RSC Advances

PAPER

View Article Online
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Cite this: *RSC Adv.*, 2021, **11**, 1287

Efficient microwave-assisted Suzuki–Miyaura cross-coupling reaction of 3-bromo pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one: towards a new access to 3,5-diarylated 7-(trifluoromethyl)pyrazolo[1,5-*a*] pyrimidine derivatives†

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Received 17th September 2020
Accepted 6th December 2020

DOI: 10.1039/d0ra07959f

rsc.li/rsc-advances

A convenient and efficient synthetic route to C3-arylated 7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-one derivatives has been reported starting from 3-bromo-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5-one through a Suzuki–Miyaura cross-coupling reaction. The arylation (heteroarylation) strategy can be performed using a wide variety of aryl and heteroaryl boronic acids and requiring a tandem catalyst XPhosPdG2/XPhos to avoid the debromination reaction. These optimized conditions were successfully extended to the synthesis of 7-, 8- and 9-arylated pyrimido[1,2-*b*]indazol-2-ones from their corresponding brominated starting materials. Furthermore, the second C-5 arylation of C3-arylated pyrazolo[1,5-*a*]pyrimidin-5-ones was achieved under standard Suzuki–Miyaura cross-coupling conditions, after activating the C–O bond of the lactam function with PyBroP, giving access to a small library of 3,5-diarylated 7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidines in good to excellent yields. The interest of this approach has been highlighted by the synthesis of a known anti-inflammatory agent. Additionally, a preliminary biological evaluation has revealed that a number of derivatives display micromolar IC_{50} values against monoamine oxidase B, an important target in the field of neurodegenerative disorders.

Introduction

Transition metal-catalyzed cross-coupling reactions are widely recognized to be powerful synthetic tools for carbon–carbon and carbon-heteroatom bond formation, giving access to more complex molecules.[1] The Suzuki–Miyaura cross-coupling reaction is one of the most useful methods to create new carbon–carbon (C sp^2–C sp^2) bonds, thanks to the stability and the low toxicity of organoboron reagents.[2] Moreover, organoboron compounds provide high selectivity in cross-coupling reactions, proving that the Suzuki–Miyaura reaction is particularly suitable for the elegant synthesis of biologically active molecules and natural products.[3,4] The use of this coupling reaction in medicinal chemistry represents a considerable asset for inducing modification of the biochemical properties by introducing a functional diversification such as a vinyl, aryl or heteroaryl moiety.[5] Despite the wide scope of this coupling reaction in various fields of chemistry, some difficulties and limitations may be encountered in the case of some heteroaromatic substrates. This is observed mainly for heterocycles having a free amino group, probably because of the complexation of the metal with NH function, leading to the inhibition or deactivation of the catalyst.[6] For these reasons, the Pd-catalyzed Suzuki–Miyaura cross-coupling involving heteroaromatic substrates is therefore a major challenge for organic chemists[7] and in the pharmaceutical discovery chemistry.[8] On the other hand, pyrazolo[1,5-*a*]pyrimidine is a basic heterocycle of a variety of complex chemical compounds having large spectrum of biological properties,[9] *viz*: COX-2 inhibitors,[10] hepatitis C virus inhibitors,[11] kinase inhibitors,[12] anticancer agents,[13] PET tumor imaging agents,[14] anxiolytic agents,[15] antimicrobial agents,[16]

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra07959f

and serotonin 5-HT6 receptor antagonists.[17] In addition, pyrazolo[1,5-*a*]pyrimidine constitute the central core of several pharmaceutical drugs, such as Indiplon and Zaleplon, which are sedative-hypnotic, used to treat insomnia, and Ocinaplon which is an anxiolytic drug. Synthetically, a wide number of approaches giving access to pyrazolo[1,5-*a*]pyrimidine derivatives have been reported.[18] The condensation of 3(5)-aminopyrazoles with 1,3-dicarbonyl compound appears to be the most general approach for the synthesis of these heterocycles.[19] Other 1,3-bis electrophilic compounds, such as alkoxymethylene β-dicarbonyl derivatives, enaminonitriles and β-enaminones, have been used to generate this class of fused heterocycles.[20]

Additionally, only few syntheses have been reported for pyrazolo[1,5-*a*]pyrimidin-5-one skeleton, involving essentially the condensation of aminopyrazoles with 1,3-dimethylluracil,[20,21] 3-ethoxyacrylate[22] or ethyl 4,4,4-trifluoroacetoacetate.[23]

To date, despite significant progress in the development of palladium-catalyzed reactions of aminopyrazoles,[24] only one example of a Suzuki–Miyaura coupling reaction has been disclosed by Ellermann and co-workers, starting from 3-halogeno pyrazolo[1,5-*a*]pyrimidin-5-ones.[25] In this case, the cross-coupling was achieved using XPhosPdG3 (10 mol%) and XPhos (10 mol%) in THF at 80 °C for 16 h, providing the C3-arylated products in low yields ranging from 3 to 41%. Furthermore, no systematic study including reaction optimization conditions was reported. Consequently, the biological potential of the target arylated pyrazolo[1,5-*a*]pyrimidine derivatives and the lack of cross coupling exploration in this heterocycle led us to further develop the C3-arylation of fluorinated pyrazolo[1,5-*a*]pyrimidin-5-one **4a**. Recently, Schmitt *et al.* have reported a two-pot synthesis of 7-(hetero)aryl pyrazolo[1,5-*a*]pyrimidin-5-ones from aryl (heteroaryl)halides and aminopyrazoles.[26] Nevertheless, these strategies have various drawbacks: the scope of the substrate is restricted and pyrazolo[1,5-*a*]pyrimidin-5-ones were obtained in low to moderate yields.

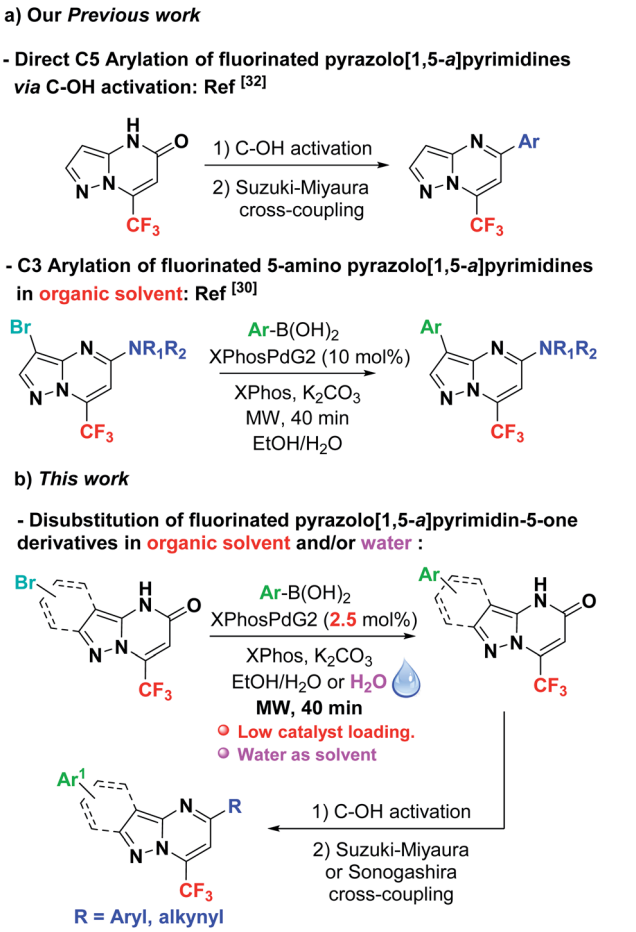
To the best of our knowledge, the Suzuki–Miyaura cross-coupling of fluorinated 3-bromo pyrazolo[1,5-*a*]pyrimidin-5-ones has never been described in the literature. This is somewhat surprising since it has been shown that the incorporation of fluorine atoms into compounds has a significant impact on their physical, chemical and biological properties.[27] For example, the presence of a CF_3 moiety contributes to increase the lipophilicity of biologically active molecules.[28] A versatile and flexible methodology for constructing 3-arylated pyrazolo [1,5-*a*]pyrimidin-5-ones, bearing a CF_3 group is thus of major importance. However, there have been few reports describing the synthesis of 3,5-disubstituted pyrazolo[1,5-*a*]pyrimidines bearing a trifluoromethyl group at C7 position.[29] Furthermore, selective and/or sequential arylation has never been studied on a pyrazolo[1,5-*a*]pyrimidin-5-one for the synthesis of substituted pyrazolo[1,5-*a*]pyrimidines.

New strategies are therefore necessary for easy and effective access to new variously substituted heterocycles targets, whose biological potential seems certain.

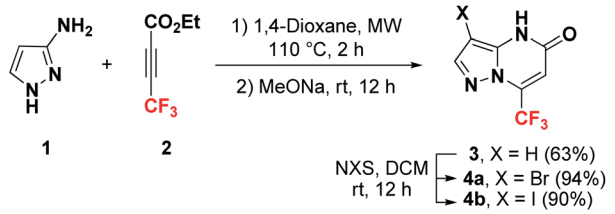
Recently, we reported the one-pot efficient regioselective synthesis of new fluorinated heterocycles *via* an addition/heterocyclization sequence using a fluorinated alkyne and 1,3-bisnucleophilic reagents.[30] Continuing our efforts to develop the synthesis of new potentially active heterocycles,[31] we report herein the first examples of a general and efficient Suzuki–Miyaura C3-arylation and heteroarylation of 3-bromo-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5-one **4a** using various aryl and heteroaryl boronic acids (Scheme 1). Some of 3-arylated pyrazolo[1,5-*a*]pyrimidin-5-ones were subsequently used as building blocks to synthesize novel fluorinated 3,5-disubstituted pyrazolo[1,5-*a*]pyrimidines. Indeed and based on our recently published work (Scheme 1),[32] an efficient and divergent method was developed to synthesize 3,5-diarylated pyrazolo[1,5-*a*]pyrimidines bearing a trifluoromethyl group at C7 position through C–O activation of the amide function.[33]

Results and discussion

The synthesis of 7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5-one 3 was accomplished according to our previously reported procedure through the condensation of commercially available 3-aminopyrazole 1 with ethyl 4,4,4-trifluorobutynoate 2 (Scheme 2).[32] The reaction proceeded smoothly to provide regioselectively 7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5-one 3 in



Scheme 1 Convergent approach to arylation of fluorinated pyrazolo [1,5-*a*]pyrimidine and fluorinated pyrazolo[1,5-*a*]pyrimidin-5-one derivatives.



Scheme 2 Synthesis of 3-halo pyrazolo[1,5-*a*]pyrimidin-5-ones **4a** and **4b**.

63% yield, without any trace of the regioisomer pyrazolo[1,5-*a*] pyrimidin-7-one (Scheme 2). It is noteworthy that for several years in our laboratory, alkyne 2 has been the subject of investigations as a basic element to synthesize new fluorinated compounds.[34] Compound **3** was subsequently converted selectively into 3-bromo and 3-iodo pyrazolo[1,5-*a*]pyrimidin-5-ones **4a** and **4b** *via* NBS or NIS-mediated bromination or iodination in CH_2Cl_2 at room temperature in excellent yields [X = Br, **4a** (94%), X = I, **4b** (90%)] (Scheme 2).

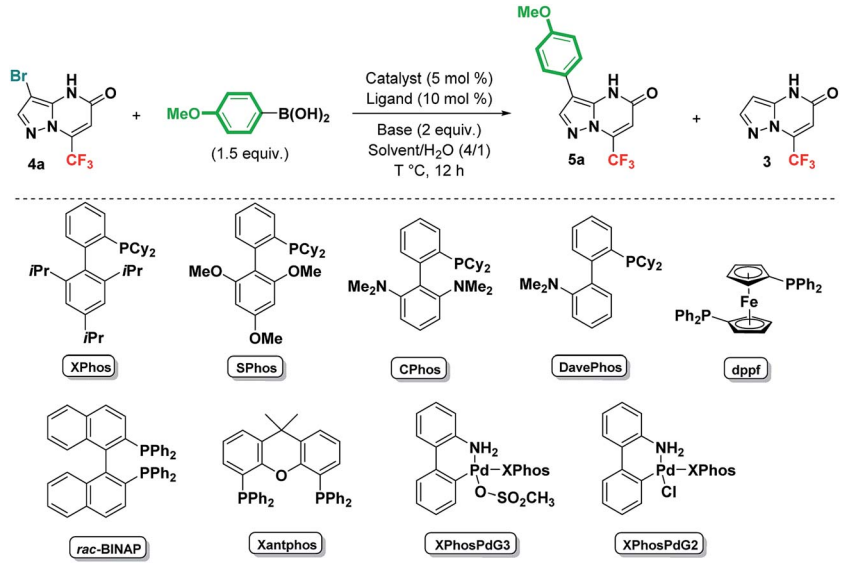
The resulting halides **4a** and **4b** could be a key building blocks to modify the C3 position through the Suzuki–Miyaura coupling reaction.[2a–c,35] This strategy is challenging because metal-catalyzed reactions present some problems and limitations especially when the used substrates contain an unprotected amino group.[36] First, we examined the coupling reaction between 3-bromo pyrazolo[1,5-*a*]pyrimidin-5-one **4a** and *p*-methoxyphenylboronic acid, using $PdCl_2(PPh_3)_2$ (5 mol%) as a catalyst in the presence of Na_2CO_3 (2 equiv.) in dioxane at 110 °C (Table 1, entry 1). The analysis of the crude ^1H and ^{19}F NMR spectrums showed 9% of the expected product 5a along with 91% of the undesired debrominated product 3 (Table 1, entry 1). To optimize the reaction conditions, the solvent, catalyst, ligand, base and temperature were carefully screened and all obtained results are summarized in Table 1. Using $PdCl_2$dppf instead of $PdCl_2(PPh_3)_2$ in the presence of Na_2CO_3 or K_2CO_3, increased slightly the yield of **5a** to 17% (Table 1, entries 2 and 3).

Under the same conditions, replacing $PdCl_2$dppf by the tandem XPhosPdG2 (5 mol%) and XPhos (10 mol%) resulted in a similar **5a**/**3** ratio (Table 1, entry 4). No improvement in the yield of the coupling product **5a** was observed when the reaction was carried out using $Pd_2(dba)_3$ (5 mol%) as a catalyst and XPhos (10 mol%) as a ligand (Table 1, entry 5). Using a polar protic solvent such as ethanol/H_2O instead of dioxane/H_2O increased the yield of the desired product **5a** to 45%, decreasing the formation of by-product **3** to 55% (Table 1, entry 6). Encouraged by this result, the mixture of EtOH/H_2O (4 : 1) was chosen as solvents for further experiments. A similar result was recorded when the reaction was performed using $Pd(OAC)_2$/XPhos tandem as catalyst (Table 1, entry 7). Additional optimizations were undertaken, using the same catalyst [$Pd(OAc)_2$] and varying the ligand. In all cases, whatever the nature of the ligand employed in these reactions (Sphos, CPhos, DavePhos, dppf, BINAP, XantPhos and PPh_3), the side product **3** was obtained mainly at the expense of the target heterocycle **5a** (Table 1, entries 8–14). Surprisingly, under Ellermann conditions (XPhosPdG3/XPhos, K_3PO_4, THF, 80 °C),[25] the yield of arylated adduct **5a** did not exceed 31%, since the debrominated product **3** was also formed in 69% yield (Table 1, entry 15). Interestingly, when the coupling reaction was performed using the XPhos derived precatalyst XPhosPdG2 in EtOH/H_2O (4 : 1) at 110 °C, the starting material was completely consumed after 12 hours, and the yield of arylated product **5a** was improved considerably to 92% (Table 1, entry 16). Nevertheless, the crude ^1H and ^{19}F NMR spectrums showed the presence of 8% of by-product **3**. Under the same reaction conditions and increasing the temperature to 135 °C, no significant difference in the result was observed (Table 1, entry 17). Using an excess of the base K_2CO_3 (3 equiv.) promoted the formation of the undesired product **3** (Table 1, entry 18). Gratifyingly, switching from conventional thermal heating to microwave irradiation at 135 °C, only the coupled product **5a** was produced in 91% isolated yield (Table 1, entry 19). Most remarkably, the reaction time was reduced from 12 h to 40 min and no trace of the debrominated product **3** was detected in crude ^1H and ^{19}F NMR spectrums. When the reaction was conducted without ligand, both heterocycles **5a** and **3** were formed equally (Table 1, entry 20), indicating the crucial role of the ligand in avoiding the side debromination reaction. Finally, reducing both XPhosPdG2 (2.5 mol%) and XPhos (5 mol%) loading did not affect significantly the reaction yield, providing compound **5a** in 89% yield (Table 1, entry 21). Very interestingly, when the reaction was carried out in water as the sole solvent, the arylation product **5a** was the only isolated product in 86% yield (Table 1, entry 22). This result was very promising since water was the solvent of choice for green chemistry. Moreover, it is known that working with water remains tricky because of its limited chemical compatibility as well as the low aqueous solubility of a large number of reagents. It is noteworthy that the nature of the halo group present on the pyrazolo[1,5-*a*]pyrimidin-5-one 3 plays an important role in this arylation reaction. In fact, whatever the conditions used, including optimized ones, the deiodination reaction cannot be avoided when the substrate **4b** was used as a starting material, presumably because of the easier reduction ability of the C–I bond to a C–H bond compared to C–Br bond.

Having established the optimized reaction conditions (Table 1, entry 22), the scope and limitations of the Suzuki–Miyaura cross-coupling reaction were examined with various aryl and heteroaryl boronic acids as coupling partners. The results are summarized in Scheme 3.

As shown in Scheme 3, in all cases the optimized conditions proved to be suitable for the coupling of **4a** with a series of boronic acids, giving the expected C3-arylated products (**5a–q**) in good to excellent yields (67–89%). Unsubstituted aryls such as phenyl, biphenyl and naphthyl groups were efficiently introduced at C3 position of the pyrazolo[1,5-*a*]pyrimidin-5-one **4a** in 74%, 79% and 85% yields, respectively (Scheme 3). A number of substituents (including functionalized ones) were tolerated on the boronic acids and very efficiently provided the desired products (**5e–q**). Arylboronic acid bearing an electron-donating group such as a methoxy group at *para, meta* or *ortho* position, reacted with **4a** leading to the corresponding

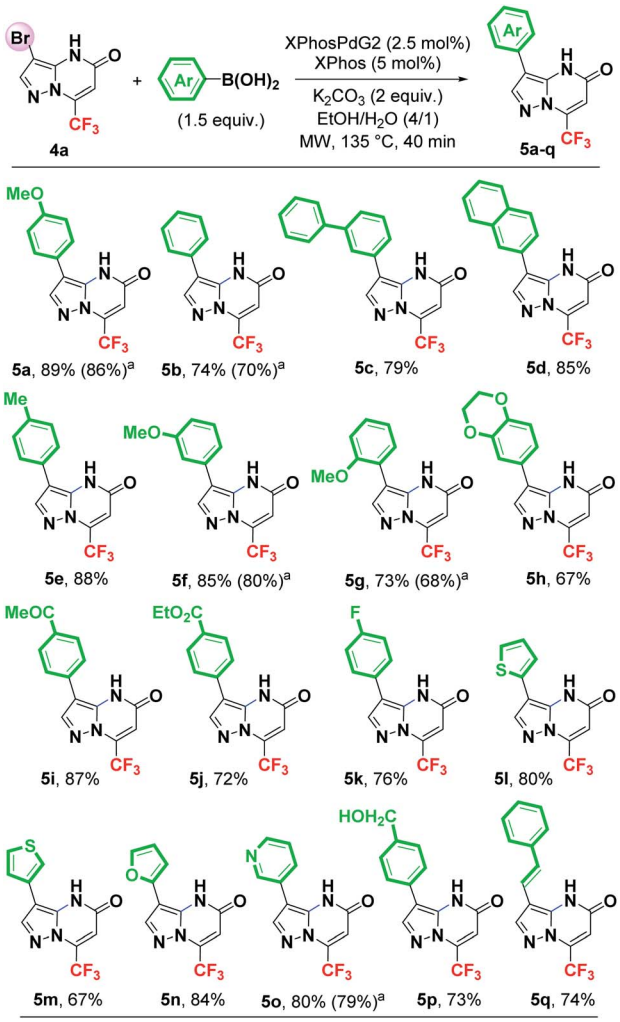
Table 1 Optimization of Suzuki–Miyaura cross-coupling conditions between **4a** and *p*-methoxyphenylboronic acid



Entry	Organic solvent	Base	Catalyst (5 mol%)	Ligand (10 mol%)	*T* (°C)	Ratio[a] 5a	3
1	Dioxane	Na_2CO_3	$PdCl_2(PPh_3)_2$	—	110	9	91
2	Dioxane	Na_2CO_3	$PdCl_2$dppf	—	110	11	89
3	Dioxane	K_2CO_3	$PdCl_2$dppf	—	110	17	83
4	Dioxane	K_2CO_3	XPhosPdG2	XPhos	110	18	82
5	Dioxane	K_2CO_3	$Pd_2(dba)_3$	XPhos	110	4	96
6	EtOH	K_2CO_3	$Pd_2(dba)_3$	XPhos	110	45	55
7	EtOH	K_2CO_3	$Pd(OAc)_2$	XPhos	110	52	48
8	EtOH	K_2CO_3	$Pd(OAc)_2$	SPhos	110	41	59
9	EtOH	K_2CO_3	$Pd(OAc)_2$	CPhos	110	24	76
10	EtOH	K_2CO_3	$Pd(OAc)_2$	DavePhos	110	21	79
11	EtOH	K_2CO_3	$Pd(OAc)_2$	Dppf	110	14	86
12	EtOH	K_2CO_3	$Pd(OAc)_2$	BINAP	110	19	81
13	EtOH	K_2CO_3	$Pd(OAc)_2$	XantPhos	110	20	80
14	EtOH	K_2CO_3	$Pd(OAc)_2$	PPh_3	110	18	82
15 (ref. 24)	THF	K_3PO_4	XPhosPdG3	Xphos	80	31	69
16	EtOH	K_2CO_3	XPhosPdG2	XPhos	110	92	8
17	EtOH	K_2CO_3	XPhosPdG2	XPhos	135	94	6
18[b]	EtOH	K_2CO_3	XPhosPdG2	XPhos	110	78	22
19[c]	**EtOH**	**K_2CO_3**	**XPhosPdG2**	**XPhos**	**135**	**100(91)**[d]	**0**
20[c]	EtOH	K_2CO_3	XPhosPdG2	—	135	45	55
21[c,e]	**EtOH**	**K_2CO_3**	**XPhosPdG2**	**XPhos**	**135**	**100(89)**[d]	**0**
22[c]	H_2O	K_2CO_3	XPhosPdG2	XPhos	135	100(86)[d]	0

[a] The ratio of mixture (**5a**/**3**) was determined from crude ^1H and ^{19}F NMR spectrums. [b] 3 equiv. of K_2CO_3 were used. [c] The reaction was carried out under microwave irradiation for 40 minutes. [d] Yield of isolated product **5a**. [e] Reaction was performed with XPhosPdG2 (2.5 mol%) and XPhos (5 mol%).

products **5a** (89%), **5f** (85%) and **5g** (73%). As observed, it appears that the steric hindrance of the *ortho*-position has a significant effect on the reaction efficiency. The cross-coupling between **4a** and 3,4-(ethylenedioxy)phenylboronic acid afforded the 3-arylated pyrazolopyrimidinone **5h** in 67% yield. Boronic acids with electron-withdrawing substituent such as 4-acetyl and ethoxycarbonyl were tolerated, yielding the desired products **5i** (87%) and **5j** (72%), respectively. Boronic acid with a fluorine atom on the aromatic ring was also found to be compatible with this coupling reaction (**5k**, 76%). Moreover, the use of heteroarylboronic acids such as 2-thienyl, 3-thienyl, 2-furyl, 3-pyridyl was effective, providing the expected heterocycles in good yields [**5l** (80%), **5m** (67%), **5n** (84%) and **5o** (80%)]. The introduction of a styryl group at C3 position was successfully achieved, affording the vinylation product **5q** in 74% yield with retention of the double bond configuration. The presence

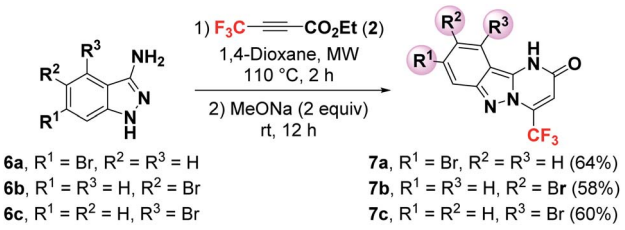


Scheme 3 Synthesis of 3-arylated(heteroarylated) pyrazolo[1,5-*a*] pyrimidin-5-ones by Suzuki–Miyaura cross-coupling reaction of **4a**. [a] Isolated yield using water as solvent.

of a free alcohol function on the boronic acid was tolerated and gave the expected product **5p** in 73% yield. The success encountered during this arylation reaction allows easy diversification into biologically important biheterocyclic frameworks.

Encouraged by the efficiency of this Suzuki–Miyaura coupling reaction enabling the introduction of aryl, heteroaryl and vinyl groups at C3 position of pyrazol[1,5-*a*]pyrimidin-5-one **4a**, we decided to extend our methodology to other electron-rich heterocycles such as pyrimido[1,2-*b*]indazol-2-ones. For this purpose, the tricyclic compounds **7a**, **7b** and **7c** were first prepared by condensation of the corresponding brominated pyrimido[1,2-*b*]indazol-2-ones **6a**, **6b** and **6c** with the fluorinated alkyne **2** in 64%, 58% and 60% yields, respectively (Scheme 4).

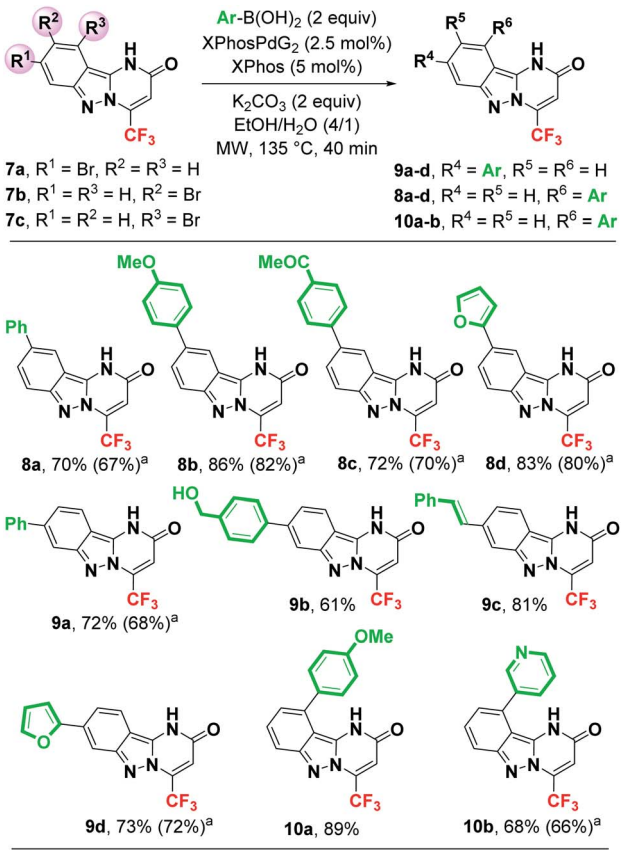
A variety of substituted arylboronic acids (with either electron-donating or electron-withdrawing groups) were used to provide the expected coupling products **8a–d**, **9a–d** and **10a,b** in good to excellent yields (61–89%) (Scheme 5). Unsubstituted phenyl boronic acid was successfully coupled with **7a** and **7b**



Scheme 4 Synthesis of **9**, **8** and 7-brominated pyrimido[1,2-*b*]indazol-2-ones **7a–c**.

giving the expected pyrimido[1,2-*b*]indazol-2-ones **8a** and **9a** in 70% and 72% isolated yields, respectively. This result demonstrated that the position of bromine on the aromatic ring has no significant effect on the effeciency of this Suzuki–Miyaura coupling. The coupling reaction of **7a** and **7b** with an heteroarylboronic acid such as 2-furylboronic acid produced the heteroarylated compounds **9d** and **8d** in 73% and 83% yields, respectively. Moreover, 3-pyridylboronic acid was effectively coupled with **7c**, providing the C-7 heteroarylated heterocycle **10b** in 68% yield (Scheme 5).

The synthesized C3 heteroarylated pyrazolo[1,5-*a*]pyrimidin-5-ones **5a–q** are attractive candidates for access to new 3,5-diarylated pyrazolo[1,5-*a*]pyrimidines because of their ability to undergo a transition-metal based coupling reaction.

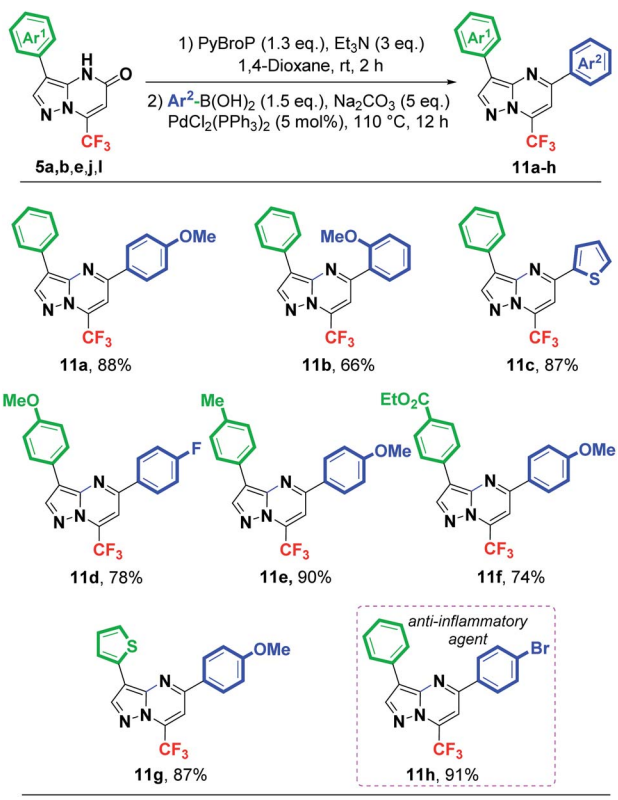


Scheme 5 Suzuki–Miyaura coupling reaction of brominated pyrimido [1,2-*b*]indazol-2-ones **7a–c**. [a] Isolated yield using water as solvent.

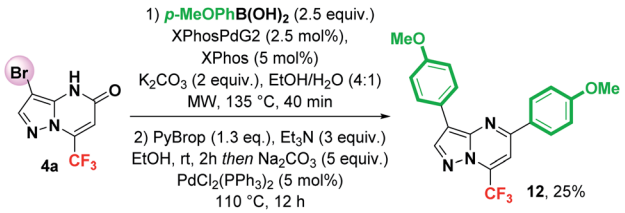
The C3-arylated pyrazolo[1,5-*a*]pyrimidin-5-ones **5a**, **5b**, **5e**, **5j** and **5l** were coupled with a variety of available boronic acids to give the desired 3,5-diarylated compounds using a combination of two conditions (Scheme 6), *i.e.*, the phosphonium coupling condition [PyBrop (1.3 equiv.), Et_3N (3 equiv.), 1,4-dioxane, rt, 2 h] then the Suzuki–Miyaura cross-coupling conditions [$PdCl_2(PPh_3)_2$, Na_2CO_3, 110 °C, 12 h]. Direct arylation proceeded successfully providing the 3,5-diarylated-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidines **11a–h** in good to excellent isolated yields (Scheme 6).

Arylboronic acid bearing an electron-donating group such as a methoxy group at *para* position was easily coupled with **5b**, **5e**, **5j** and **5l**, producing the corresponding diarylated products **11a** (88%), **11e** (90%), **11f** (74%) and **11g** (87%), respectively. Phenyl boronic acid substituted with a methoxy group at *ortho* position gave the expected coupling product **11b** in only 66% yield. Steric hindrance could explain this result. Boronic acid with an electron-withdrawing fluorine atom was also tolerated, yielding the desired product **11d** in 78% yield. Furthermore, heteroarylboronic acids such as 2-thienyl was successfully coupled with **5l** to yield the C5-heteroarylation product **11c** in 87% yield. It seems that the nature of the boronic acids used in this coupling reaction had a significant effect on the obtained results.

To demonstrate the versatility and the synthetic potential of our method, we focused our attention on the synthesis of compound having an interesting biological activity *via* the introduction of suitable aryls at C3 and C5 positions of the pyrazolo[1,5-*a*]pyrimidine core. For our delight, when the compound **5b** was subjected to the conditions of C5-arylation with *p*-bromophenylboronic acid, the known heterocyclic compound **11h** was isolated in excellent yield (91%) (Scheme 6). It is noteworthy that the 3,5-diarylated pyrazolo[1,5-*a*]pyrimidin-5-one **11h** exhibited the comparable anti-inflammatory activity (83.4%) to the standard drug Indomethacin (84.2%).[29b,37]



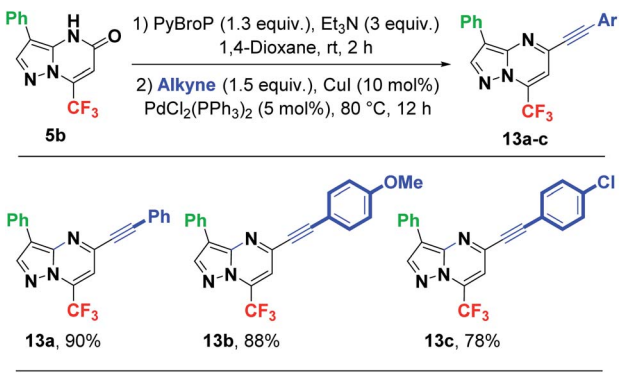
Scheme 6 Synthesis of 3,5-diarylated pyrazolo[1,5-*a*]pyrimidines **11a–h**.



Scheme 7 Sequential one-pot synthesis of fluorinated 3,5-diaryl pyrazolo[1,5-*a*]pyrimidine **12**.

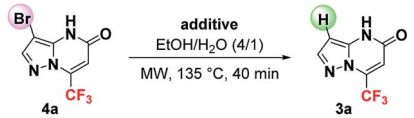
After successfully achieving stepwise sequential diarylation, we attempted to achieve this reaction sequence in a one-pot process to synthesize 3,5-diarylated pyrazolo[1,5-*a*]pyrimidines. The one-pot sequential arylation of 3-bromo pyrazolo[1,5-*a*]pyrimidin-5-one **4a** was first performed with XPhosPdG2 (2.5 mol%)/XPhos (5 mol%) as catalyst in the presence of K_2CO_3 as base (2.0 equiv.) and *p*-methoxyphenylboronic acid (2.5 equiv.) in ethanol and water (4 : 1) at 135 °C under microwave irradiation for 40 min. Upon completion of the coupling (monitored by TLC), the solvents were evaporated before using a combination of two conditions to perform the second arylation: [PyBrop (1.3 equiv.), Et_3N (3 equiv.), 1,4-dioxane, rt, 2 h], then the Suzuki–Miyaura cross-coupling conditions [$PdCl_2(PPh_3)_2$, Na_2CO_3, 110 °C, 12 h] without isolating the intermediate product. Unfortunately, the sequential one-pot coupling reaction afforded the diarylated product **12** in low 25% overall yield (Scheme 7). Note that reversing the order of the arylation reactions using the same reaction conditions was unsuccessful, since only the debrominated product was formed and no trace of the expected diarylation product **12** was observed. This result shows that the stepwise sequential arylation of **4a**, applying the earlier optimized conditions, was the best way to access 3,5-diarylated pyrazolo[1,5-*a*]pyrimidines in good yields.

After successfully performing the C5-arylation providing 3,5-diarylated pyrazolo[1,5-*a*]pyrimidines, we decided to introduce



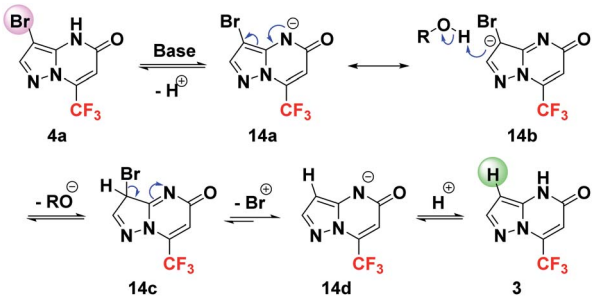
Scheme 8 Synthesis of 5-alkynyl-3-phenyl pyrazolo[1,5-*a*]pyrimidines **13a–c**.

Table 2 Mechanistic study of the debromination reaction



Entry	Additive (X equiv.)	**4a**/**3** (%)[a]
1	*p*-MeOPhB(OH)$_2$ (1.5)	100/0
2	XPhos (0.05)	100/0
3	XPhosPdG2 (0.025)	97/3
4	**K_2CO_3 (2.0)**	**0/100**
5	Na_2CO_3 (2.0)	0/100
6	KOH (2.0)	0/100
7	—	100/0

[a] The ratio **4a**/**3** was determined from the crude ^{1}H NMR spectrum.



Scheme 9 Proposed mechanism for the debromination reaction.

greater diversity using this strategy. A C5-alkynylation using the Sonogashira coupling reaction was conducted,[38] wherein alkyne (1.5 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N (5 equiv.) and dioxane were added after the prior addition of PyBroP and Et_3N at room temperature for 2 h. The mixture was subsequently heated at 80 °C for 12 h, providing 5-alkynyl-3-aryl(heteroaryl) pyrazolo[1,5-*a*]pyrimidines **13a–c** in good to excellent yields (Scheme 8). In particular, unsubstituted phenylacetylene was coupled with **5b** to afford **13a** in 90% isolated yield. Phenylacetylene with an electron-donating group such as a methoxy group at *para* position was easily coupled with **5b**, yielding the desired product **13b** in 88% yield. Phenylacetylene bearing an electron-withdrawing group such as a chlorine atom at *para* position provided the desired product **13c** in 78% yield. The electronic effect of the substituents on the aryl group seems to have a small effect on the yield of Sonogashira coupling reaction.

These successive C3-arylation/C5-arylation and C3-arylation/C5-alkynylation were carried out efficiently and open up interesting perspectives for the synthesis of diversely substituted and new potentially important biological bi (or tri)-heterocyclic frameworks.

In order to obtain further insight into the reaction mechanism of debromination, a series of control experiments were conducted to elucidate the role of each component in this reaction. The results obtained are presented in Table 2.

After examination of these results, we note that neither the presence of the boronic acid alone nor that of the ligand XPhos did not induce the formation of debrominated product **3**, since only the starting material **4a** was recovered (Table 2, entries 1 and 2). The use of XPhosPdG2 led to a low partial debromination (Table 2, entry 3). On the other hand, the treatment of compound **4a** with K_2CO_3 (2 equiv.) at 135 °C resulted in the exclusive conversion of starting material **4a** into the debrominated product **3** (Table 2, entry 4). The same result was obtained when K_2CO_3 was replaced by a base having a comparable basicity such as Na_2CO_3 or a stronger one such as KOH (Table 2, entries 5and 6). When the bromide **4a** was heated to 135 °C without any additive, no trace of the debrominated product **3** has been detected (Table 2, entry 7), confirming without a doubt the involvement of the base in the promotion of this debromination reaction. These results are completely in agreement with those reported by Cankař *et al.* in the case of the Suzuki–Miyaura coupling reaction of brominated amino pyrazoles.[39]

Basing on these experimental results and the previous literature report,[39] a possible mechanism is proposed as shown below in Scheme 9.

Table 3 AChE, BChE and MAO inhibitory potencies of active compounds

	hAChE[a]	hBChE[b]	hMAO-A[c]	hMAO-B[d]
	RA[e] at 100/10 μM	RA[e] at 100/10 μM	RA[e] at 100/10 μM	RA[e] at 100/10 μM
5a	86/93	103/90	99/95	26/73 IC_{50} = 35.0 ± 11.2 μM
5f	88/91	95/97	97/92	40/80 IC_{50} = 101.1 ± 25.7 μM
5h	86/91	95/94	95/110	**8/36** **IC_{50} = 5.36 ± 0.25 μM**
5i	91/90	99/91	98/100	21/75 IC_{50} = 26.2 ± 3.6 μM
Tacrine	IC_{50} = 0.115 ± 0.009 μM	IC_{50} = 0.023 ± 0.003 μM	n.d.[f]	n.d.[f]
Pargyline	n.d.[f]	n.d.[f]	IC_{50} = 3.97 ± 0.28 μM	IC_{50} = 0.20 ± 0.02 μM

[a] hAChE, human AChE. [b] hBChE, human BChE. [c] hMAO-A, human MAO-A. [d] hMAO-B, human MAO-B. [e] RA, residual activity at 100/10 μM compound concentration. [f] n.d., not determined.

The reaction proceeds first by a deprotonation leading to the formation of anion **14a**, which can be transformed by delocalization of electrons into the anionic species **14b**. The presence of a polar protic solvent allows a protonation of the compound **14b** giving access to the intermediate **14c**. A subsequent aromatization process occurred along with bromium (Br^+) release, affording the anionic intermediate **14d**, which after protonation, provides the debrominated product **3**.

Pyrazolopyrimidinone derivatives are also known for their activities against AChE and BuChE cholinesterases.[40] It is worth mentioning that they showed moderate selectivity for BuChE over acetylcholinesterase (AChE). They are described as potential inhibitors of BuChE with micromolar IC_{50} values. Their inhibitory potencies against BuChE were even higher than the anti-AD drug rivastigmine.

The prepared pyrazolopyrimidinones **5a–q** were thus screened against both cholinesterases (AChE and BChE), MAO-B and MAO-A using established protocols as described in the experimental section. The results of the assays are summarized in Table 3.

Interestingly, some of the tested amides showed interesting biological activities. The products which inhibit the studied targets are 7-(trifluoromethyl) pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-ones derivatives **5a**, **5f**, **5h** and **5i**. They selectively inhibit hMAO-B in the micromolar range (Table 3). This suggests that phenyl substituted at the C-3 and/or C-4 positions by an OMe or COMe group is required for inhibition of hMAO-B.[41] Compound **5h** was the most potent hMAO-B inhibitor with an IC_{50} value of 5.36 μM.

Conclusions

In conclusion, we have developed a catalytic system to synthesize a wide variety of new C3-arylated pyrazolo[1,5-*a*] pyrimidin-5-one derivatives *via* the Suzuki–Miyaura cross-coupling reaction of brominated pyrazolo[1,5-*a*]pyrimidin-5-one derivatives bearing a trifluoromethyl group, without the formation of any trace of the side debrominated product. The use of a catalytic amount of XPhosPdG2/XPhos tandem in the presence of K_2CO_3 in aqueous ethanol as green solvent allowed the efficient cross-coupling reaction of 3-bromo-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one, 7-, 8- and 9-bromo 4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-ones with a range of aryl, heteroaryl and styrylboronic acids, providing a rapid access to arylated and heteroarylated pyrazolo[1,5-*a*]pyrimidin-5-one derivatives in good to excellent yields. Some of synthesized C3-arylated pyrazolo[1,5-*a*] pyrimidin-5-ones were used as a building blocks for generating new 3,5-diarylated or 3-arylated/5-alkynylated pyrazolo [1,5-*a*]pyrimidines containing a trifluoromethyl group. The potential application of this environmentally protocol was also demonstrated by the synthesis of the known anti-inflammatory agent **11h**, opening access for the design of new functionalized pyrazolo[1,5-*a*]pyrimidines, having other potential biological activities.

Experimental

General information

Melting points of samples were measured using open capillary tubes. ^1H, ^{13}C and ^{19}F NMR spectra were recorded at 300, 75 and 282 MHz respectively with a 300 MHz Bruker Avance FT-NMR spectrometer using $CDCl_3$, acetone-*d*6, THF-*d*8 or DMSO-*d*6 as the solvents. All chemical shifts are given in ppm and they are referenced to tetramethylsilane (TMS) as an internal standard. Electrospray ionization high-resolution mass spectrometry experiments were performed with a hybrid tandem quadrupole/time-of flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Zspray) ion source (Micromass, Manchester, U.K.) operated in positive mode. Reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. All compounds were visualized by UV irradiation (longwave at 365 nm or shortwave at 254 nm). All column chromatography was performed using silica gel 60 (230–400.13 mesh, 0.040–0.063 mm). All chemicals reagents purchased from commercial suppliers were used as received. Triethylamine was distilled over calcium hydride and the 1,4-dioxane over sodium and benzophenone.

The microwave-assisted reactions were performed using a Monowave 300 (microwave synthesis reactor: Anton Paar, 300 W maximum power). Microwave irradiation was carried out in sealed 10–30 mL vessels (borosilicate glass) with a PTFE-coated silicon septum and closed with a snap cap made of PEEK. The temperatures were measured on the surface of the vial with an IR sensor (measuring range: 30 to 300 °C; uncertainty: ±5 °C) and were measured with high precision in the reaction mixture with a ruby thermometer (measuring range: 30 to 300 °C; uncertainty: ±2 °C) that could be read directly from the instrument screen. The reaction time was measured from when the reaction mixture reached the stated temperature for temperature controlled experiments. The pressure was measured with a non-invasive pressure sensor located in the swiveling cover of the Monowave 300 (measuring range: 0 to 30 bar; uncertainty: ±1.5 bar).

Preparation and analytical data for 3-halo-7-(trifluoromethyl) pyrazolo[1,5-*a*]pyrimidin-5-one (4a–b)

NBS or NIS (1.05 equiv.) was added to a solution of pyrazolo[1,5-*a*]pyrimdin-5-one 3 (100 mg, 1 equiv.) in 8 mL of CH_2Cl_2 and the reaction was stirred under an argon atmosphere at room temperature for 12 h. The progress of the reaction was monitored by TLC (PE/EtOAc, 7/3). After completion of the reaction, evaporation of the solvent under reduced pressure provided the crude product **4a** or **4b**, which was purified by column chromatography.

3-Bromo-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5-one (4a)..[30c]. The purification was carried out using (PE/EtOAc, 7.5/2.5) to afford **4a** as white solid in 94% yield (147 mg). Mp: 209–211 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 13.00 (br s, 1H), 8.07 (s, 1H), 6.74 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.7, 144.8, 140.5, 135.7 (q, J = 36.8 Hz), 119.2 (q, J = 274.6 Hz), 108.0, 75.1; ^{19}F

NMR (282 MHz, DMSO-d_6): δ −66.65; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_7H_4BrF_3N_3O$: 281.9484; found: 281.9474.

3-Iodo-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5-one (4b). The purification was carried out using (PE/EtOAc, 8/2) to afford **4b** as white solid in 90% yield (146 mg). Mp: 220–222 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.76 (br s, 1H), 7.89 (s, 1H), 6.70 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.9, 149.1, 143.6, 135.6 (q, J = 37.0 Hz), 119.2 (q, J = 274.6 Hz), 107.9, 55.3; ^{19}F NMR (282 MHz, DMSO-d_6): δ −66.70; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_7H_4IF_3N_3O$: 330.0198; found: 330.0173.

General procedure and analytical data for products 7a–c

In a microwave vial, 4(5 or 6)-bromo-1*H*-indazol-3-amine (0.47 mmol, 100 mg) was dissolved in 1,4-dioxane (4 mL). Ethyl 4,4,4-trifluorobut-2-ynoate (1.2 equiv.) was then added, and the mixture was degassed by argon bubbling for 10 min. The sealed tube was heated at 110 °C for 2 h. After cooling, MeONa (51.2 mg, 2 equiv.) was added and the reaction was stirred for 12 h at room temperature. The reaction mixture was neutralized with a solution of hydrochloric ether (2 M) and the solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography.

8-Bromo-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (7a). The purification was carried out using (EtOAc 100%) to afford **7a** as yellow solid in 64% of yield (100 mg). Mp 339–341 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.78 (br s, 1H), 7.92–7.89 (m, 2H), 7.18–7.15 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.2, 150.9, 138.6, 135.9 (q, J = 36.9 Hz), 123.9, 123.6, 123.0, 119.5 (q, J = 274.4 Hz), 118.6, 111.2, 105.7; ^{19}F NMR (282 MHz, DMSO-d_6): δ −66.71; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_6BrF_3N_3O$: 331.9641; found: 331.9644.

9-Bromo-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (7b). The purification was carried out using (EtOAc 100%) to afford **7b** as yellow solid in 58% yield (91 mg). Mp 345–347 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.69 (br s, 1H), 8.15 (d, J = 1.4 Hz, 1H), 7.60 (d, J = 9.3 Hz, 1H), 7.49 (dd, J = 9.3 Hz, 1H), 7.12 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.5, 148.8, 138.0, 135.7 (q, J = 35.8 Hz), 133.2, 122.9, 119.5 (q, J = 275.2 Hz), 118.9, 111.8, 111.4, 108.1; ^{19}F NMR (282 MHz, DMSO-d_6): δ −66.70; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_6BrF_3N_3O$: 331.9641; found: 331.9644.

10-Bromo-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (7c). The purification was carried out using (EtOAc 100%) to afford **7c** as yellow solid in 60% yield (94 mg). Mp 285–287 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.06 (br s, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.45–7.36 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.5, 151.9, 143.1, 134.8 (q, J = 37.2 Hz), 130.9, 124.1, 119.7 (q, J = 274.1 Hz), 116.0, 114.1, 109.6, 105.3; ^{19}F NMR (282 MHz, DMSO-d_6): δ −67.74; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_6BrF_3N_3O$: 331.9641; found: 331.9639.

Pd-catalyzed arylation of 3-bromo 7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimdin-5-one **4a** and C8(9 or 10)-bromo 4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2-one **7a–c** with (hetero) aryl boronic acids.

A mixture of 4-bromo-7-(trifluoromethyl)pyrazolo[1,5-*a*] pyrimidin-5-one **4a** or 8(9 or 10)-bromo-4-(trifluoromethyl) benzo[4,5]imidazo[1,2-*a*]pyrimidin-2-one **7a–c** (100 mg, 1 equiv.), boronic acid (1.5 equiv.), and K_2CO_3 (2 equiv.) in EtOH (4 mL) and water (1 mL) was thoroughly degassed with a stream of argon. Then, XPhos (5 mol%) and $XPhosPdG_2$ (2.5 mol%) were added and the microwave vial containing the mixture was capped and inserted into microwave reactor. The reaction mixture was irradiated at 135 °C for 40 min. After that, the mixture was concentrated under reduced pressure. Purification of the crude product *via* column chromatography afforded desired 3-disubstituted pyrazolo[1,5-*a*]pyrimidin-5-one **5a–q** and 8(9 or 10)- substituted benzo[4,5]imidazo[1,2-*a*]pyrimidin-2-ones **8a–d**, **9a–d** and **10a–b** as solid, which were characterized by ^{1}H, ^{13}C NMR, ^{19}F NMR and HRMS. In all cases, products were recrystallized from diethyl ether or CH_2Cl_2.

3-(4-Methoxyphenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5a).[30c] The purification was carried out using (PE/EtOAc: 8/2) to afford **5a** as yellow solid in 91% yield (100 mg). Mp 227–229 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 11.20 (br s, 1H), 8.08 (s, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 6.58 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.1, 158.5, 144.9, 144.0, 135.9 (q, J = 36.9 Hz), 128.6, 123.0, 119.5 (q, J = 274.4 Hz), 114.5 (3C), 107.6, 105.2, 55.6; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.39; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{11}F_3N_3O_2$: 310.0798; found: 310.0486.

3-Phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5b).[23a] The purification was carried out using (PE/EtOAc: 8.5/1.5) to afford **5b** as white solid in 74% yield (73 mg). Mp 240–242 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 11.27 (br s, 1H), 8.17 (s, 1H), 7.65 (d, J = 7.3 Hz, 2H), 7.44 (t, J = 7.3 Hz, 2H), 7.32 (tt, J = 7.3, 1.2 Hz, 1H), 6.62 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.4, 144.1, 136.0 (q, J = 36.6 Hz), 130.8, 129.1 (4C), 127.2, 126.9, 119.4 (q, J = 274.4 Hz), 105.6, 105.2; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.39; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_9F_3N_3O$: 280.0692; found: 280.0682.

3-(Biphenyl-3-yl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5c). The purification was carried out using (PE/EtOAc: 8.5/1.5) to afford **5c** as yellow solid in 79% yield (100 mg). Mp 259–261 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 11.49 (br s, 1H), 8.27 (s, 1H), 7.91 (t, J = 1.5 Hz, 1H), 7.75 (d, J = 7.3 Hz, 2H), 7.63 (tt, J = 7.6, 1.5 Hz, 2H), 7.55 (d, J = 7.4 Hz, 1H), 7.52 (d, J = 2.9 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.4 (tt, J = 7.3, 1.5 Hz, 1H), 6.62 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6): δ 160.4, 144.4, 141.1 (2C), 140.7, 136.0 (q, J = 36.7 Hz), 131.3, 129.7, 129.3 (2C), 128.0, 127.5 (2C), 126.5, 125.8, 125.4, 119.5 (q, J = 274.5 Hz), 106.0, 105.4; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.38; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{13}F_3N_3O$: 356.1005; found: 356.0994.

3-(Naphthalen-2-yl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5d). The purification was carried out using (PE/EtOAc: 8.5/1.5) to afford **5d** as yellow solid in 85% yield (100 mg). Mp 274–276 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 11.42 (br s, 1H), 8.31 (s, 1H), 8.18 (s, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 6.8 Hz, 1H), 7.80 (dd, J = 8.5, 1.7 Hz, 1H), 7.58–7.49 (m, 2H), 6.65 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.4, 144.3, 136.0 (q, J = 36.65 Hz), 133.7, 132.1, 129.3, 128.5, 128.2, 128.0, 126.8, 126.1, 125.8, 125.3, 125.2, 119.5 (q, J = 274.6 Hz), 105.5, 105.1; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.35; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{11}F_3N_3O$: 330.0849; found: 330.0837.

3-(*P*-Tolyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5e). The purification was carried out using (PE/EtOAc: 8/2) to afford **5e** as white solid in 88% yield (92 mg). Mp 257–259 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.62 (br s, 1H), 8.32 (s, 1H), 7.61 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 6.77 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.3, 144.9, 144.0, 136.1, 135.9 (q, J = 36.6 Hz), 129.6 (4C), 127.8, 127.1, 119.5 (q, J = 274.5 Hz), 105.5, 88.5; ^{19}F NMR (282 MHz, DMSO-d_6): δ −67.06; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{11}F_3N_3O$: 294.0849; found: 294.0847.

3-(3-Methoxyphenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5f). The purification was carried out using (PE/EtOAc: 8/2) to afford **5f** as yellow solid in 85% yield (93 mg). Mp 209–211 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 11.31 (br s, 1H), 8.18 (s, 1H), 7.35 (t, J = 8.2 Hz, 1H), 7.21–7.19 (m, 2H), 6.89 (dd, J = 8.2, 2.5 Hz, 1H), 6.63 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 160.1, 159.0, 143.5, 138.6, 136.7 (q, J = 36.8 Hz), 131.5, 129.8, 119.4, 119.2 (q, J = 274.0 Hz), 112.8, 112.4, 105.8 (q, J = 4.2 Hz), 105.0, 54.6; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.41; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{11}F_3N_3O_2$: 310.0798; found: 310.0787.

3-(2-Methoxyphenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5g). The purification was carried out using (PE/EtOAc: 8/2) to afford **5g** as yellow solid in 73% yield (80 mg). Mp 187–189 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 10.64 (br s, 1H), 8.04 (s, 1H), 7.47 (dd, J = 7.5, 1.7 Hz, 1H), 7.36 (dd, J = 7.4, 1.7 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.03 (td, J = 7.5, 1.1 Hz, 1H), 6.54 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6): δ 158.1, 156.2, 144.4, 137.9, 136.7 (q, J = 37.0 Hz), 129.7, 128.7, 121.1, 119.2 (q, J = 274.0 Hz), 118.8, 111.2, 106.5 (q, J = 4.4 Hz), 101.2, 55.0; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.16; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{11}F_3N_3O_2$: 310.0798; found: 310.0786.

3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5h). The purification was carried out using (PE/EtOAc: 8/2) to afford **5h** as yellow solid in 67% yield (80 mg). Mp 245–247 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 11.31 (br s, 1H), 8.09 (s, 1H), 7.09 (s, 1H), 7.08 (dd, J = 8.8, 2.1 Hz, 1H), 6.88 (d, J = 8.6 Hz, 1H), 6.6 (s, 1H), 4.31–4.30 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.3, 144.0, 143.9, 142.7, 135.9 (q, J = 36.6 Hz), 123.9, 120.3, 119.3 (q, J = 274.6 Hz), 117.6 (2C), 116.0, 105.2, 105.0, 64.6; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.43; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{11}F_3N_3O_3$: 338.0747; found: 338.0735.

3-(4-Acetylphenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5i). The purification was carried out using (PE/EtOAc: 6/4) to afford **5i** as yellow solid in 87% yield (99 mg). Mp 262–264 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 11.36 (br s, 1H), 8.34 (s, 1H), 8.05 (d, J = 8.6 Hz, 2H), 7.87 (d, J = 8.6 Hz, 2H), 6.72 (s, 1H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.6, 161.0, 144.3, 136.0, 137.0 (q, J = 36.8 Hz), 134.8, 129.1 (3C), 126.6 (2C), 119.4 (q, J = 274.4 Hz), 105.0, 104.9, 27.0; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.47; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{11}F_3N_3O_2$: 322.0798; found: 322.0786.

Ethyl 4-(5-oxo-7-(trifluoromethyl)-4,5-dihydropyrazolo[1,5-*a*]pyrimidin-3-yl)benzoate (5j). The purification was carried out using (PE/EtOAc: 8/2) to afford **5j** as white solid in 72% yield (90 mg). Mp 265–267 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 11.37 (br s, 1H), 8.34 (s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 7.9 Hz, 2H), 6.72 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.0, 161.0, 144.3, 141.7, 136.0, 136.0 (q, J = 36.8 Hz), 129.9 (3C), 127.7, 126.6, 119.4 (q, J = 274.4 Hz), 105.1, 104.9, 61.1, 14.6; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.46; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{13}F_3N_3O_3$: 352.0903; found: 352.0891.

3-(4-Fluorophenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5k). The purification was carried out using (PE/EtOAc: 8/2) to afford **5k** as white solid in 76% yield (80 mg). Mp 277–279 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 11.23 (br s, 1H), 8.16 (s, 1H), 7.72–7.68 (m, 2H), 7.24–7.19 (m, 2H), 6.64 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.4 (d, J = 243.3 Hz), 160.5, 144.1, 135.9 (q, J = 36.7 Hz), 129.3, 129.2, 129.2, 127.3, 119.4 (q, J = 274.3 Hz), 116.0, 115.7, 105.4, 104.7; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.43, −116.93; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_8F_4N_3O$: 298.0598; found: 298.059.

3-(Thiophen-2-yl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5l). The purification was carried out using (PE/EtOAc: 8.5/1.5) to afford **5l** as yellow solid in 80% yield (81 mg). Mp 219–221 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 11.20 (br s, 1H), 8.10 (s, 1H), 7.46 (d, J = 5.1 Hz, 1H), 7.34 (d, J = 3.5 Hz, 1H), 7.13 (dd, J = 5.1, 3.6 Hz, 1H), 6.66 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6): δ 158.8, 143.3, 138.8, 136.6 (q, J = 37.2 Hz), 131.1, 127.7, 125.0, 124.6, 119.2 (q, J = 274.0 Hz), 105.9, 99.3; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.42; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{11}H_7F_3N_3OS$: 286.0256; found: 286.0246.

3-(Thiophen-3-yl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5m). The purification was carried out using (PE/EtOAc: 8.5/1.5) to afford **5m** as yellow solid in 67% yield (68 mg). Mp 257–259 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 11.12 (br s, 1H), 8.20 (s, 1H), 7.74 (dd, J = 2.9, 1.3 Hz, 1H), 7.59 (dd, J = 5.0, 2.9 Hz, 1H), 7.50 (dd, J = 5.0, 1.3 Hz, 1H), 6.61 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.2, 144.2, 136.0 (q, J = 36.7 Hz), 130.6, 127.3, 126.7 (2C), 120.5, 119.4 (q, J = 274.5 Hz), 106.2, 101.5; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.39; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{11}H_7F_3N_3OS$: 286.0256; found: 286.0246.

3-(Furan-2-yl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5n). The purification was carried out using (PE/EtOAc: 8.5/1.5) to afford **5n** as yellow solid in 84% yield (80 mg). Mp 247–249 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 11.03 (br s, 1H), 8.17 (s, 1H), 7.60 (dd, J = 1.8, 0.7 Hz, 1H), 6.73 (dd, J = 3.4, 0.7 Hz, 1H), 6.60 (s, 1H), 6.55 (dd, J = 3.4, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.9, 144.9, 142.2, 142.0, 137.9, 135.9 (q, J = 36.7 Hz), 119.3 (q, J = 274.5 Hz), 112.0, 107.1, 105.9, 97.3; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.29; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{11}H_7F_3N_3O_2$: 270.0485; found: 270.0475.

3-(Pyridin-3-yl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5o). The purification was carried out using (PE/EtOAc: 6.5/3.5) to afford **5o** as yellow solid in 80% yield (80 mg). Mp 270–272 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 8.97 (s, 1H), 8.46 (s, 1H), 8.46–8.44 (m, 2H), 8.14 (d, J = 7.8 Hz, 1H), 7.44 (dd, J = 7.8, 4.8 Hz, 1H), 6.84 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.2, 147.9, 147.5, 143.9, 141.8, 135.7 (q, J = 36.7 Hz), 13.2, 127.3, 124.0, 119.5 (q, J = 274.3 Hz), 105.5 (q, J = 3.8 Hz),

102.3; ^{19}F NMR (282 MHz, acetone-d_6): δ −67.11; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{12}H_7F_3N_4O$: 281.0645; found: 281.0635.

3-[4-(Hydroxymethyl)phenyl]-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5p). The purification was carried out using (PE/EtOAc: 6.5/3.5) to afford **5p** as white solid in 73% yield (80 mg). Mp 241–242 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.66 (br s, 1H), 8.36 (s, 1H), 7.69 (d, J = 6.0 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 6.80 (s, 1H), 5.21 (t, J = 4.9 Hz, 1H), 4.52 (d, J = 3.6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.4, 144.1, 141.2, 135.9 (q, J = 36.7 Hz), 129.1, 127.2 (3C), 126.9, 125.8, 119.5 (q, J = 274.4 Hz), 105.5, 105.4, 36.2; ^{19}F NMR (282 MHz, DMSO-d_6): δ −67.05; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{11}F_3N_3O_2$: 310.0798; found: 310.0787.

(*E*)-3-Styryl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5q). The purification was carried out using (PE/EtOAc: 8.5/1.5) to afford **5q** as yellow solid in 74% yield (80 mg). Mp 307–309 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.88 (br s, 1H), 8.39 (s, 1H), 7.48 (d, J = 7.4 Hz, 2H), 7.41–7.35 (m, 3H), 7.23 (t, J = 7.2 Hz, 1H), 7.02 (d, J = 16.4 Hz, 1H), 6.65 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 152.3, 142.1, 138.7, 138.0, 136.0 (q, J = 36.6 Hz), 129.2 (2C), 127.5, 126.3, 126.1 (2C), 119.3 (q, J = 274.6 Hz), 116.1, 107.5, 102.7; ^{19}F NMR (282 MHz, DMSO-d_6): δ −66.70; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{11}F_3N_3O$: 306.0849; found: 306.0838.

9-Phenyl-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (8a). The purification was carried out using (EtOAc: 100%) to afford **8a** as yellow solid in 70% yield (70 mg). Mp 344–346 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 8.30 (s, 1H), 7.83 (dd, J = 9.2, 1.7 Hz, 1H), 7.73 (d, J = 7.4 Hz, 2H), 7.69 (d, J = 9.2 Hz, 1H), 7.50 (t, J = 7.4 Hz, 2H), 7.37 (t, J = 7.4 Hz, 1H), 6.98 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.0, 150.0, 140.6, 138.2, 136.0 (q, J = 36.5 Hz), 132.4, 130.3, 129.5 (2C), 127.5, 126.8 (2C), 119.1 (q, J = 274.6 Hz), 118.0, 117.2, 110.8, 107.2; ^{19}F NMR (282 MHz, DMSO-d_6): δ −66.62; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{11}F_3N_3O$: 330.0849; found: 330.0838.

9-(4-Methoxyphenyl)-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (8b). The purification was carried out using (EtOAc: 100%) to afford **8b** as yellow solid in 86% yield (93 mg). Mp 340–342 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 8.20 (s, 1H), 7.80 (dd, J = 9.2, 1.8 Hz, 1H), 7.66 (d, J = 8.8 Hz, 3H), 7.06 (d, J = 8.8 Hz, 2H), 6.96 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.3, 159.0, 150.0, 139.9, 135.5 (q, J = 36.0 Hz), 133.2, 131.5, 130.0, 127.9 (2C), 119.7 (q, J = 274.3 Hz), 117.2, 116.8, 114.9 (2C), 110.4, 107.8, 55.6; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.22; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{13}F_3N_3O_2$: 360.0954; found: 360.0941.

9-(4-Acetylphenyl)-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (8c). The purification was carried out using (EtOAc: 100%) to afford **8c** as yellow solid in 72% yield (81 mg). Mp 346–348 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.36 (s, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.86 (dd, J = 9.2, 1.8 Hz, 1H), 7.72 (d, J = 9.2 Hz, 1H), 7.09 (s, 1H), 2.63 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.8, 159.8, 150.2, 145.0, 139.9, 135.7 (q, J = 36.8 Hz), 135.6, 134.7, 130.5, 129.8, 129.6, 127.4, 126.7, 119.6 (q, J = 274.1 Hz), 119.4, 117.2, 110.9, 107.7, 27.2; ^{19}F NMR (282 MHz, DMSO-d_6): δ −66.69; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{13}F_3N_3O_2$: 372.0954; found: 372.0942.

9-(Furan-2-yl)-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (8d). The purification was carried out using (EtOAc: 100%) to afford **8d** as yellow solid in 83% yield (80 mg). Mp 325–327 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ 8.32 (t, J = 0.9 Hz, 1H), 7.84 (dd, J = 9.3, 1.7 Hz, 1H), 7.66 (dd, J = 1.8, 0.6 Hz, 1H), 7.63 (dd, J = 9.3, 0.9 Hz, 1H), 6.96 (s, 1H), 6.84 (d, J = 3.0 Hz, 1H), 6.59 (dd, J = 3.4, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, THF-d_8): δ 159.0, 154.9, 151.0, 142.7, 139.1, 137.3 (q, J = 37.1 Hz), 127.7, 124.1, 120.2 (q, J = 274.4 Hz), 118.0, 113.8, 112.3, 109.2, 107.8, 105.1; ^{19}F NMR (282 MHz, acetone-d_6): δ −68.21; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_9F_3N_3O_2$: 320.0641; found: 320.0629.

8-Phenyl-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (9a). The purification was carried out using (EtOAc: 100%) to afford **9a** as yellow solid in 72% yield (71 mg). Mp 340–342 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.74 (br s, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.88 (s, 1H), 7.80 (d, J = 6.5 Hz, 2H), 7.51–7.43 (m, 4H), 7.10 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.0, 151.2, 142.2, 140.6, 137.7, 136.0 (q, J = 36.8 Hz), 129.4 (2C), 128.4, 127.6 (2C), 121.5, 120.6, 119.6 (q, J = 274.5 Hz), 113.6, 110.6, 106.0; ^{19}F NMR (282 MHz, DMSO-d_6): δ −66.67; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{11}F_3N_3O$: 330.0849; found: 330.0836.

8-[4-(Hydroxymethyl)phenyl]-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (9b). The purification was carried out using (EtOAc: 100%) to afford **9b** as yellow solid in 61% yield (66 mg). Mp. 296–298 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.70 (br s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.84 (s, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.39 (dd, J = 8.8, 1.2 Hz, 1H), 7.05 (s, 1H), 5.26 (br s, 1H), 4.56 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.3, 151.3, 142.8, 142.1, 139.0, 138.2, 135.8 (q, J = 36.5 Hz), 127.5 (2C), 127.3 (2C), 121.5, 120.4, 119.6 (q, J = 274.5 Hz), 113.2, 110.3, 106.1, 63.0; ^{19}F NMR (282 MHz, DMSO-d_6): δ −66.74; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{13}F_3N_3O_2$: 360.0954; found: 360.0953.

(*E*)-8-Styryl-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (9c). The purification was carried out using (EtOAc: 100%) to afford **9c** as yellow solid in 81% yield (87 mg). Mp >350 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.63 (br s, 1H), 7.94 (d, J = 8.9 Hz, 1H), 7.69–7.63 (m, 3H), 7.47–7.39 (m, 5H), 7.30 (t, J = 7.4 Hz, 1H), 7.03 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.2, 151.2, 139.2, 137.9, 137.4, 135.9 (q, J = 36.6 Hz), 130.3, 129.4, 129.2 (2C), 128.4, 127.1 (2C), 121.0, 119.8 (q, J = 274.8 Hz), 118.5, 115.1, 110.3, 106.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{13}F_3N_3O$: 356.1005; found: 356.1004.

8-(Furan-2-yl)-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (9d). The purification was carried out using (EtOAc: 100%) to afford **9d** as yellow solid in 73% yield (70 mg). Mp 329–331 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.69 (br s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.85 (dd, J = 6.2, 1.2 Hz, 2H), 7.44 (dd, J = 8.8, 1.0 Hz, 1H), 7.14 (d, J = 3.3 Hz, 1H), 7.05 (s, 1H), 6.66 (dd, J = 3.3, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.2, 153.4, 150.8, 144.1, 138.1, 135.9 (q, J = 36.8 Hz), 131.8, 121.7, 119.6 (q, J = 274.2 Hz), 117.4, 112.8, 110.4, 109.5, 108.2, 105.8; ^{19}F NMR (282 MHz, DMSO-d_6): δ −66.72; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_9F_3N_3O_2$: 320.0641; found: 320.0629.

10-(4-Methoxyphenyl)-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (10a). The purification was carried out using (EtOAc: 100%) to afford **10a** as yellow solid in 89% yield (96 mg). Mp 264–266 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.49 (br s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.7 Hz, 2H), 7.56 (dd, J = 8.3, 6.9 Hz, 1H), 7.34 (s, 1H), 7.06 (d, J = 8.7, 2H), 7.04 (d, J = 6.9 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.5, 159.3, 152.2, 142.8, 137.2,

134.6 (q, J = 36.8 Hz), 131.3, 130.8 (2C), 130.3, 121.3, 119.8 (q, J = 274.2 Hz), 115.0, 114.1 (2C), 107.9, 104.6, 55.6; ^{19}F NMR (282 MHz, DMSO-d_6): δ −67.74; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{13}F_3N_3O_2$: 360.0954; found: 360.0953.

10-(Pyridin-3-yl)-4-(trifluoromethyl)pyrimido[1,2-*b*]indazol-2(1*H*)-one (10b). The purification was carried out using (EtOAc: 100%) to afford **10b** as yellow solid in 68% yield (68 mg). Mp 274–276 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.88 (s, 1H), 8.62 (d, J = 4.6 Hz, 1H), 8.13 (td, J = 7.9, 1.7 Hz, 1H), 7.74 (d, J = 8.6 Hz, 1H), 7.59 (dd, J = 8.6, 6.8 Hz, 1H), 7.51 (dd, J = 7.9, 4.6 Hz, 1H), 7.32 (s, 1H), 7.10 (d, J = 6.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.7, 151.9, 149.7, 148.9, 143.9, 137.2, 134.6, 134.1 (q, J = 36.7 Hz), 133.9, 130.1, 123.6, 121.2, 119.9 (q, J = 273.9 Hz), 116.2, 107.8, 105.0; ^{19}F NMR (282 MHz, DMSO-d_6): δ −67.74; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{10}F_3N_4O$: 331.0801; found: 331.0799.

General procedure for the direct C5 arylation of 5b, 5e, 5a, 5j and 5l with (hetero)aryl boronic acids *via* C–OH bond activation

To a stirred solution of aromatic lactam **5a**, **5b**, **5e**, **5j** or **5l** (100 mg, 1.0 equiv.) in 1,4-dioxane (3 mL) at room temperature was added PyBroP (1.3 equiv.) and Et_3N (3 equiv.). The reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. After completion of the first step, boronic acid (1.5 equiv.), Na_2CO_3 (5 equiv.), and $PdCl_2(PPh_3)_2$ (5 mol%) were added successively at room temperature. After the mixture had been stirred at 110 °C for 12 h, it was diluted with CH_2Cl_2, washed with saturated NH_4Cl solution, and dried with $MgSO_4$. The crude product was purified by column chromatography to give pure 3,5-diarylated 7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidines **11a–h**.

5-(4-Methoxyphenyl)-3-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (11a). The purification was carried out using (PE/EtOAc: 9/1) to afford **11a** as orange solid in 88% yield (116 mg). Mp 181–183 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.19 (d, J = 8.9 Hz, 2H), 8.16 (d, J = 7.2 Hz, 2H), 7.63 (s, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.35 (t, J = 7.3 Hz, 1H), 7.09 (d, J = 8.9 Hz, 2H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 154.7, 145.6, 143.9, 134.3 (q, J = 37.1 Hz), 131.5, 129.0 (2C), 128.8 (2C), 128.6, 126.7, 126.6 (2C), 119.6 (q, J = 274.6 Hz), 114.57 (2C), 111.6, 103.3 (q, J = 4.2 Hz), 55.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.91; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{15}F_3N_3O$: 370.1162; found: 370.1150.

5-(2-Methoxyphenyl)-3-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (11b). The purification was carried out using (PE/EtOAc: 9/1) to afford **11b** as yellow solid in 66% yield (87 mg). Mp 198–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.16–8.10 (m, 3H), 7.97 (s, 1H), 7.56–7.47 (m, 3H), 7.33 (tt, J = 7.4, 1.2 Hz, 1H), 7.19 (td, J = 7.5, 0.9 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 155.1, 145.6, 143.4, 132.9 (q, J = 36.9 Hz), 132.3, 131.5, 131.4, 128.8 (2C), 126.7, 126.6 (2C), 126.0, 121.5, 119.8 (q, J = 274.3 Hz), 112.0, 111.6, 108.6 (q, J = 4.4 Hz), 55.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ −69.00; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{15}F_3N_3O$: 370.1162; found: 370.1160.

3-Phenyl-5-(thiophen-2-yl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (11c)..[37] The purification was carried out using (PE/EtOAc: 9/1) to afford **11c** as orange solid in 87% yield (107 mg). Mp 184–186 °C (Lit.[37] Mp: 120–125 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.14 (dd, J = 8.3, 1.1 Hz, 2H), 7.8 (dd, J = 3.8, 1.0 Hz, 1H), 7.62 (dd, J = 5.0, 1.0 Hz, 1H), 7.54–7.49 (m, 3H), 7.35 (tt, J = 7.4, 1.1 Hz, 1H), 7.22 (dd, J = 5.0, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.3, 145.1, 143.9, 142.3, 134.3 (q, J = 37.3 Hz), 131.3, 131.1, 128.8 (2C), 128.6, 128.3, 126.8, 126.4 (2C), 119.4 (q, J = 274.7 Hz), 111.6, 102.9 (q, J = 4.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.87; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{10}F_3N_3S$: 346.0620; found: 346.0609.

5-(4-Fluorophenyl)-3-(4-methoxyphenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (11d). The purification was carried out using (PE/EtOAc: 9.5/0.5) to afford **11d** as red solid in 78% yield (98 mg). Mp 208–210 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.22 (dd, J = 8.9, 5.3 Hz, 2H), 8.06 (d, J = 8.8 Hz, 2H), 7.61 (s, 1H), 7.28 (dd, J = 8.9, 5.3 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7 (d, J = 252.6 Hz), 158.7, 153.5, 145.1, 143.7, 134.2 (q, J = 37.2 Hz), 132.4 (d, J = 3.1 Hz), 129.4, 129.3, 127.3 (2C), 123.7, 119.6 (q, J = 274.7 Hz), 116.4, 116.2, 114.4 (2C), 112.1, 103.2 (q, J = 4.1 Hz), 55.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ −69.04, −108.73; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{14}F_4N_3O$: 388.0995; found: 388.0996.

5-(4-Methoxyphenyl)-3-(*p*-tolyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (11e). The purification was carried out using (PE/EtOAc: 9.5/0.5) to afford **11e** as orange solid in 90% yield (118 mg). Mp 167–169 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.17 (d, J = 8.9 Hz, 2H), 8.03 (d, J = 8.1 Hz, 2H), 7.59 (s, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 3.93 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2, 154.4, 145.5, 143.8, 136.5, 134.2 (q, J = 36.4 Hz), 129.5 (2C), 128.9 (2C), 128.7, 128.5, 126.5 (2C), 119.6 (q, J = 274.8 Hz), 114.5 (2C), 111.7, 103.2, 55.5, 21.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.94; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{21}H_{17}F_3N_3O$: 384.1318; found: 384.1317.

Ethyl4-(5-(4-methoxyphenyl)-7(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-3-yl)benzoate (11f). The purification is carried out using (PE/EtOAc: 8.5/1.5) to afford **11f** as orange solid in 74% yield (93 mg). Mp 212–214 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.27 (d, J = 8.6 Hz, 2H), 8.26 (d, J = 8.9 Hz, 2H), 8.20 (d, J = 8.6 Hz, 2H), 7.67 (s, 1H), 7.11 (d, J = 8.9 Hz, 2H), 4.43 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 162.5, 155.4, 146.0, 144.1, 136.0, 134.5 (q, J = 37.2 Hz), 130.1 (2C), 129.1 (2C), 128.3, 128.3, 126.0 (2C), 119.5 (q, J = 274.7 Hz), 114.7 (2C), 110.5, 103.6 (q, J = 4.1 Hz), 60.90, 55.5, 14.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.80; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{23}H_{19}F_3N_3O_3$: 442.1373; found: 442.1360.

5-(4-Methoxyphenyl)-3-(thiophen-2-yl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (11g). The purification was carried out using (PE/EtOAc: 9/1) to afford **11g** as orange solid in 87% yield (114 mg). Mp 177–179 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.22 (d, J = 8.9 Hz, 2H), 7.66 (dd, J = 3.6, 1.0 Hz, 1H), 7.62 (s, 1H), 7.35 (dd, J = 5.1, 1.0 Hz, 1H), 7.17 (dd, J = 5.1, 3.6 Hz, 1H), 7.10 (d, J = 8.9 Hz, 2H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.4, 154.7, 144.7, 143.0, 134.2 (q, J = 37.2 Hz), 133.0, 129.0 (2C), 128.3, 127.4, 124.0, 123.4, 119.5 (q, J = 274.6 Hz), 114.5 (2C), 107.5, 103.3 (q, J = 4.1 Hz), 55.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.85; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{13}F_3N_3OS$: 376.0726; found: 376.0714.

5-(4-Bromophenyl)-3-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (11h).[37] The purification was carried out using (PE/EtOAc: 9.5/0.5) to afford **11h** as orange solid in 91% yield (136 mg). Mp 174–176 °C (Lit.[37] Mp: 174–176 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.13 (dd, J = 7.4, 1.2 Hz, 2H), 8.08 (d, J = 8.6 Hz, 2H), 7.72 (d, J = 8.6 Hz, 2H), 7.63 (s, 1H), 7.53 (t, J = 7.4 Hz, 2H), 7.37 (tt, J = 7.4, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9, 144.3, 135.0, 134.7 (q, J = 37.4 Hz), 132.5 (2C), 133.1, 129.2, 128.9 (2C), 128.8 (2C), 127.0, 126.7 (2C), 126.1, 119.5 (q, J = 274.7 Hz), 112.5, 103.3 (q, J = 4.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.94; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{12}BrF_3N_3$: 418.0161; found: 418.0161.

3,5-Bis(4-methoxyphenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (12). The purification was carried out using (PE/EtOAc: 9.5/0.5) to afford **12** as orange solid in 25% yield (136 mg). Mp 171–173 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.18 (d, J = 8.9 Hz, 2H), 8.08 (d, J = 8.9 Hz, 2H), 7.6 (s, 1H), 7.09 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 3.94 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2, 158.6, 154.2, 145.2, 143.4, 134.1 (q, J = 36.9 Hz), 128.8 (2C), 128.7, 127.7 (2C), 124.0, 119.6 (q, J = 274.7 Hz), 114.3 (2C), 111.5, 103.1 (q, J = 4.2 Hz), 55.5, 55.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ −68.98; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{17}F_3N_3O_2$: 400.1267; found: 400.1268.

General procedure for the direct alkynylation of 5b with alkynes *via* C–OH bond activation

To a stirred solution of aromatic lactam **5b** (1.0 equiv.) in 1,4-dioxane (3 mL) at room temperature was added PyBroP (1.3 equiv.) and Et_3N (3 equiv.). The reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC. After completion of the first step, alkyne (1.5 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (10 mol%) were added successively at room temperature. After the mixture had been stirred at 110 °C for 12 h, it was diluted with CH_2Cl_2, washed with saturated NH_4Cl solution, and dried with $MgSO_4$. The crude product was purified by column chromatography to give pure 3,5-disubstituted 7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidines **13a–c**.

3-Phenyl-5-(phenylethynyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (13a). The purification was carried out using (PE/EtOAc: 9.8/0.2) to afford **13a** as orange solid in 90% yield (117 mg). Mp 180–182 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.07 (dd, J = 8.3, 1.2 Hz, 2H), 7.70 (dd, J = 7.5, 1.8 Hz, 2H), 7.54–7.42 (m, 5H), 7.36 (s, 1H), 7.35 (tt, J = 7.5, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5, 144.2, 141.1, 133.8 (J = 37.0 Hz), 132.4 (2C), 130.6, 130.1, 128.9 (2C), 128.6 (2C), 127.2, 126.9 (2C), 121.0, 119.3 (q, J = 274.7 Hz), 112.9, 109.4, 94.6, 87.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ −69.07; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{13}F_3N_3$: 364.1056; found: 364.1055.

5-[(4-Methoxyphenyl)ethynyl]-3-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (13b). The purification was carried out using (PE/EtOAc: 9.8/0.2) to afford **13b** as red solid in 88% yield (124 mg). Mp 163–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (s, 1H), 8.07 (dd, J = 8.3, 1.2 Hz, 2H), 7.64 (d, J = 8.9 Hz, 2H), 7.51 (t, J = 7.4 Hz, 2H), 7.35 (tt, J = 7.4, 1.2 Hz, 1H), 7.33 (s, 1H), 6.96 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2, 145.5, 144.1, 141.5, 134.2 (2C), 133.7 (q, J = 37.7 Hz), 130.8, 128.9 (2C), 127.2, 126.9 (2C), 119.31 (q, J = 274.7 Hz), 114.4 (2C), 112.9, 112.7, 109.35 (q, J = 4.2 Hz), 95.52, 87.02, 55.42; ^{19}F NMR (282 MHz, $CDCl_3$): δ −69.05; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{15}F_3N_3O$: 394.1162; found: 394.1161.

5-[(4-Chlorophenyl)ethynyl]-3-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (13c). The purification was carried out using (PE/EtOAc: 9.8/0.2) to afford **13c** as orange solid in 78% yield (111 mg). Mp 152–154 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.06 (dd, J = 8.3, 1.2 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 7.51 (t, J = 7.4 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.36 (tt, J = 7.4, 1.2 Hz, 1H), 7.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5, 144.3, 140.8, 136.5, 133.9 (q, J = 38.0 Hz), 133.6 (2C), 130.6, 129.1 (2C), 128.9 (2C), 127.3, 126.9 (2C), 119.5, 119.2 (q, J = 274.9 Hz), 113.1, 109.2 (q, J = 4.1 Hz), 93.2, 88.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ −69.08; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{12}ClF_3N_3$: 398.0666; found: 398.0668.

Protocols of inhibition

Inhibition of hAChE and hBChE. Ellman's method was used to determine the inhibitory potencies of the compounds as described previously.[42] Briefly, compounds at 100 μM (1% DMSO, final concentration) were incubated with hBChE or hAChE (final concentrations of 1 nM or 50 pM, respectively) in 333 μM 5,5′-dithiobis (2-nitrobenzoic acid) for 5 min. The reactions were started by addition of the substrate (butyrylthiocholine and acetylthiocholine iodide, 500 μM final concentrations). The increases of absorbances (λ = 412 nm) were measured, and the initial velocities were calculated. The residual activities were calculated with respect to 1% DMSO. Appropriate serial dilutions of the active compounds (RAs <50% at 100 mM test compound) were made and assayed to determine residual activities, which were further used to calculate the IC_{50} with GraphPad Prism 6 software (GraphPad Software, CA, USA).

Inhibition of hMAO-A and hMAO-B. The inhibitory potencies were determined as described previously.[43] For screening purposes, the compound at 100 μM was incubated with hMAO-A or hMAO-B in 50 mM phosphate buffer (pH 7.4, 0.05% [v/v] Triton X-114) for 15 min at 37 °C. The enzyme reaction was started by adding final concentrations of 250 μM Amplex Red reagent, 4 U mL^{-1} horseradish peroxidase, and 1 mM *p*-tyramine (final volume, 200 μL). The increase in the fluorescence intensity (λ_{ex} = 530 nm, λ_{em} = 590 nm) was measured at 37 °C over a period of 20 min, and velocities were calculated thereof. For control experiments, DMSO was used instead of the compounds. To determine the blank value, a phosphate-buffered solution replaced the enzyme solution. The residual activities were calculated from the velocities measured. Appropriate serial dilutions of the active compound were made and assayed to determine residual activities, which were further used to calculate the IC_{50} with GraphPad Prism 6 software (GraphPad Software, CA, USA).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the "Département d'analyses Chimiques et Médicales" (Tours, France) for chemical analyses. We would also like to thank Dr Damijan Knez from Ljubljana University for his help in carrying out the first biological tests.

Notes and references

1 (*a*) C. C. C. J. Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem., Int. Ed.*, 2012, **51**, 5062–5085; (*b*) F. S. Han, *Chem. Soc. Rev.*, 2013, **42**, 5270–5298; (*c*) J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177–2250.

2 (*a*) N. Miyaura and A. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1979, 866–867; (*b*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483; (*c*) A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147–168; (*d*) J. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev.*, 2014, **43**, 412–443; (*e*) J. P. G. Rygus and C. M. Crudden, *J. Am. Chem. Soc.*, 2017, **139**, 18124–18137.

3 *Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective*, ed M. L. Crawley and B. M. Trost, John Wiley & Sons, 2012.

4 (*a*) C. Torborg and M. Beller, *Adv. Synth. Catal.*, 2009, **351**, 3027–3043; (*b*) V. Chandrasekhar, R. S. Narayanan and P. Thilagar, *Organometallics*, 2009, **28**, 5883–5888; (*c*) M. Arthuis, R. Pontikis and J.-C. Florent, *Org. Lett.*, 2009, **11**, 4608–4611; (*d*) B. Bhayana, B. P. Fors and S. L. Buchwald, *Org. Lett.*, 2009, **11**, 3954–3957; (*e*) T. Martin, C. Laguerre, C. Hoarau and F. Marsais, *Org. Lett.*, 2009, **11**, 3690–3693; (*f*) C. A. James, A. L. Coelho, M. Gevaert, P. Forgione and V. Snieckus, *J. Org. Chem.*, 2009, **74**, 4094–4103; (*g*) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451–3479.

5 (*a*) F. Bellina, A. Carpita and R. Rossi, *Synthesis*, 2004, 2419–2440; (*b*) C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah and M. G. Organ, *Angew. Chem., Int. Ed.*, 2012, **51**, 3314–3332; (*c*) S. Handa, M. Andersson, F. Gallou, J. Reilly and B. H. Lipshutz, *Angew. Chem., Int. Ed.*, 2016, **55**, 4914–4918.

6 (*a*) M. A. Dufert, K. L. Billingsley and S. L. Buchwald, *J. Am. Chem. Soc.*, 2013, **135**, 12877–12885; (*b*) J. Almond-Thynne, D. C. Blakemore, D. C. Pryde and A. C. Spivey, *Chem. Sci.*, 2017, **8**, 40–62; (*c*) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**(11), 1461–1473.

7 (*a*) M. Prieto, E. Zurita, E. Rosa, L. Munoz, P. Lloyd-Williams and E. Giralt, *J. Org. Chem.*, 2004, **69**, 6812–6820; (*b*) T. Itoh and T. Mase, *Tetrahedron Lett.*, 2005, **46**, 3573–3577; (*c*) P. Gunda, L. M. Russon and M. K. Lakshman, *Angew. Chem., Int. Ed.*, 2004, **43**, 6372–6377.

8 S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451–3479.

9 (*a*) S. Vichier-Guerre, L. Dugué and S. Pochet, *Tetrahedron Lett.*, 2014, **55**, 6347–6350; (*b*) J. Tan, Y. Chen, H. Li and N. Yasuda, *J. Org. Chem.*, 2014, **79**, 8871–8876; (*c*) E. Bratt, O. Verho, M. J. Johansson and J.-E. Bäckvall, *J. Org. Chem.*, 2014, **79**, 3946–3954; (*d*) Y. Qian, M. Hamilton, A. Sidduri, S. Gabriel, Y. Ren, R. Peng, R. Kondru, A. Narayanan, T. Truitt, R. Hamid, Y. Chen, L. Zhang, A. J. Fretland, R. A. Sanchez, K.-C. Chang, M. Lucas, R. C. Schoenfeld, D. Laine, M. E. Fuentes, C. S. Stevenson and D. C. Budd, *J. Med. Chem.*, 2012, **55**, 7920–7939.

10 C. Almansa, A. F. de Arriba, F. L. Cavalcanti, L. A. Gomez, A. Miralles, M. Merlos, J. Garcia-Rafanell and J. Forn, *J. Med. Chem.*, 2001, **44**, 350–361.

11 J. Y. Hwang, M. P. Windisch, S. Jo, H. C. Kim, S. Kim, H. Kim, M. E. Lee, D.-S. Park, E. Park, S. Ahn, J. Cechetto, J. Kim, M. Liuzzi, Z. No and J. Lee, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 7297–7301.

12 (*a*) T. Asano, H. Yamazaki, C. Kasahara, H. Kubota, T. Kontani, Y. Harayama, K. Ohno, H. Mizuhara, M. Yokomoto, K. Misumi, T. Kinoshita, M. Ohta and M. Takeuchi, *J. Med. Chem.*, 2012, **55**, 7772–7785; (*b*) T. Kosugi, D. R. Mitchell, A. Fujino, M. Imai, M. Kambe, S. Kobayashi, H. Makino, Y. Matsueda, Y. Oue, K. Komatsu, K. Imaizumi, Y. Sakai, S. Sugiura, O. Takenouchi, G. Unoki, Y. Yamakoshi, V. Cunliffe, J. Frearson, R. Gordon, C. J. Harris, H. Kalloo-Hosein, J. Le, G. Patel, D. J. Simpson, B. Sherborne, P. S. Thomas, N. Suzuki, M. Takimoto-Kamimura and K. Kataoka, *J. Med. Chem.*, 2012, **55**, 6700–6715.

13 (*a*) A. Kamal, J. R. Tamboli, V. L. Nayak, S. F. Adil, M. V. P. S. Vishnuvardhan and S. Ramakrishna, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 3208–3215; (*b*) D. S. Williamson, M. J. Parratt, J. F. Bower, J. D Moore, C. M. Richardson, P. Dokurno, A. D. Cansfield, G. L. Francis, R. J. Hebdon, R. Howes, P. S. Jackson, A. M. Lockie, J. B. Murray, C. L. Nunns, J. Powles, A. Robertson, A. E. Surgenor and C. J. Torrance, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 863–867; (*c*) K. Paruch, M. P. Dwyer, C. Alvarez, C. Brown, T. Y. Chan, R. J. Doll, K. Keertikar, C. Knutson, B. McKittrick, J. Rivera, R. Rossman, G. Tucker, T. O. Fischmann, A. Hruza, V. Madison, A. A. Nomeir, Y. Wang, E. Lees, D. Parry, N. Sgambellone, W. Seghezzi, L. Schultz, F. Shanahan, D. Wiswell, X. Xu, Q. Zhou, R. A. James, V. M. Paradkar, H. Park, L. R. Rokosz, T. M. Stauffer and T. J. Guzi, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6220–6223; (*d*) S. Ali, D. A. Heathcote, S. H. B. Kroll, S. Jogalekar, B. Scheiper, H. Patel, J. Brackow, A. Siwicka, M. J. Fuchter, M. Periyasamy, R. S. Tolhurst, S. K. Kanneganti, J. P. Snyder, D. C. Liotta, E. O. Aboagye, A. G. Barrett and R. C. Coombes, *Cancer Res.*, 2009, **69**, 6208–6215.

14 J. Xu, H. Liu, G. Li, Y. He, R. Ding, X. Wang, M. Feng, S. Zhang, Y. Chen, S. Li, M. Zhao, Y. Li and C. Qi, *Naturforsch*, 2012, **67**, 827–834.

15 (*a*) S. Selleri, F. Bruni, C. Costagli, A. Costanzo, G. Guerrini, G. Ciciani, P. Gratteri, F. Besnard, B. Costa, M. Montali, C. Martini, J. Fohlin, G. D. Siena and P. M. Aiello, *J. Med. Chem.*, 2005, **48**, 6756–6760; (*b*) Y. L. Chen, WO1998008847A1, 1998; (*c*) J. P. Dusza, J. D. Albright A. S. Tomcufcik, *U.S. Pat.*5538977, 1996.

16 S. Bondock, W. Fadaly and M. A. Metwally, *Eur. J. Med. Chem.*, 2010, **45**, 3692–3701.

17 A. V. Ivashchenko, E. S. Golovina, M. G. Kadieva, V. M. Kysil, O. D. Mitkin and I. M. Okun, *Pharm. Chem. J.*, 2012, **46**, 406–410.

18 (*a*) I. L. Dalinger, I. A. Vatsadse, S. A. Shevelev and A. V. Ivachtchenko, *J. Comb. Chem.*, 2005, **7**, 236–245; (*b*) M. Drev, U. Groselj, S. Mevec, E. Pusavec, J. Strekelj, A. Golobic, G. Dahmann, B. Stanovnik and J. Svete, *Tetrahedron*, 2014, **70**, 8267–8279; (*c*) M. H. Elnagdi and A. W. Erian, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1854–1856; (*d*) S. M. Hussain, A. M. El-Reedy and S. A. El-Sharabasy, *Tetrahedron*, 1988, **44**, 241–246; (*e*) W. Ried and S. Aboul-Fetouh, *Tetrahedron*, 1988, **44**, 7155–7162.

19 (*a*) D. R. Compton, S. Sheng, K. E. Carlson, N. A. Rebacz, I. Y. Lee, B. S. Katzenellenbogen and J. A. Katzenellenbogen, *J. Med. Chem.*, 2004, **47**, 5872–5893; (*b*) P. J. Gilligan, C. Baldauf, A. Cocuzza, D. Chidester, R. Zaczek, L. W. Fitzgerald, J. McElroy, M. A. Smith, H. S. L. Shen, J. A. Saye, D. Christ, G. Trainor, D. W. Robertson and P. Hartig, *Bioorg. Med. Chem.*, 2000, **8**, 181–189; (*c*) M. E. Fraley, W. F. Hoffman, R. S. Rubino, R. W. Hungate, A. J. Tebben, R. Z. Rutledge, R. C. McFall, W. R. Huckle, R. L. Kendall, K. E. Coll and K. A. Thomas, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2767–2770; (*d*) B. T. Gregg, D. O. Tymoshenko, D. A. Razzano and M. R. Johnson, *J. Comb. Chem.*, 2007, **9**, 507–512; (*e*) J. Quiroga, J. Portilla, R. Abonía, B. Insuasty, M. Nogueras and J. Cobo, *Tetrahedron Lett.*, 2007, **48**, 6352–6355; (*f*) H. B. Abed, O. Mammoliti, G. V. Lommen and P. Herdewijn, *Tetrahedron Lett.*, 2013, **54**, 2612–2614; (*g*) J. Blaney, P. A. Gibbons, E. Hanan, J. P. Lyssikatos, S. R. Magnuson, R. Pastor, T. E. Rawson, A. Zhou, B.-Y. Zhu, WO2010051549 A1; 2010*US Pat.063014, 2009; (*h*) *S. Hölder, M. Vennemann, G. Beneke, A. Zülch, V. Gekeler, T. Beckers, A. Zimmermann, H. Joshi, WO2009021992 A2* EP Pat. *060690, 2008; 2009; (*i*) *B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfield,* J. Med. Chem.*, 1988, **31**, 2235–2246; (*j*) *D. A. Horton, G. T. Bourne and M. L. Smythe,* Chem. Rev.*, 2003, **103**, 893–930; (*k*) *D. A. Griffith, D. M. Hargrove, T. S. Maurer, C. A. Blum, S. De Lombaert, J. K. Inthavongsay, L. E. Klade, C. M. Mack, C. R. Rose, M. J. Sanders and P. A. Carpino,* Bioorg. Med. Chem. Lett.*, 2011, **21**, 2641–2645; (*l*) *H. Mukaiyama, T. Nishimura, S. Kobayashi, Y. Komatsu, S. Kikuchi, T. Ozawa, N. Kamada and H. Ohnota,* Bioorg. Med. Chem.*, 2008, **16**, 909–921; (*m*) *H. Mukaiyama, T. Nishimura, S. Kobayashi, T. Ozawa, N. Kamada, Y. Komatsu, S. Kikuchi, H. Oonota and H. Kusama,* Bioorg. Med. Chem.*, 2007, **15**, 868–885; (*n*) *H. Tye, S. G. Mueller, J. Prestle, S. Scheuerer, M. Schindler, B. Nosse, N. Prevost, C. J. Brown, A. Heifetz, C. Moeller, A. Pedret-Dunn and M. Whittaker,* ACS Med. Chem. Lett.*, 2011, **21**, 34–37.*

20 (*a*) M. H. Elnagdi, M. R. H. Elmoghayar and G. H. Elgemeie, *Adv. Heterocycl. Chem.*, 1987, **41**, 319–376; (*b*) J. Quiroga, A. Hormaza, B. Insuasty, C. Saitz, C. Jullian and A. Cannete, *J. Heterocycl. Chem.*, 1998, **35**, 61–64; (*c*) F. M. A. El-Taweel and T. M. Abu Elmaati, *J. Chin. Chem. Soc.*, 2002, **49**, 1051–1055; (*d*) R. Daniels, K. Kim, E. Lebois, H. Muchalski, M. Hughes and C. Lindsley, *Tetrahedron Lett.*, 2008, **49**, 305–310; (*e*) A. V. Ivachtchenko, E. S. Golovina, M. G. Kadieva, V. M. Kysil, O. D. Mitkin, S. E. Tkachenko and I. M. Okun, *J. Med. Chem.*, 2011, **54**, 8161–8173; (*f*) S. Ahmetaj, N. Velikanje, U. Grošelj, I. Šterbal, B. Prek, A. Golobič, D. Kočar, G. Dahmann, B. Stanovnik and J. Svete, *Mol. Diversity*, 2013, **17**, 731–743; (*g*) K. D. Khalil, H. M. Al-Matar, D. M. Al-Dorri and M. H. Elnagdi, *Tetrahedron*, 2009, **65**, 9421–9427; (*h*) J. Quiroga, D. Mejia, B. Insuasty, R. Abonia, M. Nogueras, A. Sanchez and J. Cobo, *J. Heterocycl. Chem.*, 2002, **39**, 51–54.

21 L. K. Gavrin, A. Lee, B. A. Provencher, W. W. Massefski, S. D. Huhn, G. M. Ciszewski, D. C. Cole and J. C. McKew, *J. Org. Chem.*, 2007, **72**, 1043–1046.

22 T. Haga, H. Kimura, M. Morita, T. Ueda, T. Ueki, K. Kiriyama, K. Yoshida, T. Hamamoto and T. Kodama, WO2010018853A1, February 18, 2010.

23 (*a*) R. Balicki, *Pol. J. Chem.*, 1983, **57**, 789–797; (*b*) M. Yoshida, A. Mori, A. Inaba, M. Oka, H. Makino, M. Yamaguchi, H. Fujita, T. Kawamoto, M. Goto, H. Kimura, A. Baba and T. Yasuma, *Bioorg. Med. Chem.*, 2010, **18**, 8501–8511.

24 (*a*) L. Jedinák and P. Cankař, *Eur. J. Org. Chem.*, 2016, 2013–2023; (*b*) H. A. Malik, B. L. H. Taylor, J. R. Kerrigan, J. E. Grob, K. N. Houk, J. Du Bois, L. G. Hamann and A. W. Pattersona, *Chem. Sci.*, 2014, **5**, 2352–2361.

25 M. Ellermann, G. Valot, Y. Cancho Grande, J. Haßfeld, T. Kinzel, J. Köbberling, K. Beyer, S. Röhrig, WO2016071216A1, May 12, 2016.

26 D. C. Schmitt, N. Niljianskul, N. W. Sach and J. I. Trujillo, *ACS Comb. Sci.*, 2018, **20**, 256–260.

27 (*a*) E. P. Gillis, J. K. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359; (*b*) P. Shah and A. D. Westwell, *J. Enzyme Inhib. Med. Chem.*, 2007, **22**, 527–540; (*c*) T. Yamazaki, T. Taguchi, I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, 2009, pp. 3–46; (*d*) R. Filler, Y. Kobayashi, L. M. Yugapolskii, *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993.

28 (*a*) G. B. Elion, S. Gallawan, H. Nathan, S. Bicher, R. W. Randler and G. H. Hitchings, *Biochem. Pharmacol.*, 1963, **12**, 85–93; (*b*) F. Ismail, *J. Fluorine Chem.*, 2002, **118**, 27–33; (*c*) H.-J. Bohm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Muller, U. Obst-Sander and M. Stahl, *ChemBioChem*, 2004, **5**, 637–643; (*d*) C. Isanbor and D. O'Hagan, *J. Fluorine Chem.*, 2006, **127**, 303–319; (*e*) J.-P. Bégué and D. Bonnet-Delpon, *J. Fluorine Chem.*, 2006, **127**, 992–1012; (*f*) K. Muller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886; (*g*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (*h*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 2108–2114.

29 (*a*) H. Wenyong, W. Jianshu, H. Kaishun, P. Li, Z. Yujue, C. Yongzheng, C. N. Faming Zhuanli Shenqing, Patent

CN110627725A, December 31, 2019; (*b*) W. Jian-Shu, H. Kai-Shun, H. Wen-Yong, C. Bao-Dong, W. Nan-Wei and C. Yong-Zheng, *Org. Lett.*, 2019, **21**, 8751–8755; (*c*) E. E. Emelina, A. A. Petrov and A. V. Firsov, *Russ. J. Org. Chem.*, 2001, **37**, 852–858.

30 (*a*) J. Petrignet, E. Thiery, L. Silpa and M. Abarbri, *Synthesis*, 2014, **46**, 947–954; (*b*) L. Silpa, J. Petrignet and M. Abarbri, *Synlett*, 2014, **25**, 1827–1830; (*c*) B. Jismy, A. Tikad, M. Akssira, G. Guillaumet and M. Abarbri, *Molecules*, 2020, **25**, 2062.

31 (*a*) B. Jismy, G. Guillaumet, H. Allouchi, M. Akssira and M. Abarbri, *Eur. J. Org. Chem.*, 2017, 6168–6178; (*b*) L. Silpa, A. Niepceron, F. Laurent, F. Brossier, M. Pénichon, C. Enguehart-Gueiffier, M. Abarbri, A. Silvestre and J. Petrignet, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 114–120.

32 B. Jismy, H. Allouchi, G. Guillaumet, M. Akssira and M. Abarbri, *Synthesis*, 2018, **50**, 1675–1686.

33 (*a*) F. A. Kang, Z. Sui and W. V. Murray, *J. Am. Chem. Soc.*, 2008, **130**, 11300–11302; (*b*) F. A. Kang, Z. Sui and W. V. Murray, *Eur. J. Org. Chem.*, 2009, 461–479; (*c*) F.-A. Kang, J. C. Lanter, C. Cai, Z. Sui and W. V. Murray, *Chem. Commun.*, 2010, **46**, 1347–1349; (*d*) C. Shi and C. C. Aldrich, *Org. Lett.*, 2010, **12**, 2286–2289; (*e*) V. P. Mehta, S. G. Modha and E. Van der Eycken, *J. Org. Chem.*, 2010, **75**, 976–979; (*f*) S.-M. Li, J. Huang, G.-J. Chena and F.-S. Han, *Chem. Commun.*, 2011, **47**, 12840–12842; (*g*) R. Belaroussi, A. El Hakmaoui, M. Akssira, G. Guillaumet and S. Routier, *Eur. J. Org. Chem.*, 2016, 3550–3558.

34 (*a*) G. Prié, J. Thibonnet, M. Abarbri, J.-L. Parrain and A. Duchêne, *Synlett*, 1998, 839–840; (*b*) J. Thibonnet, G. Prié, M. Abarbri, J.-L. Parrain and A. Duchêne, *Tetrahedron Lett.*, 1999, **40**, 3151–3154; (*c*) Y. Carcenac, K. Zine, J. C. Kizirian, J. Thibonnet, A. Duchêne, J.-L. Parrain and M. Abarbri, *Adv. Synth. Catal.*, 2010, **352**, 949–954; (*d*) K. Zine, J. Petrignet, J. Thibonnet and M. Abarbri, *Synlett*, 2012, **23**, 755–759.

35 (*a*) S. Kotha, K. Lahiri and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633–9695; (*b*) F. Bellina, A. Carpita and R. Rossi, *Synthesis*, 2004, 2419–2440; (*c*) N. T. S. Phan, N. M. Van Der Sluys and C. W. Jones, *Adv. Synth. Catal.*, 2006, **348**, 609–679.

36 (*a*) L. Jedinak and P. Cankař, *Eur. J. Org. Chem.*, 2016, 2013–2023; (*b*) S. Vichier-Guerre, L. Dugue and S. Pochet, *Tetrahedron Lett.*, 2014, **55**, 6347–6350; (*c*) J. Tan, Y. Chen, H. Li and N. Yasuda, *J. Org. Chem.*, 2014, **79**, 8871–8876; (*d*) E. Bratt, O. Verho, M. J. Johansson and J.-E. Backvall, *J. Org. Chem.*, 2014, **79**, 3946–3954; (*e*) Y. Qian, M. Hamilton, A. Sidduri, S. Gabriel, Y. Ren, R. Peng, R. Kondru, A. Narayanan, T. Truitt, R. Hamid, Y. Chen, L. Zhang, A. J. Fretland, R. A. Sanchez, K.-C. Chang, M. Lucas, R. C. Schoenfeld, D. Laine, M. E. Fuentes, C. S. Stevenson and D. C. Budd, *J. Med. Chem.*, 2012, **55**, 7920–7939; (*f*) S. D. Walker, T. E. Barder, J. R. Martinelli and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2004, **43**, 1871–1876; *Angew. Chem.*, 2004, **116**, 1907–1912.

37 R. Aggarwala, E. Masana, P. Kaushik, D. Kaushik, C. Sharma and K. R. Aneja, *J. Fluorine Chem.*, 2014, **168**, 16–24.

38 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **50**, 4467–4470.

39 L. Jedinák, R. Zatopkova, H. Zemankova, A. Sustkova and P. Cankař, *J. Org. Chem.*, 2017, **82**, 157–169.

40 Y. F. Yu, Y. D. Huang, C. Zhang, X. N. Wu, Q. Zhou, D. Wu, Y. Wu and H. B. Luo, *Neurosci*, 2017, **8**, 2522–2534.

41 (*a*) C. Herrera-Arozamena, M. Estrada-Valencia, C. L. Pérez, L. Lagartera, J. A. Morales-García, A. Pérez-Castillo, J. F. Franco-Gonzalez, P. Michalska, P. Duarte, R. León, M. G. López, A. Mills, F. Gago, Á. J. García-Yagüe, R. Fernández-Ginés, A. Cuadrado and M. I. Rodríguez-Franco, *Eur. J. Med. Chem.*, 2020, **190**, 112090–112114; (*b*) Z. Sang, K. Wang, P. Bai, A. Wu, J. Shi, W. Liu, G. Zhu, Y. Wang, Y. Lan, Z. Chen, Y. Zhao, Z. Qiao, C. Wang and Z. Tan, *Eur. J. Med. Chem.*, 2020, **194**, 112265; (*c*) G. Zhu, K. Wang, J. Shi, P. Zhang, D. Yang, X. Fan, Z. Zhang, W. Liu and Z. Sang, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 126625–126631.

42 (*a*) M. B. Youdim, D. Edmondson and K. F. Tipton, *Nat. Rev. Neurosci.*, 2006, **7**, 295–309; (*b*) S. F. Carter, K. Herholz, P. Rosa-Neto, L. Pellerin, A. Nordberg and E. R. Zimmer, *Trends Mol. Med.*, 2019, **25**, 77–95.

43 U. Kosak, D. Knez, N. Coquelle, B. Brus, A. Pislar, F. Nachon, X. Brazzolotto, J. Kos, J. P. Colletier and S. Gobec, *Bioorg. Med. Chem.*, 2017, **25**, 633–645.