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

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7
5
6


10


11

Figure 1 Examples of biologically active pyrazolo[3,4-b]pyridine derivatives 1-11 ${ }^{1-10}$
finity and efficacy at both the cannabinoid receptor subtypes 1 and $2 .{ }^{10}$

As part of ongoing work in our laboratory, we became interested in accessing a series of N -1-substituted pyrazo-lo[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 $\mathbf{1 2}$. However, several previous reports ${ }^{10-14}$ outlining the preparation of $\mathrm{N}-1-$

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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 ${ }^{\circledR}$ ). 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 ${ }^{\circledR}$ (Bayer)] and 2 [vericiguat, Verquvo ${ }^{\circledR}$ (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 pyrazo-lo[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 af-
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 $(\mathrm{n}=3)$ of 3-iodo-1H-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 $\mathbf{1 2}$ 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, ${ }^{20,21}$ transi-tion-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 $\left.{ }^{\circledR}\right)^{20}$ and ex situ generated $\mathrm{CO},{ }^{33}$ on the conversion of aryl iodide $\mathbf{1 5}^{37}$ to exemplar pyrazolo[3,4-b]pyridine 16 (Table 1 ).

The reaction of aryl iodide $\mathbf{1 5}$ with our chosen amine nucleophile, benzylamine, proceeded smoothly to furnish the desired C-3 carboxamide $\mathbf{1 6}$ in good to excellent yield when employing several palladium catalyst precursors (5 $\mathrm{mol} \%$ ), including $\mathrm{PdCl}_{2}$ (72\%), $\mathrm{Pd}(\mathrm{dba})_{2}$ (84\%), and $\mathrm{Pd}(\mathrm{OAc})_{2}$ (95\%) (Table 1, entries 1-3), in the presence of Xantphos (L1) ( $5 \mathrm{~mol} \%$ ). Taking $\mathrm{Pd}(\mathrm{OAc})_{2}$ 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 $107^{\circ}$ ) ( $95 \%$ yield 16; Table 1, entry 3), DPEphos (L2, bite angle $103^{\circ}$ ), dppf ( $\mathbf{L 3}$, bite angle $96^{\circ}$ ), and dppp ( $\mathbf{L 4}$, bite angle $91^{\circ}$ ) 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 $\mathbf{1 5}$ to C-3 carboxamide $\mathbf{1 6}$ 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 $\mathbf{L 1}$ (flexibility range 97$\left.133^{\circ}\right)^{40}$ 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 $\mathrm{PPh}_{3}\left(\mathbf{L 5} ;\right.$ Tolman cone angle $\left.\Theta=145^{\circ}\right), \mathrm{PCy}_{3}(\mathbf{L 6} ; \Theta=$ $\left.170^{\circ}\right),{ }^{41}$ MePhos (L7; $\Theta=190^{\circ}$ ), and SPhos (L8; $\left.\Theta=205^{\circ}\right),{ }^{42}$ were investigated (Table 1, entries 7-10). While $\mathrm{PPh}_{3}$ 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 ( $\geq 170^{\circ}$ ) 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

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Table 1 Effect of Pd Catalyst Precursor and Phosphine Ligand on the Yield of $\mathbf{1 6}^{\text {a,b,c }}$



L1


L2


L5


L6


L3


L7


L4


| Entry | Catalyst precursor | Ligand (mol\%) | Yield of $\mathbf{1 6}(\%)^{\text {d }}$ |
| :---: | :---: | :---: | :---: |
| 1 | PdCl | $\mathbf{2}$ | $\mathbf{7 2}$ |
| 2 | $\mathrm{Pd}(\mathrm{dba})_{2}$ | $\mathbf{L 1}(5)$ | 84 |
| 3 | $\mathrm{Pd}(\mathrm{OAC})_{2}$ | $\mathbf{L 1}(5)$ | 95 |
| 4 | $\mathrm{Pd}(\mathrm{OAC})_{2}$ | $\mathbf{L 1}(5)$ | 46 |
| 5 | $\mathrm{Pd}(\mathrm{OAC})_{2}$ | $\mathbf{L 2}(5)$ | 26 |
| 6 | $\mathrm{Pd}(\mathrm{OAC})_{2}$ | $\mathbf{L 3}(5)$ | 16 |
| 7 | $\mathrm{Pd}(\mathrm{OAC})_{2}$ | $\mathbf{L 4}(5)$ | 87 |
| 8 | $\mathrm{Pd}(\mathrm{OAC})_{2}$ | $\mathbf{L 5}(10)$ | 62 |
| 9 | $\mathrm{Pd}(\mathrm{OAC})_{2}$ | $\mathbf{L 6}(10)$ | 68 |
| 11 | $\mathrm{Pd}(\mathrm{OAC})_{2}$ | $\mathbf{L 7}(10)$ | 64 |
| 12 | $\mathrm{Pd}(\mathrm{OAC})_{2}$ | $\mathbf{L 8}(10)$ | 22 |

${ }^{\text {a }}$ Reaction scale: 0.14 mmol (with respect to aryl iodide 15).
${ }^{\mathrm{b}}$ Reaction concentration: 0.5 M (with respect to aryl iodide 15).
${ }^{c} \mathrm{CO}$ was generated ex situ. ${ }^{33}$
${ }^{\mathrm{d}}$ 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 $\mathbf{L 1}$ as the optimal ligand for the carbonylation of $\mathbf{1 5}$ 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 $\mathbf{1 6}$ is significantly reduced ( $22 \%$ vs $95 \%$, Table 1 , entries 11 and 3, respectively). As expected, in the absence of $\mathrm{Pd}(\mathrm{OAc})_{2}$, the formation of carboxamide $\mathbf{1 6}$ was not observed (Table 1, entry 12). These latter control experiments highlight the crucial role that both $\mathrm{Pd}(\mathrm{OAc})_{2}$ and Xantphos play in the aminocarbonylation of aryl iodide $\mathbf{1 5}$ to afford 16. Attempts to substitute sodium carbonate with other bases, such as potassium carbonate or triethylamine did not significantly impact the yield of $\mathbf{1 6}$ (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 $\mathbf{1 6}$ 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 $\mathbf{1 5}$ to carboxamide $\mathbf{1 6}$ 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 ${ }^{\circledR}$ apparatus volume ( 20 mL ). Notably, lowering the CO

Table 2 Effect of Base and Solvent on the Yield of $\mathbf{1 6}^{\text {a,b,c }}$


15


16

| Entry | Base | Solvent | Yield of $\mathbf{1 6}(\%)^{\text {d }}$ |
| :--- | :--- | :--- | :--- |
| 1 | $\mathrm{~K}_{2} \mathrm{CO}_{3}$ | toluene | 90 |
| 2 | $\mathrm{NEt}_{3}$ | toluene | 86 |
| 3 | $\mathrm{Na}_{2} \mathrm{CO}_{3}$ | DMF | 58 |
| 4 | $\mathrm{Na}_{2} \mathrm{CO}_{3}$ | DMSO | 38 |

${ }^{\text {a }}$ Reaction scale: 0.14 mmol (with respect to aryl iodide 15).
${ }^{\mathrm{b}}$ Reaction concentration: 0.5 M (with respect to aryl iodide 15).
${ }^{\text {c CO }}$ was generated ex situ. ${ }^{33}$
${ }^{\mathrm{d}}$ 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 $\mathbf{1 5}$, did not cause a significant decline in the yield of carboxamide 16 ( $95 \%$ vs $89 \%$, respectively). However, a significant decrease in the yield of $\mathbf{1 6}$ 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 ${ }^{\circledR}$ apparatus volume ( 20 mL ) constant, permitted access to amide 16 in a comparably high yield (94\%). The latter result indicates that $\mathbf{1 6}$ 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 $\mathbf{1 6}^{\text {a,b }}$


[^0]Efforts to examine the effect of catalyst loading on the yield of 16 (Table 4, entries $1-3$ ) from $5 \mathrm{~mol} \% \mathrm{Pd}(\mathrm{OAc})_{2}$ 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 $0.5 \mathrm{~mol} \% \mathrm{Pd}(\mathrm{OAc})_{2}$ and L1, respectively (Table 4, entry 3). Furthermore, attempts to reduce the reaction time for the transformation of $\mathbf{1 5}$ to $\mathbf{1 6}$ (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 $\mathbf{1 7}$ was similarly obtained in excellent yield ( $93 \%$, Table 4 , entry 7 ).

Table 4 Optimization of Catalyst Loading and Reaction Time for Carboxamides 16-19a,b,c

${ }^{\text {a }}$ Reaction scale: 0.14 mmol (with respect to aryl iodide 15 ).
${ }^{\mathrm{b}}$ Reaction concentration: 0.5 M (with respect to aryl iodide 15).
c CO was generated ex situ. ${ }^{33}$
${ }^{\text {d }}$ 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, $\alpha$-keto amine nucleophile $\mathbf{2 0}$ (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 $0.5 \mathrm{~mol} \%$ to $1 \mathrm{~mol} \%$ 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 $5 \mathrm{~mol} \%$ 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 $18{ }^{\mathrm{a}, \mathrm{b}, \mathrm{c}}$
2
${ }^{\text {a }}$ Reaction scale: 0.14 mmol (with respect to aryl iodide 15).
${ }^{\mathrm{b}}$ Reaction concentration: 0.5 M (with respect to aryl iodide 15).
${ }^{\text {c CO }}$ was generated ex situ. ${ }^{33}$
${ }^{\mathrm{d}}$ 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 pyrazo-lo[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 $\mathbf{1 7}$ ( $p-\mathrm{OMe}$ ) and $\mathbf{2 2 - 2 5}$. For example, the inclusion of electron-withdrawing substituents ( $p-\mathrm{NO}_{2}$ and $p-\mathrm{CF}_{3}$ ) 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 $\mathbf{2 2}$ 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 $\mathbf{2 4}$ in excellent yields of $93 \%$ and $89 \%$, respectively.

The protocol tolerates the presence of a $p-\mathrm{Br}$ 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 pyra-zolo[3,4-b]pyridine $\mathbf{2 5}$. Further incorporation of sterically hindered amine nucleophiles, including cumylamine and 1adamantylamine, 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 $\mathbf{2 8}$ 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 $\mathbf{> 9 0 \%} \mathbf{2 9 - 3 1}$ ). 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 $(S)$ - $\mathbf{3 6}$ and $(R)$ - $\mathbf{3 6}$ 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 $\alpha$-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 $\alpha$-amino amide nucleophile gave the corresponding primary amide derivative 37 in significantly poor yield (28\%), alongside the formation of by-product $\mathbf{3 8}$ (59\% yield, Figure 2). The structural elucidation of $\mathbf{3 8}$ was accomplished using a combination of nuclear magnetic resonance (NMR) spectroscopy, including ${ }^{1} \mathrm{H}-{ }^{15} \mathrm{~N}$ heteronuclear multiple bond correlation (HMBC), and HRMS. While aryl imide bond formation has previously been documented using Pd catalysis, in the presence of $\mathrm{CO}^{54}$ it is reasonable that pyrazolo[3,4-b]pyridine dimer $\mathbf{3 8}$ may have similarly arisen from the carbonylative cross-coupling of amide 37 and aryl iodide 15.

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$22\left(\mathrm{R}=\mathrm{NO}_{2}\right): 84 \%$
$23\left(\mathrm{R}=\mathrm{CF}_{3}\right): 84 \%$
17 ( $\mathrm{R}=\mathrm{OMe}$ ): $93 \%$
25 ( $\mathrm{R}=\mathrm{Br}$ ): $90 \%$


29, $96 \%$


34, $97 \%$

$39,95 \%$


26, $98 \%$


30, $92 \%$


35, 89\%


40, 98\%



27, $95 \%$

(S) $-36,97 \%$ (> $99 \%$ ee) (R) $-\mathbf{3 6}, 90 \%$ (> $99 \%$ ee)


41, 89\%


32, 62\%


37, 28\%


21


28, 98\%


18, $93 \%$


33, $94 \%$


19, $95 \%$

$42(R=H): 99 \%$
$43(R=M e): 95 \%$

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 $(0.28 \mathrm{mmol})$, amine ( 0.42 mmol ), $\mathrm{Pd}(\mathrm{OAC})_{2}(5 \mathrm{~mol} \%)$, Xantphos ( $5 \mathrm{~mol} \%$ ), $\mathrm{Na}_{2} \mathrm{CO}_{3}\left(3\right.$ equiv.), toluene ( 0.56 mL ), CO surrogate ( 5 equiv.), $100{ }^{\circ} \mathrm{C}, 18 \mathrm{~h}$.


38
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 $\mathrm{Pd}(\mathrm{OAc})_{2}$ 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 $\mathbf{1 5}$ to give a wide range of secondary amides $\mathbf{1 7 - 1 9 , 2 2 - 3 7}$, 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 ), $\mathrm{Pd}(\mathrm{OAc})_{2}$ ( $5 \mathrm{~mol} \%$ ), Xantphos ( $5 \mathrm{~mol} \%$ ), $\mathrm{Na}_{2} \mathrm{CO}_{3}$ (3 equiv.), toluene ( 0.56 mL ), CO surrogate ( 5 equiv.), $100^{\circ} \mathrm{C}, 18 \mathrm{~h}$.

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-6azaspiro[3.3]heptane and tetrahydroisoquinoline, could be utilized to afford the corresponding tertiary amides $\mathbf{5 0}$ 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-1H-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 $\alpha$-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 ${ }^{\circledR}$ ). 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 $3 \AA$ molecular sieves (which were dried prior to use, by heating to $175{ }^{\circ} \mathrm{C}$ for 48 h ). Room temperature (rt) ranged between $16.5-24^{\circ} \mathrm{C}$ with an average value of $20^{\circ} \mathrm{C}$. 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 $0.040-0.063 \mathrm{~mm}$, density $0.8 \mathrm{~g} / \mathrm{cm}^{3}$ ).
${ }^{1} \mathrm{H}(300 \mathrm{MHz})$ and ${ }^{13} \mathrm{C}(75 \mathrm{MHz})$ NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. ${ }^{1} \mathrm{H}(400 \mathrm{MHz})$ and ${ }^{13} \mathrm{C}$ ( 100 MHz ) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. ${ }^{1} \mathrm{H}(600 \mathrm{MHz})$ and ${ }^{13} \mathrm{C}(150 \mathrm{MHz})$ 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 ${ }^{\circ} \mathrm{C}$, using $\mathrm{CDCl}_{3}$ (with TMS as internal standard, $\delta_{\mathrm{H}}=0.00$ ) as sample solvent. Chemical shift values ( $\delta_{\mathrm{H}}$ and $\delta_{\mathrm{C}}$ ) are reported in ppm relative to TMS $\left(\mathrm{CDCl}_{3}\right)$ and coupling constants ( $J$ ) are expressed in hertz ( Hz ), in the following format: chemical shift value (multiplicity, coupling constant, integration). ${ }^{1} \mathrm{H}$ NMR spectral data are described, using the standard abbreviations. ${ }^{13} \mathrm{C}$ NMR spectral data were calibrated using the solvent signal for $\mathrm{CDCl}_{3}\left(\delta_{\mathrm{C}}=77.0, \mathrm{t}\right)$.
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 ${ }^{\circledR} \mathrm{V}$ 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 $\mathrm{MeCN} / \mathrm{H}_{2} \mathrm{O}$ (1:1) and contained $0.1 \% \mathrm{v} / \mathrm{v}$ formic acid. HRMS experiments were performed using leucine enkephalin as an internal calibrant.

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

To a 100 mL round-bottomed flask was added 3-iodo-1H-pyrazolo-[3,4-b]pyridine ( $1.8 \mathrm{~g}, 7.35 \mathrm{mmol}$ ) and DMF ( 7.5 mL ). The resulting solution was treated with $\mathrm{Cs}_{2} \mathrm{CO}_{3}(2.633 \mathrm{~g}, 8.08 \mathrm{mmol})$ and allowed to stir at rt for a further 30 min . 4-Fluorobenzyl bromide ( $1 \mathrm{~mL}, 8.08$ 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 $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}(100 \mathrm{~mL})$ and further stirred at rt for 1 h . The suspension was filtered under vacuum and the resulting solids were subsequently washed with $\mathrm{H}_{2} \mathrm{O}(3 \times 20 \mathrm{~mL})$. Recrystallization from EtOH furnished title compound 15; yield: $1.950 \mathrm{~g}(75 \%)$; fine colorless needles; mp $132-133^{\circ} \mathrm{C}(\mathrm{EtOH}) ; R_{f}=0.67$ (EtOAc/hexane 3:7).
IR (ATR): 3058, 3040, 3010, 2953, 1599, 1567, 1507, 1452, 1264, 1211, 1157, 1121, 970, 779, 765, $479 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.58(\mathrm{dd}, J=4.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.80(\mathrm{dd}$, $J=8.1,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.39-7.35(\mathrm{~m}, 2 \mathrm{H}), 7.18(\mathrm{dd}, J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H})$, 7.01-6.95 (m, 2 H ), 5.67 (s, 2 H ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.3 \mathrm{~Hz}\right), 150.3,150.1$, $132.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 130.6,129.9\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2 \mathrm{~Hz}\right), 120.5,117.7,115.5$ $\left(\mathrm{d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 90.2,50.4$.
${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.3$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{13} \mathrm{H}_{10} \mathrm{FIN}_{3}$ : 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 ${ }^{\circledR}$ ) was added $\mathrm{Pd}(\mathrm{OAc})_{2}(3.14 \mathrm{mg}, 14 \mu \mathrm{~mol})$ in anhyd toluene $(0.2 \mathrm{~mL})$, Xantphos ( $8.1 \mathrm{mg}, 14 \mu \mathrm{~mol}$ ) in anhyd toluene ( 0.3 mL ), anhyd toluene $(0.06 \mathrm{~mL}), \mathrm{Na}_{2} \mathrm{CO}_{3}(90 \mathrm{mg}, 0.42 \mathrm{mmol})$, 3-iodo- 1 H -pyra-zolo[3,4-b]pyridine ( $100 \mathrm{mg}, 0.28 \mathrm{mmol}$ ), and appropriate amine ( 0.42 mmol ). To Chamber B of the two-chamber reactor was added formic acid ( $0.05 \mathrm{~mL}, 1.4 \mathrm{mmol}$ ) and $\mathrm{MsCl}(0.11 \mathrm{~mL}, 1.4 \mathrm{mmol})$. The vessel was then flushed with $\mathrm{N}_{2}$ for $10 \mathrm{~min}\left(\mathrm{~N}_{2}\right.$ flow inlet through Chamber A and flow outlet through Chamber B). Chamber B was treated with $\mathrm{NEt}_{3}(0.39 \mathrm{~mL}, 2.8 \mathrm{mmol})$ 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 $100^{\circ} \mathrm{C}$ 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 ( $5 \times 2 \mathrm{~mL}$ ), 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)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide (16)

Yield: 96 mg (95\%); pale yellow crystalline solid; mp $105^{\circ} \mathrm{C} ; R_{f}=0.20$ (EtOAc/hexane 1:3).
IR (ATR): 3291, 3030, 2940, 1638, 1542, 1510, 1391, 1222, 1165, 1138, 781, 737, 695, 525, 521, $423 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.70(\mathrm{dd}, J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.60(\mathrm{dd}$, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.40-7.26(\mathrm{~m}, 9 \mathrm{H}), 5.66(\mathrm{~s}, 2 \mathrm{H}), 4.68(\mathrm{~d}, J=6.0 \mathrm{~Hz}$, 2 H ).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.7 \mathrm{~Hz}\right), 161.7,149.6$, $138.2,136.9,132.2,132.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 129.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2 \mathrm{~Hz}\right)$, $128.7,127.9,127.5,118.9,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.9,50.4,43.0$.
${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.1$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{21} \mathrm{H}_{18} \mathrm{FN}_{4} \mathrm{O}$ : 361.1459; found: 361.1465.

## 1-(4-Fluorobenzyl)-N-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyri-dine-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, $1223,1172,1033,812,782,774,520 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR $\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.70(\mathrm{dd}, J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.59(\mathrm{dd}$, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.33-7.25(\mathrm{~m}, 6 \mathrm{H}), 7.00-6.93(\mathrm{~m}, 2 \mathrm{H}), 6.91-6.86$ (m, 2 H$), 5.65(\mathrm{~s}, 2 \mathrm{H}), 4.61(\mathrm{~d}, J=6.0 \mathrm{~Hz}, 2 \mathrm{H}), 3.80(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.6 \mathrm{~Hz}\right), 161.6,159.0$, $151.0,149.6,137.0,132.1,132.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 130.2,129.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=\right.$ $8.2 \mathrm{~Hz}), 129.2,118.8,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.8,114.1,55.2,50.3$, 42.5.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.1$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{22} \mathrm{H}_{20} \mathrm{FN}_{4} \mathrm{O}_{2}$ : 391.1565; found: 391.1557.

## N -(3,3-Dimethyl-2-oxobutyl)-1-(4-fluorobenzyl)-1H-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, $1493,1222,1158,781,755,608,562,520,483 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.63(\mathrm{dd}, J=8.0,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.59(\mathrm{dd}$, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.75(\mathrm{t}, J=4.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.40-7.35(\mathrm{~m}, 2 \mathrm{H}), 7.26$ (dd, $J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.03-6.95(\mathrm{~m}, 2 \mathrm{H}), 5.70(\mathrm{~s}, 2 \mathrm{H}), 4.51$ (d, $J=$ $4.7 \mathrm{~Hz}, 2 \mathrm{H}), 1.26(\mathrm{~s}, 9 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=210.3,162.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.7 \mathrm{~Hz}\right), 161.9$, $151.0,149.6,136.6,132.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 131.9,130.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2\right.$ $\mathrm{Hz}), 118.9,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.5 \mathrm{~Hz}\right), 114.8,50.5,44.3,43.2,24.6$.
${ }^{19}$ F NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.2$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{20} \mathrm{H}_{22} \mathrm{FN}_{4} \mathrm{O}_{2}$ : 369.1721; found: 369.1723.

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

Yield: 96 mg (95\%); yellow crystalline solid; $\mathrm{mp} 159{ }^{\circ} \mathrm{C} ; R_{f}=0.27$ (EtOAc/hexane 3:1).
IR (ATR): 3539, 3411, 3314, 3061, 2936, 1660, 1536, 1510, 1493, 1392, $1272,1222,1158,1018,811,773,484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.71(\mathrm{~d}, J=1.1 \mathrm{~Hz}, 1 \mathrm{H}), 8.66(\mathrm{dd}, J=8.1$, $1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.59(\mathrm{dd}, J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.54(\mathrm{dd}, J=2.4,1.5 \mathrm{~Hz}, 1 \mathrm{H})$, $8.50(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.92(\mathrm{t}, \mathrm{J}=5.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.36-7.31(\mathrm{~m}, 2 \mathrm{H})$, 7.27 (dd, $J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.01-6.94(\mathrm{~m}, 2 \mathrm{H}), 5.69(\mathrm{~s}, 2 \mathrm{H}), 4.85(\mathrm{~d}$, $J=5.9 \mathrm{~Hz}, 2 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.7 \mathrm{~Hz}\right), 162.0,152.8$, $151.0,149.6,144.0,143.9,143.5,136.6,131.94\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=2.8 \mathrm{~Hz}\right)$, $131.92,129.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2 \mathrm{~Hz}\right), 118.9,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.7 \mathrm{~Hz}\right), 114.8$, 50.4, 42.1.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.0$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{19} \mathrm{H}_{16} \mathrm{FN}_{6} \mathrm{O}: 363.1364$; found: 363.1358.

## 1-(4-Fluorobenzyl)-N-(4-nitrobenzyl)-1H-pyrazolo[3,4-b]pyri-

 dine-3-carboxamide (22)Yield: 95 mg ( $84 \%$ ); pale yellow solid; $\mathrm{mp} 160{ }^{\circ} \mathrm{C} ; R_{f}=0.27$ (EtOAc/ hexane 2:3).
IR (ATR): 3411, 3312, 3073, 2937, 1662, 1510, 1499, 1343, 1222, 731 $\mathrm{cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.66(\mathrm{dd}, J=8.1,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 8.62(\mathrm{dd}$, $J=4.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 8.18(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 7.53(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H})$, $7.35-7.27$ (m, 4 H), 7.01-6.95 (m, 2 H ), 5.68 (s, 2 H ), 4.76 (d, J = 6.3 Hz , $2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR $\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=162.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.9 \mathrm{~Hz}\right), 162.1,151.1$, $149.9,147.3,145.9,136.5,132.00,131.95\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.5 \mathrm{~Hz}\right), 129.8(\mathrm{~d}$, $\left.J_{C, F}=8.2 \mathrm{~Hz}\right), 128.3,123.9,119.2,115.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.8,50.5$, 42.4 .
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-113.9$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{21} \mathrm{H}_{17} \mathrm{FN}_{5} \mathrm{O}_{3}$ : 406.1310; found: 406.1308.

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

Yield: 101 mg (84\%); beige crystalline solid; $\mathrm{mp} 138{ }^{\circ} \mathrm{C} ; R_{f}=0.23$ (EtOAc/hexane 3:7).
IR (ATR): 3422, 3317, 3064, 2940, 1660, 1533, 1510, 1323, 1270, 1224, $1159,1120,1110,1066,837,810,782,773 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.67(\mathrm{dd}, J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.60(\mathrm{dd}$, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.59(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.50-7.44(\mathrm{~m}, 3 \mathrm{H}), 7.35-$ 7.25 (m, 3 H ), 7.01-6.93 (m, 2 H ), 5.67 ( $\mathrm{s}, 2 \mathrm{H}), 4.72$ (d, J = $6.2 \mathrm{~Hz}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.8 \mathrm{~Hz}\right), 162.0,151.1$, $149.8,142.4\left(\mathrm{app} d, J_{\mathrm{C}, \mathrm{F}}=0.9 \mathrm{~Hz}\right), 136.7,132.1,132.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.3 \mathrm{~Hz}\right)$, $129.81\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2 \mathrm{~Hz}\right), 129.78\left(\mathrm{q}, J_{\mathrm{C}, \mathrm{F}}=32.4 \mathrm{~Hz}\right), 128.0,125.7\left(\mathrm{q}, J_{\mathrm{C}, \mathrm{F}}=\right.$ $3.8 \mathrm{~Hz}), 124.1\left(\mathrm{q}, J_{\mathrm{C}, \mathrm{F}}=272.0 \mathrm{~Hz}\right), 119.1,115.6\left(\mathrm{q}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.9$, 50.5, 42.5.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-62.5,-114.0$.
HRMS-ESI: $m / z[M+H]+$ calcd for $\mathrm{C}_{22} \mathrm{H}_{17} \mathrm{~F}_{4} \mathrm{~N}_{4} \mathrm{O}$ : 429.1333; found: 429.1326.

## 1-(4-Fluorobenzyl)-N-(4-methylbenzyl)-1H-pyrazolo[3,4-b]pyri-dine-3-carboxamide (24)

Yield: 93 mg (89\%); pale yellow crystalline solid; mp $136^{\circ} \mathrm{C} ; R_{f}=0.60$ (EtOAc/hexane 1:1).
IR (ATR): 3419, 3316, 3064, 3023, 2924, 2859, 1658, 1531, 1509, 1498, 1390, 1269, 1222, 1158, 811, 781, 774, $483 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.69(\mathrm{dd}, J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.58(\mathrm{dd}$, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.33-7.24(\mathrm{~m}, 6 \mathrm{H}), 7.15(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.00-$ $6.92(\mathrm{~m}, 2 \mathrm{H}), 5.64(\mathrm{~s}, 2 \mathrm{H}), 4.63(\mathrm{~d}, J=6.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.33(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.6 \mathrm{~Hz}\right), 161.7,151.0$, $149.6,137.2,137.0,135.1,132.2,132.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 129.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=\right.$ $8.2 \mathrm{~Hz}), 129.4,127.9,118.9,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.7 \mathrm{~Hz}\right), 114.9,50.4,42.8$, 21.0.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.1$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{22} \mathrm{H}_{20} \mathrm{FN}_{4} \mathrm{O}$ : 375.1616; found: 375.1607.

## $N$-(4-Bromobenzyl)-1-(4-fluorobenzyl)-1H-pyrazolo[3,4-b]pyri-dine-3-carboxamide (25) <br> Yield: 111 mg (90\%); colorless crystalline solid; $\mathrm{mp} 143-144{ }^{\circ} \mathrm{C}$; $R_{f}=$ 0.60 (EtOAc/hexane 1:1).

IR (ATR): 3413, 3316, 3064, 2936, 1548, 1531, 1509, 1488, 1269, 1222, 1158, 1011, 810, 775, 520, $483 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.67(\mathrm{dd}, J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.59(\mathrm{dd}$, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.47-7.43(\mathrm{~m}, 2 \mathrm{H}), 7.38(\mathrm{t}, J=5.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.34-$ $7.23(\mathrm{~m}, 5 \mathrm{H}), 7.00-6.92(\mathrm{~m}, 2 \mathrm{H}), 5.65(\mathrm{~s}, 2 \mathrm{H}), 4.61(\mathrm{~d}, \mathrm{~J}=6.2 \mathrm{~Hz}, 2 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR $\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.6 \mathrm{~Hz}\right), 161.8,151.0$, $149.7,137.3,136.7,132.05,131.96\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 131.7,129.7(\mathrm{~d}$, $\left.J_{C, F}=8.2 \mathrm{~Hz}\right), 129.4,121.4,119.0,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.8,50.4$, 42.3.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.0$.
HRMS-ESI: $m / z[\mathrm{M}+\mathrm{H}]^{+}$calcd for $\mathrm{C}_{21} \mathrm{H}_{17}{ }^{79} \mathrm{BrFN}_{4} \mathrm{O}$ : 439.0564; found: 439.0549.

## 1-(4-Fluorobenzyl)-N-(2-phenylpropan-2-yl)-1H-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, $1158,849,781,762,698,563,547,520,484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.62(\mathrm{dd}, J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.56(\mathrm{dd}$, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.51-7.48(\mathrm{~m}, 2 \mathrm{H}), 7.37-7.33(\mathrm{~m}, 5 \mathrm{H}), 7.26-7.19$ (m, 2 H ), 7.03-6.98 (m, 2 H$), 5.70(\mathrm{~s}, 2 \mathrm{H}), 1.85(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.6 \mathrm{~Hz}\right), 160.9,151.0$, $149.5,146.8,137.6,132.4,132.1\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 129.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2\right.$ $\mathrm{Hz}), 128.4,126.7,124.7,118.7,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.8,55.9$, 50.4, 29.5.
${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.1$.
HRMS-ESI: $m / z[\mathrm{M}+\mathrm{Na}]^{+}$calcd for $\mathrm{C}_{23} \mathrm{H}_{21} \mathrm{FN}_{4} \mathrm{ONa}$ : 411.1591; found: 411.1574.

## $N$-[(3s,5s,7s)-Adamantan-1-yl]-1-(4-fluorobenzyl)-1H-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, $861,778,731,519,484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.67(\mathrm{dd}, J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.57$ (dd, $J=4.5,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.35-7.28(\mathrm{~m}, 2 \mathrm{H}), 7.24(\mathrm{dd}, J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H})$, 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).
${ }^{13} \mathrm{C}$ NMR ( $100 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.4\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}, \mathrm{F}}=246.5 \mathrm{~Hz}\right), 161.2,151.0$, $149.4,137.9,132.3,132.2\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 129.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.3 \mathrm{~Hz}\right)$, $118.7,115.5\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.8,52.0,50.3,41.7,36.3,29.4$.
${ }^{19} \mathrm{~F}$ NMR ( $376 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.2$.
HRMS-ESI: $m / z[\mathrm{M}+\mathrm{H}]^{+}$calcd for $\mathrm{C}_{24} \mathrm{H}_{26} \mathrm{FN}_{4} \mathrm{O}$ : 405.2085; found: 405.2082.
$N$-[(1R,2R,4S)-Bicyclo[2.2.1]heptan-2-yl]-1-(4-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide (28)
Yield: $100 \mathrm{mg}(98 \%)$; amber oil; $[\alpha]_{\mathrm{D}}{ }^{25}+4.50\left(c 0.10, \mathrm{CHCl}_{3}\right) ; R_{f}=0.33$ (EtOAc/hexane 3:7).
IR (ATR): 3423, 3317, 3068, 2952, 2871, 1652, 1526, 1510, 1493, 1275, $1222,1157,781,730,520,484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.67$ (dd, $J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.58 (dd, $J=4.5,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.35-7.28(\mathrm{~m}, 2 \mathrm{H}), 7.25(\mathrm{dd}, J=8.2,4.6 \mathrm{~Hz}, 1 \mathrm{H})$, 7.02-6.94 (m, 2 H ), 6.85 (d, $J=7.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 5.68 ( $\mathrm{s}, 2 \mathrm{H}$ ), 3.95 (app dt, $J=7.5,3.5 \mathrm{~Hz}, 1 \mathrm{H}), 2.38-2.34(\mathrm{~m}, 2 \mathrm{H}), 1.93-1.86(\mathrm{~m}, 1 \mathrm{H}), 1.63-1.05$ (m, 7 H ).
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.6 \mathrm{~Hz}\right), 161.1,151.1$, $149.6,137.3,132.3,132.2\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.3 \mathrm{~Hz}\right), 129.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2 \mathrm{~Hz}\right)$, $118.8,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.9,52.6,50.4,42.5,40.3,35.76$, 35.71, 28.2, 26.5.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.2$.
HRMS-ESI: $m / z[\mathrm{M}+\mathrm{H}]^{+}$calcd for $\mathrm{C}_{21} \mathrm{H}_{22} \mathrm{FN}_{4} \mathrm{O}$ : 365.1772; found: 365.1769.

## 1-(4-Fluorobenzyl)-N-[2-(methylsulfonyl)ethyl]-1H-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, $1220,1128,956,766,625,522,500,484,418 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.61(\mathrm{dd}, J=3.7,1.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), $8.59(\mathrm{~s}, 1$ H), $7.64(\mathrm{t}, J=6.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.39-7.32(\mathrm{~m}, 2 \mathrm{H}), 7.29-7.25(\mathrm{~m}, 1 \mathrm{H})$, 7.02-6.94 (m, 2 H), 5.67 (s, 2 H ), 4.00 (dd, J = 6.1, $6.1 \mathrm{~Hz}, 2 \mathrm{H}$ ), 3.40 (t, $J=6.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.99(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.9 \mathrm{~Hz}\right), 162.2,150.9$, $149.7,136.2,131.8\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.3 \mathrm{~Hz}\right), 131.7,129.9\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2 \mathrm{~Hz}\right)$, $119.0,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.7,54.0,50.5,41.7,33.0$.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.0$.
HRMS-ESI: $m / z[\mathrm{M}+\mathrm{H}]^{+}$calcd for $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{FN}_{4} \mathrm{O}_{3} \mathrm{~S}$ : 377.1078; found: 377.1074.

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

Yield: 120 mg (92\%); beige solid; mp $142{ }^{\circ} \mathrm{C} ; R_{f}=0.48$ (EtOAc).
IR (ATR): 3265, 3063, 2935, 2876, 1652, 1538, 1510, 1156, 1092, 907, $727,661,549 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.54$ (dd, $J=4.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.52 (dd, $J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.72(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.43(\mathrm{t}, J=6.1 \mathrm{~Hz}, 1 \mathrm{H})$, $7.36-7.30(\mathrm{~m}, 2 \mathrm{H}), 7.20(\mathrm{dd}, J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.13(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2$ H), 6.99-6.91 (m, 2 H ), $5.87(\mathrm{t}, J=5.9 \mathrm{~Hz}, 1 \mathrm{H}), 5.60(\mathrm{~s}, 2 \mathrm{H}), 3.58$ (dt, $J=5.9,5.8 \mathrm{~Hz}, 2 \mathrm{H}), 3.22(\mathrm{dt}, J=5.9,5.8 \mathrm{~Hz}, 2 \mathrm{H}), 2.27(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.5,162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.6 \mathrm{~Hz}\right), 150.6$, $149.4,143.2,136.7,136.3,131.83\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 131.79,129.9\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}\right.$ $=8.5 \mathrm{~Hz}), 129.5,126.9,118.9,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.7 \mathrm{~Hz}\right), 114.6,50.3$, 43.2, 39.0, 21.3.
${ }^{19}$ F NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.0$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{23} \mathrm{H}_{23} \mathrm{FN}_{5} \mathrm{O}_{3} \mathrm{~S}: 468.1500$; found: 468.1497.

## 1-(4-Fluorobenzyl)-N-(2-methylallyl)-1H-pyrazolo[3,4-b]pyri-dine-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, $1221,1158,810,772,483,419 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.68$ (dd, $J=8.1,1.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.59 (dd, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.37-7.30(\mathrm{~m}, 2 \mathrm{H}), 7.26(\mathrm{dd}, J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H})$, 7.17 (t, J = 5.6 Hz, 1 H), 7.02-6.94 (m, 2 H$), 5.68(\mathrm{~s}, 2 \mathrm{H}), 4.96-4.89(\mathrm{~m}$, $2 \mathrm{H}), 4.04(\mathrm{~d}, \mathrm{~J}=6.3 \mathrm{~Hz}, 2 \mathrm{H}), 1.81(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.7 \mathrm{~Hz}\right), 161.7,151.0$, $149.6,141.9,136.9,132.1,132.0\left(\mathrm{~d}, J_{C, F}=3.2 \mathrm{~Hz}\right), 129.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2\right.$ $\mathrm{Hz}), 118.8,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.8,111.2,50.3,44.5,20.3$. ${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-14.1$.

HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{18} \mathrm{H}_{18} \mathrm{FN}_{4} \mathrm{O}$ : 325.1459; found: 325.1465 .

## 1-(4-Fluorobenzyl)-N-(2-methylbut-3-yn-2-yl)-1H-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, $484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.70$ (dd, $J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.58 (dd, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.34-7.29(\mathrm{~m}, 2 \mathrm{H}), 7.26(\mathrm{dd}, J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H})$, 7.10 (br s, 1 H ), $7.63-6.95$ (s, 2 H ), 2.42 (s, 1 H ), 1.80 (s, 6 H ).
${ }^{13} \mathrm{C}$ NMR $\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=162.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.6 \mathrm{~Hz}\right), 161.0,151.1$, $149.7,137.2,132.3,132.1\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.3 \mathrm{~Hz}\right), 129.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2 \mathrm{~Hz}\right)$, $118.9,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.8,87.0,69.4,50.4,47.4,29.3$.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.1$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{19} \mathrm{H}_{18} \mathrm{FN}_{4} \mathrm{O}$ : 337.1459; found: 337.1449.

1-(4-Fluorobenzyl)-N-(2-hydroxyethyl)-1H-pyrazolo[3,4-b]pyri-dine-3-carboxamide (33)
Yield: 83 mg (94\%); colorless solid; $\mathrm{mp} 108{ }^{\circ} \mathrm{C} ; R_{f}=0.27$ (EtOAc) hexane 1:3).
IR (ATR): 3415, 3321, 3071, 2937, 2877, 1650, 1539, 1509, 1494, 1392, $1272,1221,1171,1159,1061,774,520,484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.60(\mathrm{dd}, J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.56(\mathrm{dd}$, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.50(\mathrm{t}, J=5.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.32-7.27(\mathrm{~m}, 2 \mathrm{H}), 7.22$ (dd, $J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.99-6.92(\mathrm{~m}, 2 \mathrm{H}), 5.63(\mathrm{~s}, 2 \mathrm{H}), 3.86-3.83$ (m, 2 H ), 3.67-3.61 (m, 2 H ), 2.95 (br s, 1 H ).
${ }^{13} \mathrm{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.7,162.3\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.7 \mathrm{~Hz}\right), 150.8$, $149.6,136.7,132.0,131.9\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.0 \mathrm{~Hz}\right), 129.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.5 \mathrm{~Hz}\right)$, $118.9,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.8 \mathrm{~Hz}\right), 114.7,62.0,50.3,42.0$.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.0$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{16} \mathrm{H}_{16} \mathrm{FN}_{4} \mathrm{O}_{2}: 315.1252$; found: 315.1198.

1-(4-Fluorobenzyl)-N-(2-hydroxy-2-methylpropyl)-1H-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, $484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.64(\mathrm{dd}, J=8.1,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 8.58(\mathrm{dd}$, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{t}, J=6.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.36-7.22(\mathrm{~m}, 2 \mathrm{H}), 7.24$ (dd, $J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.01-6.93(\mathrm{~m}, 2 \mathrm{H}), 5.67(\mathrm{~s}, 2 \mathrm{H}), 3.50(\mathrm{~d}, J=$ 6.3 Hz, 2 H), 2.81 (s, 1 H$), 1.31(\mathrm{~s}, 6 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.8,162.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.7 \mathrm{~Hz}\right), 151.0$, $149.6,136.8,132.1,132.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.3 \mathrm{~Hz}\right), 129.8\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.3 \mathrm{~Hz}\right)$, $118.9,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.9,71.1,50.4,50.0,27.4$.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.1$
HRMS-ESI: $m / z[M+N a]^{+}$calcd for $\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{FN}_{4} \mathrm{O}_{2} \mathrm{Na}$ : 365.1384; found: 365.1386.

1-(4-Fluorobenzyl)-N-(2-oxoazepan-3-yl)-1H-pyrazolo[3,4-b]pyri-dine-3-carboxamide (35)
Yield: 95 mg (89\%); beige crystalline solid; $\mathrm{mp} 218-219{ }^{\circ} \mathrm{C} ; R_{f}=0.63$ (EtOAc/hexane 3:1).

IR (ATR): 3381, 3291, 3073, 2933, 2854, 1650, 1510, 1222, 910, 783, $727,576 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.63(\mathrm{dd}, J=8.1,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 8.58$ (dd, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.30(\mathrm{~d}, J=6.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.41-7.35(\mathrm{~m}, 2 \mathrm{H}), 7.25$ (dd, $J=8.1,4.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.02-6.94(\mathrm{~m}, 2 \mathrm{H}), 6.56(\mathrm{t}, J=6.1 \mathrm{~Hz}, 1 \mathrm{H})$, $5.71\left(\mathrm{ABq}, \Delta \delta \mathrm{AB}=0.05, J_{\mathrm{A}, \mathrm{B}}=14.9 \mathrm{~Hz}, 2 \mathrm{H}\right), 4.78(\mathrm{ddd}, J=11.0,6.3,1.5$ $\mathrm{Hz}, 1 \mathrm{H}), 3.42-3.25(\mathrm{~m}, 2 \mathrm{H}), 2.28-2.24(\mathrm{~m}, 1 \mathrm{H}), 2.11-2.04(\mathrm{~m}, 1 \mathrm{H})$, 1.99-1.85 (m, 2 H), 1.72-1.58 (m, 1 H$), 1.53-1.39$ (m, 1 H ).
${ }^{13} \mathrm{C}$ NMR $\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=175.3,162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.5 \mathrm{~Hz}\right), 161.1$, $150.9,149.4,136.7,132.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.3 \mathrm{~Hz}\right), 131.8,129.9\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2\right.$ $\mathrm{Hz}), 118.8,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.9,52.0,50.4,42.1,31.7,29.0$, 28.0.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.3$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{20} \mathrm{H}_{21} \mathrm{FN}_{5} \mathrm{O}_{2}$ : 382.1674; found: 382.1666.

Methyl [1-(4-Fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-car-bonyl]-L-phenylalaninate [(S)-36]
Yield: 117 mg (97\%); pale yellow oil; $[\alpha]_{\mathrm{D}}{ }^{25}+46.5\left(c 0.10, \mathrm{CHCl}_{3}\right) ; R_{f}=$ 0.13 (EtOAc/hexane 1:3).

IR (ATR): 3415, 3325, 3068, 3034, 2952, 1740, 1663, 1526, 1510, 1278, 1219, 1169, 781, 730, 700, 520, $483 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.61(\mathrm{dd}, J=8.0,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.58(\mathrm{dd}$, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.45(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.38-7.33(\mathrm{~m}, 2 \mathrm{H}), 7.30-$ $7.16(\mathrm{~m}, 6 \mathrm{H}), 7.03-6.95(\mathrm{~m}, 2 \mathrm{H}), 5.66\left(\mathrm{ABq}, \Delta \delta \mathrm{AB}=0.06, J_{\mathrm{A}, \mathrm{B}}=14.9\right.$ $\mathrm{Hz}, 2 \mathrm{H}), 5.09(\mathrm{dt}, J=8.1,6.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.74\left(\mathrm{ABX}, J_{\mathrm{A}, \mathrm{B}}=13.9 \mathrm{~Hz}, J_{\mathrm{B}, \mathrm{X}}=6.2\right.$ $\left.\mathrm{Hz}, J_{\mathrm{A}, \mathrm{X}}=6.0 \mathrm{~Hz}, 2 \mathrm{H}\right)$.
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=171.9,162.5\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}, \mathrm{F}}=246.6 \mathrm{~Hz}\right), 161.4$, $151.0,149.6,136.3,135.9,132.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.7 \mathrm{~Hz}\right), 131.9,130.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=\right.$ $8.2 \mathrm{~Hz}), 129.3,128.6,127.1,119.0,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.9,52.9$, 52.4, 50.5, 38.3.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.1$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{24} \mathrm{H}_{22} \mathrm{FN}_{4} \mathrm{O}_{3}$ : 433.1670; found: 433.1664.

## Methyl [1-(4-Fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-car-bonyl]-D-phenylalaninate [(R)-36]

Yield: $109 \mathrm{mg}(90 \%)$; colorless oil; $[\alpha]_{\mathrm{D}}^{25}-31.0\left(c 0.10, \mathrm{CHCl}_{3}\right) ; R_{f}=$ 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, $484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.62(\mathrm{dd}, J=8.0,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 8.58$ (dd, $J=4.5,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.37-7.34(\mathrm{~m}, 2 \mathrm{H}), 7.29-$ 7.23 (m, 4 H$), 7.19-7.17$ (m, 2 H ), 7.01-6.98 (m, 2 H$), 5.67$ (ABq, $\Delta \delta A B$ $\left.=0.06, J_{\mathrm{A}, \mathrm{B}}=15.0 \mathrm{~Hz}, 2 \mathrm{H}\right), 5.10(\mathrm{dt}, J=7.9,6.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.75(\mathrm{~s}, 3 \mathrm{H}$, $\left.\mathrm{ABX}, J_{\mathrm{A}, \mathrm{B}}=13.9 \mathrm{~Hz}, J_{\mathrm{B}, \mathrm{X}}=6.2 \mathrm{~Hz}, J_{\mathrm{A}, \mathrm{X}}=6.1 \mathrm{~Hz}, 2 \mathrm{H}\right)$.
${ }^{13} \mathrm{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=171.9,162.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.5 \mathrm{~Hz}\right), 161.3$, $150.9,149.5,136.2,135.9,131.97,131.96,130.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.1 \mathrm{~Hz}\right)$, $129.3,128.6,127.1,119.0,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.8 \mathrm{~Hz}\right), 114.9,52.9,52.4$, 50.5, 38.2.
${ }^{19} \mathrm{~F}$ NMR ( $565 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.0$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{24} \mathrm{H}_{22} \mathrm{FN}_{4} \mathrm{O}_{3}$ : 433.1670; found: 433.1664.

## $N$-(1-Carbamoylcyclopentyl)-1-(4-fluorobenzyl)-1H-pyrazolo-

 [3,4-b]pyridine-3-carboxamide (37)Yield: 30 mg (28\%); colorless solid; mp 209-210 ${ }^{\circ} \mathrm{C} ; R_{f}=0.43$ (EtOAc/ hexane 1:1).
IR (ATR): 3364, 2966, 2880, 1752, 1652, 1509, 1470, 1220, 1124, 773, $556,521,485 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR $\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.66(\mathrm{dd}, J=8.0,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 8.46(\mathrm{dd}$, $J=4.5,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 8.51(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.37-7.35(\mathrm{~m}, 2 \mathrm{H}), 7.29(\mathrm{dd}, J=$ $8.0,4.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.00-6.98(\mathrm{~m}, 2 \mathrm{H}), 5.70(\mathrm{~s}, 2 \mathrm{H}), 2.11-1.93(\mathrm{~m}, 8 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=186.4,162.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.6 \mathrm{~Hz}\right), 151.8$, $151.1,150.0,133.5,132.1,131.9\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 130.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.3\right.$ $\mathrm{Hz}), 118.8,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.1,78.7,50.5,37.7,26.1$.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-113.9$.
HRMS-ESI: $m / z\left[M-\mathrm{H}_{2} \mathrm{O}\right]^{+}$calcd for $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{FN}_{5} \mathrm{O}$ : 364.1568 ; found: 364.1567.

1-(4-Fluorobenzyl)-N-(1-\{[1-(4-fluorobenzyl)-1H-pyrazolo[3,4-b]-pyridine-3-carbonyl]carbamoyl\}cyclopentyl)-1H-pyrazolo[3,4-b]-pyridine-3-carboxamide (38)
Yield: 52 mg (59\%); colorless solid; mp $214-215^{\circ} \mathrm{C} ; R_{f}=0.23$ (EtOAc/ hexane 1:1).
IR (ATR): 3360, 2964, 2883, 1752, 1652, 1509, 1470, 1220, 1124, 773, $556,521,485,422 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $600 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=10.95(\mathrm{~s}, 1 \mathrm{H}), 8.64-8.61(\mathrm{~m}, 2 \mathrm{H}), 8.59-$ $8.56(\mathrm{~m}, 2 \mathrm{H}), 7.42(\mathrm{~s}, 1 \mathrm{H}), 7.41-7.39(\mathrm{~m}, 2 \mathrm{H}), 7.28-7.26(\mathrm{~m}, 1 \mathrm{H})$, 7.24 (dd, $J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.06-7.03(\mathrm{~m}, 2 \mathrm{H}), 6.97(\mathrm{app} \mathrm{t}, J=8.6 \mathrm{~Hz}$, $2 \mathrm{H}), 6.62$ (app t, J = 8.6 Hz, 2 H ), 5.71 ( $\mathrm{s}, 2 \mathrm{H}$ ), 5.44 ( $\mathrm{s}, 2 \mathrm{H}$ ), 2.67-2.62 (m, 2 H ), 2.26-2.22 (m, 2 H ), 1.96-1.85 (m, 4 H ).
${ }^{13} \mathrm{C}$ NMR ( $151 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=171.5,162.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.8 \mathrm{~Hz}\right), 162.4$, $162.3\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.7 \mathrm{~Hz}\right), 159.2,151.0,149.99,149.97,136.3,136.1$, $131.96,131.91,131.8\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.1 \mathrm{~Hz}\right), 131.4(\mathrm{~d}, J=3.2 \mathrm{~Hz}), 130.0(\mathrm{~d}$, $\left.J_{C, F}=7.9 \mathrm{~Hz}\right), 129.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.4 \mathrm{~Hz}\right), 119.6,119.2,115.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=22.0\right.$ $\mathrm{Hz}), 115.3\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.7,68.4,50.64,50.58,36.9,24.2$.
${ }^{19}$ F NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-113.66,-113.79$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{34} \mathrm{H}_{29} \mathrm{~F}_{2} \mathrm{~N}_{8} \mathrm{O}_{3}$ : 635.2325; found: 635.2318.

1-(4-Fluorobenzyl)- $N$-(thiophen-2-ylmethyl)-1H-pyrazolo[3,4-b]-pyridine-3-carboxamide (39)
Yield: 97 mg (95\%); colorless crystalline solid; mp $129^{\circ} \mathrm{C} ; R_{f}=0.27$ (EtOAc/hexane 3:7).
IR (ATR): 3410, 3318, 3071, 2932, 1659, 1526, 1510, 1391, 1221, 1158, 810, 781, 701, 520, $484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.68(\mathrm{dd}, J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.58(\mathrm{dd}$, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.44(\mathrm{t}, J=5.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.33-7.20(\mathrm{~m}, 4 \mathrm{H}), 7.04$ (dd, $J=3.4,1.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.99-6.91(\mathrm{~m}, 3 \mathrm{H}), 5.64(\mathrm{~s}, 2 \mathrm{H}), 4.83(\mathrm{~d}, J=$ $6.0 \mathrm{~Hz}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.3\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{C}, \mathrm{F}}=246.5 \mathrm{~Hz}\right), 161.4,150.9$ $149.5,140.7,136.7,132.1,131.9\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 129.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.1\right.$ $\mathrm{Hz}), 126.8,126.1,125.2,118.9,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.9 \mathrm{~Hz}\right), 114.8,50.3$, 37.6.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.0$.
HRMS-ESI: $m / z[\mathrm{M}+\mathrm{H}]^{+}$calcd for $\mathrm{C}_{19} \mathrm{H}_{16} \mathrm{FN}_{4} \mathrm{OS}$ : 367.1023 ; found: 367.1019.

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

Yield: 97 mg ( $98 \%$ ); beige solid; $\mathrm{mp} 186-189^{\circ} \mathrm{C} ; R_{f}=0.20$ (EtOAc/hexane $1: 1$ ).
IR (ATR): 3526, 3411, 3314, 3073, 2954, 2848, 1652, 1530, 1510, 1494, $1384,1222,1139,1088,811,776,781,484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR $\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.66(\mathrm{dd}, J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.59(\mathrm{dd}$, $J=4.5,1.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.37-7.30(\mathrm{~m}, 2 \mathrm{H}), 7.27(\mathrm{dd}, J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H})$, $7.03-6.95(\mathrm{~m}, 2 \mathrm{H}), 6.91(\mathrm{~d}, \mathrm{~J}=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 5.69(\mathrm{~s}, 2 \mathrm{H}), 4.24$ (tdt, $J=$ $11.8,8.1,4.1 \mathrm{~Hz}, 1 \mathrm{H}$ ), 4.02 (ddd, $J=12.0,3.9,2.8 \mathrm{~Hz}, 2 \mathrm{H}$ ), 3.55 (ddd, $J=11.7,11.7,2.1 \mathrm{~Hz}, 2 \mathrm{H}), 2.05-2.00(\mathrm{~m}, 2 \mathrm{H}), 1.66$ (dddd, $J=12.8$, $11.4,11.4,4.5 \mathrm{~Hz}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR $\left(75 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=162.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.8 \mathrm{~Hz}\right), 161.2,151.1$, $149.7,137.0,132.14,132.10\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.3 \mathrm{~Hz}\right), 129.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2 \mathrm{~Hz}\right)$, $118.9,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.9,66.8,50.4,45.5,33.2$.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.1$
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FN}_{4} \mathrm{O}_{2}$ : 355.1565; found: 355.1558.

1-(4-Fluorobenzyl)- N -(piperidin-2-ylmethyl)-1H-pyrazolo[3,4-b]-pyridine-3-carboxamide (41)
Yield: 95 mg (89\%); colorless oil; $R_{f}=0.30\left(1 \% \mathrm{v} / \mathrm{v} \mathrm{NEt}_{3}\right.$ in $\mathrm{MeOH} / \mathrm{CH}_{2} \mathrm{Cl}_{2}$ 1:39).
IR (ATR): 3410, 3300, 2933, 2856, 1651, 1538, 1510, 1271, 1222, 1159, $915,810,781,730,484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.51$ (dd, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.48 (dd, $J=8.1,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.89(\mathrm{t}, J=5.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.39-7.32(\mathrm{~m}, 2 \mathrm{H}), 7.18$ (dd, $J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 6.99-6.91(\mathrm{~m}, 2 \mathrm{H}), 5.59-5.56(\mathrm{~m}, 3 \mathrm{H}), 3.89-$ 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$)$.
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=163.1,162.3\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.7 \mathrm{~Hz}\right), 150.6$, $149.5,136.0,131.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 131.4,130.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.3 \mathrm{~Hz}\right)$, $118.9,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.4,57.0,50.3,45.2,42.3,26.9,22.6$, 22.3.
${ }^{19}$ F NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.0$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{20} \mathrm{H}_{16} \mathrm{FN}_{4} \mathrm{O}$ : 368.1881; found: 368.1877.

1-(4-Fluorobenzyl)-N-phenyl-1H-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, $1461,1312,1223,1157,1121,781,753,691 \mathrm{~cm}^{-1}$.
1H NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.82$ ( $\mathrm{s}, 1 \mathrm{H}$ ), $8.70(\mathrm{dd}, J=8.1,1.6 \mathrm{~Hz}, 1$ H), 8.61 (dd, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.72 (dd, $J=8.6,1.0 \mathrm{~Hz}, 2 \mathrm{H}), 7.40-$ 7.31 (m, 4 H ), 7.27 (dd, $J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.13$ (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 ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.9 \mathrm{~Hz}\right.$ ), 159.6, 151.2, $149.8,137.5,137.0,132.1,131.9\left(\mathrm{~d}, J_{C, F}=3.3 \mathrm{~Hz}\right), 129.8\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2\right.$ $\mathrm{Hz}), 129.0,124.3,119.8,119.1,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right), 114.9,50.5$.
19F NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-113.9$.
HRMS-ESI: $m / z[\mathrm{M}+\mathrm{H}]^{+}$calcd for $\mathrm{C}_{20} \mathrm{H}_{16} \mathrm{FN}_{4} \mathrm{O}$ : 347.1303; found: 347.1303.

1-(4-Fluorobenzyl)-N-(o-tolyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamide (43)
Yield: 96 mg (95\%); colorless crystalline solid; mp $130{ }^{\circ} \mathrm{C} ; R_{f}=0.30$ (EtOAc/hexane 1:4).
IR (ATR): 3407, 3064, 3021, 2979, 2936, 2867, 1681, 1589, 1530, 1510, $1462,1222,1157,1126,842,775,754,606 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.76(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 8.71(\mathrm{dd}, J=8.1,1.6 \mathrm{~Hz}$, $1 \mathrm{H}), 8.62(\mathrm{dd}, J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.13(\mathrm{dd}, J=8.0,0.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.42-$ $7.35(\mathrm{~m}, 2 \mathrm{H}), 7.31-7.21(\mathrm{~m}, 3 \mathrm{H}), 7.09(\mathrm{dt}, J=7.4,1.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.04-$ 6.97 (m, 2 H$), 5.73$ (s, 2 H$), 2.38(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.9 \mathrm{~Hz}\right), 159.6,151.2$, $149.8,137.2,135.5,132.1,131.9\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.3 \mathrm{~Hz}\right), 130.5,129.9\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=\right.$ $8.2 \mathrm{~Hz}), 128.2,126.8,124.8,122.0,119.1,115.6\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.6 \mathrm{~Hz}\right)$, 114.9, 50.5, 17.6.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-113.9$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{21} \mathrm{H}_{18} \mathrm{FN}_{4} \mathrm{O}$ : 361.1459; found: 361.1456.

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

Yield: 69 mg ( $82 \%$ ); beige crystalline solid; $\mathrm{mp} 92^{\circ} \mathrm{C} ; R_{f}=0.27$ (EtOAc/ hexane 1:1).
IR (ATR): 3061, 3023, 2936, 1622, 1509, 1276, 1221, 1154, 1107, 1011, $895,793,780,680,521,484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H} \operatorname{NMR}\left(600 \mathrm{MHz}, \mathrm{CDCl}_{3}\right): \delta=8.58(\mathrm{dd}, J=4.5,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 8.54$ (dd, $J=8.1,1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.36-7.34(\mathrm{~m}, 2 \mathrm{H}), 7.23(\mathrm{dd}, J=8.1,4.5 \mathrm{~Hz}, 1 \mathrm{H})$, 7.00-6.96 (m, 2 H ), 5.70 ( $\mathrm{s}, 2 \mathrm{H}$ ), 3.47 ( $\mathrm{s}, 3 \mathrm{H}$ ), 3.18 ( $\mathrm{s}, 3 \mathrm{H}$ ).
${ }^{13} \mathrm{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=163.0,162.3\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.4 \mathrm{~Hz}\right), 150.2$, $149.3,138.1,132.3,131.2\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.1 \mathrm{~Hz}\right), 129.7\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=7.9 \mathrm{~Hz}\right)$, $118.4,116.6,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.8 \mathrm{~Hz}\right), 50.2,38.9,36.2$.
${ }^{19}$ F NMR ( $565 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.3$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{16} \mathrm{H}_{16} \mathrm{FN}_{4} \mathrm{O}$ : 299.1303; found: 299.1300.

1-(4-Fluorobenzyl)- N -methyl- N -phenyl-1H-pyrazolo[3,4-b]pyri-dine-3-carboxamide (47)
Yield: 58 mg (57\%); beige crystalline solid; $\mathrm{mp} 127{ }^{\circ} \mathrm{C} ; R_{f}=0.07$ (EtOAc/hexane 1:4).
IR (ATR): 3068, 3026, 2936, 1634, 1595, 1509, 1495, 1475, 1338, 1277, 1221, 1112, 979, 864, 774, 697, $484 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.51(\mathrm{dd}, J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 8.46(\mathrm{dd}$, $J=8.1,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.30-7.15(\mathrm{~m}, 6 \mathrm{H}), 7.03-6.99(\mathrm{~m}, 2 \mathrm{H}), 6.91-6.85$ (m, 2 H), $5.40(\mathrm{~s}, 2 \mathrm{H}), 3.56(\mathrm{~s}, 3 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=163.2,162.3\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.1 \mathrm{~Hz}\right), 150.0$, $149.2,145.0,137.6,132.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 131.6,129.9\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.2\right.$ $\mathrm{Hz}), 129.0,127.1,126.8,118.4,116.1,115.2\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.5 \mathrm{~Hz}\right), 50.1$, 38.6.
${ }^{19} \mathrm{~F}$ NMR ( $282 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.6$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{21} \mathrm{H}_{18} \mathrm{FN}_{4} \mathrm{O}$ : 361.1459; found: 361.1457.
[1-(4-Fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl](2-oxa-6-aza-spiro%5B3.3%5Dheptan-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, $731 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.64(\mathrm{dd}, J=8.0,1.6 \mathrm{~Hz}, 1 \mathrm{H}$ ), 8.58 (dd, $J=4.5,1.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.39-7.32(\mathrm{~m}, 2 \mathrm{H}), 7.24(\mathrm{dd}, J=8.0,4.5 \mathrm{~Hz}, 1 \mathrm{H})$, 7.04-6.96 (m, 2 H), $5.69(\mathrm{~s}, 2 \mathrm{H}), 4.85(\mathrm{~s}, 4 \mathrm{H}), 4.80(\mathrm{~s}, 2 \mathrm{H}), 4.37$ (s, 2 H).
${ }^{13} \mathrm{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.3\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.6 \mathrm{~Hz}\right), 161.8,150.2$, $149.4,137.0,132.2,132.0\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=3.2 \mathrm{~Hz}\right), 129.8\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=8.0 \mathrm{~Hz}\right)$, $118.8,115.7,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.2 \mathrm{~Hz}\right), 80.8,63.1,57.7,50.3,38.9$.
${ }^{19} \mathrm{~F}$ NMR ( $565 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.0$.
HRMS-ESI: $m / z[M+H]^{+}$calcd for $\mathrm{C}_{19} \mathrm{H}_{18} \mathrm{FN}_{4} \mathrm{O}_{2}$ : 353.1408; found: 353.1410.

## (3,4-Dihydroisoquinolin-2(1H)-yl)[1-(4-fluorobenzyl)-1H-pyrazo-lo[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, $1222,1158,1136,792,780,747,732 \mathrm{~cm}^{-1}$.
${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=8.58(\mathrm{dd}, J=4.5,1.5 \mathrm{~Hz}, 1 \mathrm{H}), 8.54(\mathrm{~d}, \mathrm{~J}=$ $8.0 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.40-7.35 (m, 2 H ), 7.25-7.18 (m, 5 H ), 7.02-6.97 (m, 2 H), $5.72(\mathrm{~m}, 2 \mathrm{H}), 5.29(\mathrm{~s}, 1 \mathrm{H}), 4.95(\mathrm{~s}, 1 \mathrm{H}), 4.30(\mathrm{t}, \mathrm{J}=5.6 \mathrm{~Hz}, 1 \mathrm{H})$, $4.04(\mathrm{t}, J=5.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.00(\mathrm{app} \mathrm{t}, J=5.9 \mathrm{~Hz}, 2 \mathrm{H})$.
${ }^{13} \mathrm{C}$ NMR ( $150 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=162.4\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=246.5 \mathrm{~Hz}\right), 162.2,161.9$, 150.2, 149.4, 138.0, 137.8, 134.7, 134.5, 133.5, 133.1, 132.25, 132.18, $129.9,129.8,128.8,128.5,126.67,126.64,126.5,126.4,126.3,125.9$, $118.5,116.6,115.5\left(\mathrm{~d}, J_{\mathrm{C}, \mathrm{F}}=21.7 \mathrm{~Hz}\right), 50.3,48.8,45.2,44.7,40.9,29.7$, 28.3.

Note: Peaks in ${ }^{13} \mathrm{C}$ 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 ( $565 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ): $\delta=-114.1$.
HRMS-ESI: $m / z[\mathrm{M}+\mathrm{H}]^{+}$calcd for $\mathrm{C}_{23} \mathrm{H}_{20} \mathrm{FN}_{4} \mathrm{O}$ : 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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[^0]:    ${ }^{\text {a }}$ Reaction concentration: 0.5 M (with respect to aryl iodide 15).
    ${ }^{\mathrm{b}} \mathrm{CO}$ was generated ex situ. ${ }^{33}$
    ${ }^{\text {c }}$ Isolated yield following wet flash column chromatography.
    ${ }^{d}$ Reaction scale: 0.14 mmol (with respect to aryl iodide 15).
    ${ }^{\mathrm{e}}$ Reaction scale: 1 mmol (with respect to aryl iodide 15).

