 1510, 1494, 1277, 1223, 861, 778, 731, 519, 484 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (dd, J = 8.1, 1.6 Hz, 1 H), 8.57 (dd, J = 4.5, 1.7 Hz, 1 H), 7.35–7.28 (m, 2 H), 7.24 (dd, J = 8.1, 4.5 Hz, 1 H), 7.03–6.95 (m, 2 H), 6.77 (br s, 1 H), 5.67 (s, 2 H), 2.18–2.14 (m, 9 H), 1.78–1.69 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.5 Hz), 161.2, 151.0, 149.4, 137.9, 132.3, 132.2 (d, $J_{C,F}$ = 3.2 Hz), 129.6 (d, $J_{C,F}$ = 8.3 Hz), 118.7, 115.5 (d, $J_{C,F}$ = 21.6 Hz), 114.8, 52.0, 50.3, 41.7, 36.3, 29.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –114.2.

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{24}H_{26}FN_4O$: 405.2085; found: 405.2082.

***N*-[(1*R*,2*R*,4*S*)-Bicyclo[2.2.1]heptan-2-yl]-1-(4-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (28)**

Yield: 100 mg (98%); amber oil; $[\alpha]_D^{25}$ +4.50 (*c* 0.10, $CHCl_3$); R_f = 0.33 (EtOAc/hexane 3:7).

IR (ATR): 3423, 3317, 3068, 2952, 2871, 1652, 1526, 1510, 1493, 1275, 1222, 1157, 781, 730, 520, 484 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (dd, J = 8.1, 1.6 Hz, 1 H), 8.58 (dd, J = 4.5, 1.7 Hz, 1 H), 7.35–7.28 (m, 2 H), 7.25 (dd, J = 8.2, 4.6 Hz, 1 H), 7.02–6.94 (m, 2 H), 6.85 (d, J = 7.2 Hz, 1 H), 5.68 (s, 2 H), 3.95 (app dt, J = 7.5, 3.5 Hz, 1 H), 2.38–2.34 (m, 2 H), 1.93–1.86 (m, 1 H), 1.63–1.05 (m, 7 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.6 Hz), 161.1, 151.1, 149.6, 137.3, 132.3, 132.2 (d, $J_{C,F}$ = 3.3 Hz), 129.7 (d, $J_{C,F}$ = 8.2 Hz), 118.8, 115.6 (d, $J_{C,F}$ = 21.6 Hz), 114.9, 52.6, 50.4, 42.5, 40.3, 35.76, 35.71, 28.2, 26.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.2.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}FN_4O$: 365.1772; found: 365.1769.

1-(4-Fluorobenzyl)-*N*-[2-(methylsulfonyl)ethyl]-1*H*-pyrazolo-[3,4-*b*]pyridine-3-carboxamide (29)

Yield: 50 mg (96%); colorless oil; R_f = 0.23 (EtOAc/hexane 3:1).

IR (ATR): 3287, 3030, 3004, 2953, 2927, 1656, 1542, 1511, 1291, 1273, 1220, 1128, 956, 766, 625, 522, 500, 484, 418 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61 (dd, *J* = 3.7, 1.6 Hz, 1 H), 8.59 (s, 1 H), 7.64 (t, *J* =6.1 Hz, 1 H), 7.39–7.32 (m, 2 H), 7.29–7.25 (m, 1 H), 7.02–6.94 (m, 2 H), 5.67 (s, 2 H), 4.00 (dd, *J* = 6.1, 6.1 Hz, 2 H), 3.40 (t, *J* = 6.1 Hz, 2 H), 2.99 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.9 Hz), 162.2, 150.9, 149.7, 136.2, 131.8 (d, $J_{C,F}$ = 3.3 Hz), 131.7, 129.9 (d, $J_{C,F}$ = 8.2 Hz), 119.0, 115.5 (d, $J_{C,F}$ = 21.6 Hz), 114.7, 54.0, 50.5, 41.7, 33.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}FN_4O_3S$: 377.1078; found: 377.1074.

1-(4-Fluorobenzyl)-*N*-{2-[(4-methylphenyl)sulfonamido]ethyl}-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (30)

Yield: 120 mg (92%); beige solid; mp 142 °C; R_f = 0.48 (EtOAc).

IR (ATR): 3265, 3063, 2935, 2876, 1652, 1538, 1510, 1156, 1092, 907, 727, 661, 549 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (dd, *J* = 4.5, 1.2 Hz, 1 H), 8.52 (dd, *J* = 8.1, 1.6 Hz, 1 H), 7.72 (d, *J* = 8.3 Hz, 2 H), 7.43 (t, *J* = 6.1 Hz, 1 H), 7.36–7.30 (m, 2 H), 7.20 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 6.99–6.91 (m, 2 H), 5.87 (t, *J* = 5.9 Hz, 1 H), 5.60 (s, 2 H), 3.58 (dt, *J* = 5.9, 5.8 Hz, 2 H), 3.22 (dt, *J* = 5.9, 5.8 Hz, 2 H), 2.27 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.5, 162.4 (d, $J_{C,F}$ = 246.6 Hz), 150.6, 149.4, 143.2, 136.7, 136.3, 131.83 (d, $J_{C,F}$ = 3.2 Hz), 131.79, 129.9 (d, $J_{C,F}$ = 8.5 Hz), 129.5, 126.9, 118.9, 115.5 (d, $J_{C,F}$ = 21.7 Hz), 114.6, 50.3, 43.2, 39.0, 21.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{23}FN_5O_3S$: 468.1500; found: 468.1497.

1-(4-Fluorobenzyl)-*N*-(2-methylallyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (31)

Yield: 89 mg (98%); dark red oil; R_f = 0.30 (EtOAc/hexane 3:7).

IR (ATR): 3526, 3424, 3321, 3073, 2974, 2923, 1652, 1532, 1509, 1270, 1221, 1158, 810, 772, 483, 419 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (dd, *J* = 8.1, 1.7 Hz, 1 H), 8.59 (dd, *J* = 4.5, 1.6 Hz, 1 H), 7.37–7.30 (m, 2 H), 7.26 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.17 (t, *J* = 5.6 Hz, 1 H), 7.02–6.94 (m, 2 H), 5.68 (s, 2 H), 4.96–4.89 (m, 2 H), 4.04 (d, *J* = 6.3 Hz, 2 H), 1.81 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.7 Hz), 161.7, 151.0, 149.6, 141.9, 136.9, 132.1, 132.0 (d, $J_{C,F}$ = 3.2 Hz), 129.7 (d, $J_{C,F}$ = 8.2 Hz), 118.8, 115.5 (d, $J_{C,F}$ = 21.6 Hz), 114.8, 111.2, 50.3, 44.5, 20.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –14.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}FN_4O$: 325.1459; found: 325.1465.

1-(4-Fluorobenzyl)-*N*-(2-methylbut-3-yn-2-yl)-1*H*-pyrazolo-[3,4-*b*]pyridine-3-carboxamide (32)

Yield: 58 mg (62%); colorless oil; R_f = 0.42 (EtOAc/hexane 3:7).

IR (ATR): 3411, 3301, 3253, 3060, 2983, 2936, 1669, 1523, 1510, 1493, 1382, 1269, 1221, 1158, 858, 776, 730, 484 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.70 (dd, *J* = 8.1, 1.6 Hz, 1 H), 8.58 (dd, *J* = 4.5, 1.6 Hz, 1 H), 7.34–7.29 (m , 2 H), 7.26 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.10 (br s, 1 H), 7.63–6.95 (s, 2 H), 2.42 (s, 1 H), 1.80 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5 (d, $J_{C,F}$ = 246.6 Hz), 161.0, 151.1, 149.7, 137.2, 132.3, 132.1 (d, $J_{C,F}$ = 3.3 Hz), 129.7 (d, $J_{C,F}$ = 8.2 Hz), 118.9, 115.6 (d, $J_{C,F}$ = 21.6 Hz), 114.8, 87.0, 69.4, 50.4, 47.4, 29.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{18}FN_4O$: 337.1459; found: 337.1449.

1-(4-Fluorobenzyl)-*N*-(2-hydroxyethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (33)

Yield: 83 mg (94%); colorless solid; mp 108 °C; R_f = 0.27 (EtOAc/hexane 1:3).

IR (ATR): 3415, 3321, 3071, 2937, 2877, 1650, 1539, 1509, 1494, 1392, 1272, 1221, 1171, 1159, 1061, 774, 520, 484 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (dd, *J* = 8.1, 1.6 Hz, 1 H), 8.56 (dd, *J* = 4.5, 1.6 Hz, 1 H), 7.50 (t, *J* = 5.3 Hz, 1 H), 7.32–7.27 (m, 2 H), 7.22 (dd, *J* = 8.1, 4.5 Hz, 1 H), 6.99–6.92 (m, 2 H), 5.63 (s, 2 H), 3.86–3.83 (m, 2 H), 3.67–3.61 (m, 2 H), 2.95 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.7, 162.3 (d, $J_{C,F}$ = 246.7 Hz), 150.8, 149.6, 136.7, 132.0, 131.9 (d, $J_{C,F}$ = 3.0 Hz), 129.7 (d, $J_{C,F}$ = 8.5 Hz), 118.9, 115.5 (d, $J_{C,F}$ = 21.8 Hz), 114.7, 62.0, 50.3, 42.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}FN_4O_2$: 315.1252; found: 315.1198.

1-(4-Fluorobenzyl)-*N*-(2-hydroxy-2-methylpropyl)-1*H*-pyrazolo-[3,4-*b*]pyridine-3-carboxamide (34)

Yield: 93 mg (97%); amber oil; R_f = 0.20 (EtOAc/hexane 1:1).

IR (ATR): 3412, 3068, 2973, 2932, 1740, 1651, 1539, 1510, 1392, 1274, 1222, 1158, 1139, 919, 812, 774, 610, 521, 484 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (dd, *J* = 8.1, 1.7 Hz, 1 H), 8.58 (dd, *J* = 4.5, 1.6 Hz, 1 H), 7.46 (t, *J* = 6.1 Hz, 1 H), 7.36–7.22 (m, 2 H), 7.24 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.01–6.93 (m, 2 H), 5.67 (s, 2 H), 3.50 (d, *J* = 6.3 Hz, 2 H), 2.81 (s, 1 H), 1.31 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 162.5 (d, $J_{C,F}$ = 246.7 Hz), 151.0, 149.6, 136.8, 132.1, 132.0 (d, $J_{C,F}$ = 3.3 Hz), 129.8 (d, $J_{C,F}$ = 8.3 Hz), 118.9, 115.6 (d, $J_{C,F}$ = 21.6 Hz), 114.9, 71.1, 50.4, 50.0, 27.4.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.1

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{19}FN_4O_2Na$: 365.1384; found: 365.1386.

1-(4-Fluorobenzyl)-*N*-(2-oxoazepan-3-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (35)

Yield: 95 mg (89%); beige crystalline solid; mp 218–219 °C; R_f = 0.63 (EtOAc/hexane 3:1).

IR (ATR): 3381, 3291, 3073, 2933, 2854, 1650, 1510, 1222, 910, 783, 727, 576 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.63 (dd, *J* = 8.1, 1.5 Hz, 1 H), 8.58 (dd, *J* = 4.5, 1.6 Hz, 1 H), 8.30 (d, *J* = 6.2 Hz, 1 H), 7.41–7.35 (m, 2 H), 7.25 (dd, *J* = 8.1, 4.6 Hz, 1 H), 7.02–6.94 (m, 2 H), 6.56 (t, *J* = 6.1 Hz, 1 H), 5.71 (ABq, ΔδAB = 0.05, $J_{A,B}$ =14.9 Hz, 2 H), 4.78 (ddd, *J* = 11.0, 6.3, 1.5 Hz, 1 H), 3.42–3.25 (m, 2 H), 2.28–2.24 (m, 1 H), 2.11–2.04 (m, 1 H), 1.99–1.85 (m, 2 H), 1.72–1.58 (m, 1 H), 1.53–1.39 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.3, 162.4 (d, $J_{C,F}$ = 246.5 Hz), 161.1, 150.9, 149.4, 136.7, 132.0 (d, $J_{C,F}$ = 3.3 Hz), 131.8, 129.9 (d, $J_{C,F}$ = 8.2 Hz), 118.8, 115.5 (d, $J_{C,F}$ = 21.6 Hz), 114.9, 52.0, 50.4, 42.1, 31.7, 29.0, 28.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}FN_5O_2$: 382.1674; found: 382.1666.

Methyl [1-(4-Fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl]-L-phenylalaninate [(*S*)-36]

Yield: 117 mg (97%); pale yellow oil; $[\alpha]_D^{25}$ +46.5 (*c* 0.10, $CHCl_3$); R_f = 0.13 (EtOAc/hexane 1:3).

IR (ATR): 3415, 3325, 3068, 3034, 2952, 1740, 1663, 1526, 1510, 1278, 1219, 1169, 781, 730, 700, 520, 483 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.61 (dd, *J* = 8.0, 1.6 Hz, 1 H), 8.58 (dd, *J* = 4.5, 1.6 Hz, 1 H), 7.45 (d, *J* = 8.1 Hz, 1 H), 7.38–7.33 (m, 2 H), 7.30–7.16 (m, 6 H), 7.03–6.95 (m, 2 H), 5.66 (ABq, ΔδAB = 0.06, $J_{A,B}$ = 14.9 Hz, 2 H), 5.09 (dt, *J* = 8.1, 6.1 Hz, 1 H), 3.74 (ABX, $J_{A,B}$ = 13.9 Hz, $J_{B,X}$ = 6.2 Hz, $J_{A,X}$ = 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 162.5 (d, $J_{C,F}$ = 246.6 Hz), 161.4, 151.0, 149.6, 136.3, 135.9, 132.0 (d, $J_{C,F}$ = 3.7 Hz), 131.9, 130.0 (d, $J_{C,F}$ = 8.2 Hz), 129.3, 128.6, 127.1, 119.0, 115.6 (d, $J_{C,F}$ = 21.6 Hz), 114.9, 52.9, 52.4, 50.5, 38.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{22}FN_4O_3$: 433.1670; found: 433.1664.

Methyl [1-(4-Fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carbonyl]-D-phenylalaninate [(*R*)-36]

Yield: 109 mg (90%); colorless oil; $[\alpha]_D^{25}$ –31.0 (*c* 0.10, $CHCl_3$); R_f = 0.13 (EtOAc/hexane 1:3).

IR (ATR): 3411, 3330, 3064, 3029, 2952, 1740, 1663, 1527, 1511, 1493, 1279, 1219, 1169, 1158, 782, 731, 701, 484 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.62 (dd, *J* = 8.0, 1.4 Hz, 1 H), 8.58 (dd, *J* = 4.5, 1.4 Hz, 1 H), 7.46 (d, *J* = 8.1 Hz, 1 H), 7.37–7.34 (m, 2 H), 7.29–7.23 (m, 4 H), 7.19–7.17 (m, 2 H), 7.01–6.98 (m, 2 H), 5.67 (ABq, ΔδAB = 0.06, $J_{A,B}$ = 15.0 Hz, 2 H), 5.10 (dt, *J* = 7.9, 6.2 Hz, 1 H), 3.75 (s, 3 H, ABX, $J_{A,B}$ = 13.9 Hz, $J_{B,X}$ = 6.2 Hz, $J_{A,X}$ = 6.1 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.9, 162.5 (d, $J_{C,F}$ = 246.5 Hz), 161.3, 150.9, 149.5, 136.2, 135.9, 131.97, 131.96, 130.0 (d, $J_{C,F}$ = 8.1 Hz), 129.3, 128.6, 127.1, 119.0, 115.6 (d, $J_{C,F}$ = 21.8 Hz), 114.9, 52.9, 52.4, 50.5, 38.2.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –114.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{22}FN_4O_3$: 433.1670; found: 433.1664.

***N*-(1-Carbamoylcyclopentyl)-1-(4-fluorobenzyl)-1*H*-pyrazolo-[3,4-*b*]pyridine-3-carboxamide (37)**

Yield: 30 mg (28%); colorless solid; mp 209–210 °C; R_f = 0.43 (EtOAc/hexane 1:1).

IR (ATR): 3364, 2966, 2880, 1752, 1652, 1509, 1470, 1220, 1124, 773, 556, 521, 485 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.66 (dd, *J* = 8.0, 1.0 Hz, 1 H), 8.46 (dd, *J* = 4.5, 1.2 Hz, 1 H), 8.51 (br s, 1 H), 7.37–7.35 (m, 2 H), 7.29 (dd, *J* = 8.0, 4.6 Hz, 1 H), 7.00–6.98 (m, 2 H), 5.70 (s, 2 H), 2.11–1.93 (m, 8 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 186.4, 162.5 (d, $J_{C,F}$ = 246.6 Hz), 151.8, 151.1, 150.0, 133.5, 132.1, 131.9 (d, $J_{C,F}$ = 3.2 Hz), 130.0 (d, $J_{C,F}$ = 8.3 Hz), 118.8, 115.6 (d, $J_{C,F}$ = 21.6 Hz), 114.1, 78.7, 50.5, 37.7, 26.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –113.9.

HRMS-ESI: *m*/*z* [M – H_2O]$^+$ calcd for $C_{20}H_{18}FN_5O$: 364.1568; found: 364.1567.

1-(4-Fluorobenzyl)-*N*-(1-{[1-(4-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]-pyridine-3-carbonyl]carbamoyl}cyclopentyl)-1*H*-pyrazolo[3,4-*b*]-pyridine-3-carboxamide (38)

Yield: 52 mg (59%); colorless solid; mp 214–215 °C; R_f = 0.23 (EtOAc/hexane 1:1).

IR (ATR): 3360, 2964, 2883, 1752, 1652, 1509, 1470, 1220, 1124, 773, 556, 521, 485, 422 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 10.95 (s, 1 H), 8.64–8.61 (m, 2 H), 8.59–8.56 (m, 2 H), 7.42 (s, 1 H), 7.41–7.39 (m, 2 H), 7.28–7.26 (m, 1 H), 7.24 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.06–7.03 (m, 2 H), 6.97 (app t, *J* = 8.6 Hz, 2 H), 6.62 (app t, *J* = 8.6 Hz, 2 H), 5.71 (s, 2 H), 5.44 (s, 2 H), 2.67–2.62 (m, 2 H), 2.26–2.22 (m, 2 H), 1.96–1.85 (m, 4 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 171.5, 162.5 (d, $J_{C,F}$ = 246.8 Hz), 162.4, 162.3 (d, $J_{C,F}$ =246.7 Hz), 159.2, 151.0, 149.99, 149.97, 136.3, 136.1, 131.96, 131.91, 131.8 (d, $J_{C,F}$ = 3.1 Hz), 131.4 (d, *J* = 3.2 Hz), 130.0 (d, $J_{C,F}$ =7.9 Hz), 129.6 (d, $J_{C,F}$ = 8.4 Hz), 119.6, 119.2, 115.7 (d, $J_{C,F}$ = 22.0 Hz), 115.3 (d, $J_{C,F}$ = 21.6 Hz), 114.7, 68.4, 50.64, 50.58, 36.9, 24.2.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –113.66, –113.79.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{29}F_2N_8O_3$: 635.2325; found: 635.2318.

1-(4-Fluorobenzyl)-*N*-(thiophen-2-ylmethyl)-1*H*-pyrazolo[3,4-*b*]-pyridine-3-carboxamide (39)

Yield: 97 mg (95%); colorless crystalline solid; mp 129 °C; R_f = 0.27 (EtOAc/hexane 3:7).

IR (ATR): 3410, 3318, 3071, 2932, 1659, 1526, 1510, 1391, 1221, 1158, 810, 781, 701, 520, 484 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.68 (dd, *J* = 8.1, 1.6 Hz, 1 H), 8.58 (dd, *J* = 4.5, 1.6 Hz, 1 H), 7.44 (t, *J* = 5.6 Hz, 1 H), 7.33–7.20 (m, 4 H), 7.04 (dd, *J* = 3.4, 1.0 Hz, 1 H), 6.99–6.91 (m, 3 H), 5.64 (s, 2 H), 4.83 (d, *J* = 6.0 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.3 (d, $J_{C,F}$ = 246.5 Hz), 161.4, 150.9 149.5, 140.7, 136.7, 132.1, 131.9 (d, $J_{C,F}$ = 3.2 Hz), 129.7 (d, $J_{C,F}$ = 8.1 Hz), 126.8, 126.1, 125.2, 118.9, 115.5 (d, $J_{C,F}$ = 21.9 Hz), 114.8, 50.3, 37.6.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}FN_4OS$: 367.1023; found: 367.1019.

1-(4-Fluorobenzyl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazolo-[3,4-*b*]pyridine-3-carboxamide (40)

Yield: 97 mg (98%); beige solid; mp 186–189 °C; R_f = 0.20 (EtOAc/hexane 1:1).

IR (ATR): 3526, 3411, 3314, 3073, 2954, 2848, 1652, 1530, 1510, 1494, 1384, 1222, 1139, 1088, 811, 776, 781, 484 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.66 (dd, *J* = 8.1, 1.6 Hz, 1 H), 8.59 (dd, *J* = 4.5, 1.7 Hz, 1 H), 7.37–7.30 (m, 2 H), 7.27 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.03–6.95 (m, 2 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 5.69 (s, 2 H), 4.24 (tdt, *J* = 11.8, 8.1, 4.1 Hz, 1 H), 4.02 (ddd, *J* = 12.0, 3.9, 2.8 Hz, 2 H), 3.55 (ddd, *J* = 11.7, 11.7, 2.1 Hz, 2 H), 2.05–2.00 (m, 2 H), 1.66 (dddd, *J* = 12.8, 11.4, 11.4, 4.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5 (d, $J_{C,F}$ = 246.8 Hz), 161.2, 151.1, 149.7, 137.0, 132.14, 132.10 (d, $J_{C,F}$ = 3.3 Hz), 129.7 (d, $J_{C,F}$ = 8.2 Hz), 118.9, 115.6 (d, $J_{C,F}$ = 21.6 Hz), 114.9, 66.8, 50.4, 45.5, 33.2.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.1

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}FN_4O_2$: 355.1565; found: 355.1558.

1-(4-Fluorobenzyl)-*N*-(piperidin-2-ylmethyl)-1*H*-pyrazolo[3,4-*b*]-pyridine-3-carboxamide (41)

Yield: 95 mg (89%); colorless oil; R_f = 0.30 (1% v/v NEt_3 in MeOH/CH_2Cl_2 1:39).

IR (ATR): 3410, 3300, 2933, 2856, 1651, 1538, 1510, 1271, 1222, 1159, 915, 810, 781, 730, 484 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.51 (dd, *J* = 4.5, 1.6 Hz, 1 H), 8.48 (dd, *J* = 8.1, 1.6 Hz, 1 H), 7.89 (t, *J* = 5.5 Hz, 1 H), 7.39–7.32 (m, 2 H), 7.18 (dd, *J* = 8.1, 4.5 Hz, 1 H), 6.99–6.91 (m, 2 H), 5.59–5.56 (m, 3 H), 3.89–3.79 (m, 2 H), 3.50–3.43 (m, 2 H), 2.93–2.83 (m, 1 H), 1.98–1.70 (m, 5 H), 1.56–1.48 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.1, 162.3 (d, $J_{C,F}$ = 246.7 Hz), 150.6, 149.5, 136.0, 131.7 (d, $J_{C,F}$ = 3.2 Hz), 131.4, 130.0 (d, $J_{C,F}$ = 8.3 Hz), 118.9, 115.5 (d, $J_{C,F}$ = 21.6 Hz), 114.4, 57.0, 50.3, 45.2, 42.3, 26.9, 22.6, 22.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}FN_4O$: 368.1881; found: 368.1877.

1-(4-Fluorobenzyl)-*N*-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (42)

Yield: 96 mg (99%); brown oil; R_f = 0.42 (EtOAc/hexane 3:7).

IR (ATR): 3389, 3312, 3193, 3060, 3021, 2940, 1674, 1595, 1531, 1510, 1461, 1312, 1223, 1157, 1121, 781, 753, 691 cm^{-1}.

1H NMR (300 MHz, $CDCl_3$): δ = 8.82 (s, 1 H), 8.70 (dd, *J* = 8.1, 1.6 Hz, 1 H), 8.61 (dd, *J* = 4.5, 1.6 Hz, 1 H), 7.72 (dd, *J* = 8.6, 1.0 Hz, 2 H), 7.40–7.31 (m, 4 H), 7.27 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.13 (ddd, *J* = 7.4, 1.1, 1.1 Hz, 1 H), 7.03–6.95 (m, 2 H), 5.71 (s, 2 H).

13C NMR (75 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.9 Hz), 159.6, 151.2, 149.8, 137.5, 137.0, 132.1, 131.9 (d, $J_{C,F}$ = 3.3 Hz), 129.8 (d, $J_{C,F}$ = 8.2 Hz), 129.0, 124.3, 119.8, 119.1, 115.6 (d, $J_{C,F}$ = 21.6 Hz), 114.9, 50.5.

19F NMR (282 MHz, $CDCl_3$): δ = –113.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}FN_4O$: 347.1303; found: 347.1303.

1-(4-Fluorobenzyl)-*N*-(*o*-tolyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (43)

Yield: 96 mg (95%); colorless crystalline solid; mp 130 °C; R_f = 0.30 (EtOAc/hexane 1:4).

IR (ATR): 3407, 3064, 3021, 2979, 2936, 2867, 1681, 1589, 1530, 1510, 1462, 1222, 1157, 1126, 842, 775, 754, 606 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.76 (br s, 1 H), 8.71 (dd, *J* = 8.1, 1.6 Hz, 1 H), 8.62 (dd, *J* = 4.5, 1.6 Hz, 1 H), 8.13 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.42–7.35 (m, 2 H), 7.31–7.21 (m, 3 H), 7.09 (dt, *J* = 7.4, 1.2 Hz, 1 H), 7.04–6.97 (m, 2 H), 5.73 (s, 2 H), 2.38 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5 (d, $J_{C,F}$ = 246.9 Hz), 159.6, 151.2, 149.8, 137.2, 135.5, 132.1, 131.9 (d, $J_{C,F}$ = 3.3 Hz), 130.5, 129.9 (d, $J_{C,F}$ = 8.2 Hz), 128.2, 126.8, 124.8, 122.0, 119.1, 115.6 (d, $J_{C,F}$ = 21.6 Hz), 114.9, 50.5, 17.6.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –113.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}FN_4O$: 361.1459; found: 361.1456.

1-(4-Fluorobenzyl)-*N*,*N*-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (46)

Yield: 69 mg (82%); beige crystalline solid; mp 92 °C; R_f = 0.27 (EtOAc/hexane 1:1).

IR (ATR): 3061, 3023, 2936, 1622, 1509, 1276, 1221, 1154, 1107, 1011, 895, 793, 780, 680, 521, 484 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.58 (dd, *J* = 4.5, 1.4 Hz, 1 H), 8.54 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.36–7.34 (m, 2 H), 7.23 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.00–6.96 (m, 2 H), 5.70 (s, 2 H), 3.47 (s, 3 H), 3.18 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.0, 162.3 (d, $J_{C,F}$ = 246.4 Hz), 150.2, 149.3, 138.1, 132.3, 131.2 (d, $J_{C,F}$ = 3.1 Hz), 129.7 (d, $J_{C,F}$ = 7.9 Hz), 118.4, 116.6, 115.5 (d, $J_{C,F}$ = 21.8 Hz), 50.2, 38.9, 36.2.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –114.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}FN_4O$: 299.1303; found: 299.1300.

1-(4-Fluorobenzyl)-*N*-methyl-*N*-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (47)

Yield: 58 mg (57%); beige crystalline solid; mp 127 °C; R_f = 0.07 (EtOAc/hexane 1:4).

IR (ATR): 3068, 3026, 2936, 1634, 1595, 1509, 1495, 1475, 1338, 1277, 1221, 1112, 979, 864, 774, 697, 484 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.51 (dd, *J* = 4.5, 1.6 Hz, 1 H), 8.46 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.30–7.15 (m, 6 H), 7.03–6.99 (m, 2 H), 6.91–6.85 (m, 2 H), 5.40 (s, 2 H), 3.56 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2, 162.3 (d, $J_{C,F}$ = 246.1 Hz), 150.0, 149.2, 145.0, 137.6, 132.0 (d, $J_{C,F}$ = 3.2 Hz), 131.6, 129.9 (d, $J_{C,F}$ = 8.2 Hz), 129.0, 127.1, 126.8, 118.4, 116.1, 115.2 (d, $J_{C,F}$ = 21.5 Hz), 50.1, 38.6.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.6.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}FN_4O$: 361.1459; found: 361.1457.

[1-(4-Fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl](2-oxa-6-aza-spiro[3.3]heptan-6-yl)methanone (50)

Yield: 74 mg (75%); colorless oil; R_f = 0.30 (EtOAc).

IR (ATR): 2944, 2869, 1630, 1509, 1485, 1342, 1221, 976, 857, 786, 731 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (dd, *J* = 8.0, 1.6 Hz, 1 H), 8.58 (dd, *J* = 4.5, 1.6 Hz, 1 H), 7.39–7.32 (m, 2 H), 7.24 (dd, *J* = 8.0, 4.5 Hz, 1 H), 7.04–6.96 (m, 2 H), 5.69 (s, 2 H), 4.85 (s, 4 H), 4.80 (s, 2 H), 4.37 (s, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.3 (d, $J_{C,F}$ = 246.6 Hz), 161.8, 150.2, 149.4, 137.0, 132.2, 132.0 (d, $J_{C,F}$ = 3.2 Hz), 129.8 (d, $J_{C,F}$ = 8.0 Hz), 118.8, 115.7, 115.5 (d, $J_{C,F}$ = 21.2 Hz), 80.8, 63.1, 57.7, 50.3, 38.9.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –114.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{18}FN_4O_2$: 353.1408; found: 353.1410.

(3,4-Dihydroisoquinolin-2(1*H*)-yl)[1-(4-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]methanone (51)

Yield: 106 mg (98%); pale yellow oil; R_f = 0.50 (EtOAc/hexane 1:1).

IR (ATR): 3068, 3030, 2936, 2850, 1620, 1509, 1482, 1443, 1379, 1279, 1222, 1158, 1136, 792, 780, 747, 732 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (dd, *J* = 4.5, 1.5 Hz, 1 H), 8.54 (d, *J* = 8.0 Hz, 1 H), 7.40–7.35 (m, 2 H), 7.25–7.18 (m, 5 H), 7.02–6.97 (m, 2 H), 5.72 (m, 2 H), 5.29 (s, 1 H), 4.95 (s, 1 H), 4.30 (t, *J* = 5.6 Hz, 1 H), 4.04 (t, *J* = 5.6 Hz, 1 H), 3.00 (app t, *J* = 5.9 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.4 (d, $J_{C,F}$ = 246.5 Hz), 162.2, 161.9, 150.2, 149.4, 138.0, 137.8, 134.7, 134.5, 133.5, 133.1, 132.25, 132.18, 129.9, 129.8, 128.8, 128.5, 126.67, 126.64, 126.5, 126.4, 126.3, 125.9, 118.5, 116.6, 115.5 (d, $J_{C,F}$ = 21.7 Hz), 50.3, 48.8, 45.2, 44.7, 40.9, 29.7, 28.3.

Note: Peaks in ^{13}C NMR spectrum split as a ca. 1:1 mixture of rotamers. Both rotamers are described. Several rotamer peaks missing due to signal overlap.

^{19}F NMR (565 MHz, $CDCl_3$): δ = –114.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{20}FN_4O$: 387.1616; found: 387.1604.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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References

(1) Zheng, W.; Wang, Z.; Jiang, X.; Zhao, Q.; Shen, J. *J. Med. Chem.* **2020**, *63*, 15153.
(2) Smith, L. M.; Ladziata, V.; Delucca, I.; Pinto, D. J. P.; Orwat, M. J.; Dilger, A. K.; Pabbisetty, K. B.; Yang, W.; Shaw, S. A.; Glunz, P. W.; Panda, M. WO 2017123860A1, **2017**.
(3) Shi, J.; Xu, G.; Zhu, W.; Ye, H.; Yang, S.; Luo, Y.; Han, J.; Yang, J.; Li, R.; Wei, Y.; Chen, L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4273.
(4) Lin, R.; Connolly, P. J.; Lu, Y.; Chiu, G.; Li, S.; Yu, Y.; Huang, S.; Li, X.; Emanuel, S. L.; Middleton, S. A.; Gruninger, R. H.; Adams, M.; Fuentes-Pesquera, A. R.; Greenberger, L. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4297.
(5) Andoh, N.; Sanpei, O.; Toga, T.; Morris, D. L.; Aston, R.; Tanaka, K.; Hino, T. World Patent WO2015037747A1, **2016**.
(6) Xing, Y.; Zuo, J.; Krogstad, P.; Jung, M. E. *J. Med. Chem.* **2018**, *61*, 1688.
(7) Collier, P. N.; Twin, H. C.; Knegtel, R. M. A.; Boyall, D.; Brenchley, G.; Davis, C. J.; Keily, S.; Mak, C.; Miller, A.; Pierard, F.; Settimo, L.; Bolton, C. M.; Chiu, P.; Curnock, A.; Doyle, E.; Tanner, A. J.; Jimenez, J. *ACS Med. Chem. Lett.* **2019**, *10*, 1134.
(8) Panarese, J. D.; Engers, D. W.; Wu, Y.; Bronson, J. J.; Macor, J. E.; Chun, A.; Rodriguez, A. L.; Felts, A. S.; Engers, J. L.; Loch, M. T.; Emmitte, K. A.; Castelhano, A. L.; Kates, M. J.; Nader, M. A.; Jones, C. K.; Blobaum, A. L.; Conn, P. J.; Niswender, C. M.; Hopkins, C. R.; Lindsley, C. W. *ACS Med. Chem. Lett.* **2019**, *10*, 255.
(9) Umar, T.; Shalini, S.; Raza, M. K.; Gusain, S.; Kumar, J.; Seth, P.; Tiwari, M.; Hoda, N. *Eur. J. Med. Chem.* **2019**, *175*, 2.
(10) Moir, M.; Lane, S.; Lai, F.; Connor, M.; Hibbs, D. E.; Kassiou, M. *Eur. J. Med. Chem.* **2019**, *180*, 291.
(11) Aronov, A.; Lauffer, D. J.; Li, P.; Tomlinson, R. C. WO2003078423A1, **2005**.
(12) Lynch, B. M.; Khan, M. A.; Teo, H. C.; Pedrotti, F. *Can. J. Chem.* **1988**, *66*, 420.
(13) Mittendorf, J.; Weigand, S.; Alonso-Alija, C.; Bischoff, E.; Feurer, A.; Gerisch, M.; Kern, A.; Knorr, A.; Lang, D.; Muenter, K.; Radtke, M.; Schirok, H.; Schlemmer, K.; Stahl, E.; Straub, A.; Wunder, F.; Stasch, J. *ChemMedChem* **2009**, *4*, 853.
(14) (a) Buchler, I. P.; Hayes, M. J.; Hegde, S. G.; Hockerman, S. L.; Jones, D. E.; Kortum, S. W.; Rico, J. G.; Tenbrink, R. E.; Wu, K. K. WO2009106980, **2009**. (b) Buchler, I. P.; Hayes, M. J.; Hegde, S. G.; Hockerman, S. L.; Jones, D. E.; Kortum, S. W.; Rico, J. G.; Tenbrink, R. E.; Wu, K. K. WO2009106982, **2009**.
(15) Buchstaller, H.; Wilkinson, K.; Burek, K.; Nisar, Y. *Synthesis* **2011**, 3089.
(16) Blaquiere, N.; Burch, J.; Castanedo, G.; Feng, J. A.; Hu, B.; Staben, S.; Wu, G.; Yuen, P. WO 2015025025A1, **2015**.
(17) Blake, J. F.; Boyd, S. A.; Cohen, F.; De Messe, J.; Fong, K. C.; Gaudino, J. J.; Kaplan, T.; Marlow, A. L.; Seo, J.; Thomas, A. A.; Tian, H.; Young, W. B. WO 2007103308, **2007**.
(18) Kannaboina, P.; Raina, G.; Kumar, K. A.; Das, P. *Chem. Commun.* **2017**, *53*, 9446.
(19) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114.
(20) Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. *Acc. Chem. Res.* **2016**, *49*, 594.
(21) Neumann, K. T.; Lindhardt, A. T.; Bang-Andersen, B.; Skrydstrup, T. *Org. Lett.* **2015**, *17*, 2094.
(22) Bhilare, S.; Shah, J.; Gaikwad, V.; Gupta, G.; Sanghvi, Y. S.; Bhanage, B. M.; Kapdi, A. R. *Synthesis* **2019**, *51*, 4239.
(23) Gockel, S. N.; Hull, K. L. *Org. Lett.* **2015**, *17*, 3236.

(24) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232.
(25) Kaiser, N. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109.
(26) Mamone, M.; Aziz, J.; Le Bescont, J.; Piguel, S. *Synthesis* **2018**, *50*, 1521.
(27) Babjak, M.; Caletková, O.; Ďurišová, D.; Gracza, T. *Synlett* **2014**, *25*, 2579.
(28) Friis, S. D.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 18114.
(29) Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061.
(30) Flinker, M.; Lopez, S.; Nielsen, D. U.; Daasbjerg, K.; Jensen, F.; Skrydstrup, T. *Synlett* **2017**, *28*, 2439.
(31) Yin, Z.; Wu, X. *Org. Process Res. Dev.* **2017**, *21*, 1869.
(32) Markovič, M.; Lopatka, P.; Kóóš, P.; Gracza, T. *Org. Lett.* **2015**, *17*, 5618.
(33) Veryser, C.; Van Mileghem, S.; Egle, B.; Gilles, P.; De Borggraeve, W. M. *React. Chem. Eng.* **2016**, *1*, 142.
(34) Peng, J.; Geng, H.; Wu, X. *Chem* **2019**, *5*, 526.
(35) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402.
(36) Fang, W.; Zhu, H.; Deng, Q.; Liu, S.; Liu, X.; Shen, Y.; Tu, T. *Synthesis* **2014**, *46*, 1689.
(37) Jian, X.; Yang, F.; Jiang, C.; You, W.; Zhao, P. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 127025.
(38) Dierkes, P.; Van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519.
(39) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102.
(40) Van der Veen, L. A.; Keeven, P. H.; Schoemaker, G. C.; Reek, J. N. H.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Lutz, M.; Spek, A. L. *Organometallics* **2000**, *19*, 872.
(41) Jover, J.; Cirera, J. *Dalton Trans.* **2019**, 15036.
(42) Doherty, S.; Knight, J. G.; Ward, N. A. B.; Bittner, D. M.; Wills, C.; McFarlane, W.; Clegg, W.; Harrington, R. W. *Organometallics* **2013**, *32*, 1773.
(43) Roy, S.; Roy, S.; Gribble, G. W. *Tetrahedron* **2012**, *68*, 9867.
(44) Beller, M.; Wu, X. *A Discussion Between Carbonylation, Noncarbonylation and Decarbonylation. Transition Metal Catalyzed Carbonylation Reactions: Carbonylative Activation of C-X Bonds*; Springer-Verlag: Berlin, **2013**, 215–221.
(45) Langueux-Tremblay, P.; Fabrikant, A.; Arndtsen, B. A. *ACS Catal.* **2018**, *8*, 5350.
(46) Nielsen, D. U.; Taaning, R. H.; Lindhardt, A. T.; Gøgsig, T. M.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 4454.
(47) Ismael, A.; Gevorgyan, A.; Skrydstrup, T.; Bayer, A. *Org. Process Res. Dev.* **2020**, *24*, 2665.
(48) Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750.
(49) Åkerbladh, L.; Schembri, L. S.; Larhed, M.; Odell, L. R. *J. Org. Chem.* **2017**, *82*, 12520.
(50) Boyarskii, V. P. *Russ. J. Gen. Chem.* **2008**, *78*, 1511.
(51) Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M. *J. Organomet. Chem.* **2001**, *622*, 84.
(52) Dong, Y.; Sun, S.; Yang, F.; Zhu, Y.; Zhu, W.; Qiao, H.; Wu, Y.; Wu, Y. *Org. Chem. Front.* **2016**, *3*, 720.
(53) Hughes, N. L.; Brown, C. L.; Irwin, A. A.; Cao, Q.; Muldoon, M. J. *ChemSusChem* **2017**, *10*, 675.
(54) Ran, L.; Ren, Z.; Wang, Y.; Guan, Z. *Chem. Asian J.* **2014**, *9*, 577.
(55) Das, D.; Bhanage, B. M. *Adv. Synth. Catal.* **2020**, *362*, 3022.