



**HAL**  
open science

**Microwave-assisted Suzuki-Miyaura and Sonogashira  
coupling of  
4-Chloro-2-(trifluoromethyl)pyrido[1,2-e]purine  
derivatives**

Zahira Tber, Nicolas G. Biteau, Luigi Agrofoglio, Julien Cros, Stéphane Goffinont, Bertrand Castaing, Cyril Nicolas, Vincent Roy

► **To cite this version:**

Zahira Tber, Nicolas G. Biteau, Luigi Agrofoglio, Julien Cros, Stéphane Goffinont, et al.. Microwave-assisted Suzuki-Miyaura and Sonogashira coupling of 4-Chloro-2-(trifluoromethyl)pyrido[1,2-e]purine derivatives. *European Journal of Organic Chemistry*, 2019, 2019, pp.5756-5767. 10.1002/ejoc.201900921 . hal-02347523

**HAL Id: hal-02347523**

**<https://hal.science/hal-02347523v1>**

Submitted on 5 Nov 2019

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Microwave-Assisted Suzuki–Miyaura and Sonogashira Coupling of 4-Chloro-2-(trifluoromethyl)pyrido[1,2-*e*]purine Derivatives

Zahira Tber,<sup>[a]</sup> Nicolas G. Biteau,<sup>[a]</sup> Luigi Agrofoglio,<sup>\*[a]</sup> Julien Cros,<sup>[b]</sup> Stéphane Goffinont,<sup>[b]</sup> Bertrand Castaing,<sup>[b]</sup> Cyril Nicolas,<sup>[a]</sup> and Vincent Roy<sup>\*[a]</sup>

Dedication ((optional))

**Abstract:** The convenient preparation of three imidazo[1,2-*a*]pyridine-2-carboxamide intermediates is reported through known Strecker–Ugi type multicomponent reactions, Tschitschibabin type condensations and further synthetic sequences. The derivatives were then efficiently converted to novel 4-chloro-2-(trifluoromethyl)pyrido[1,2-*e*]purines by way of their original reactions with 2,2,2-trifluoroacetamide, followed by subsequent dehydrochlorination reactions. These compounds were cross-coupled under microwave irradiation through Suzuki–Miyaura and Sonogashira palladium(0) catalysis to various aromatic and alkynyl reagents, thus providing the related C-4 substituted pyrido[1,2-*e*]purines of biological interest in good yields.

## Introduction

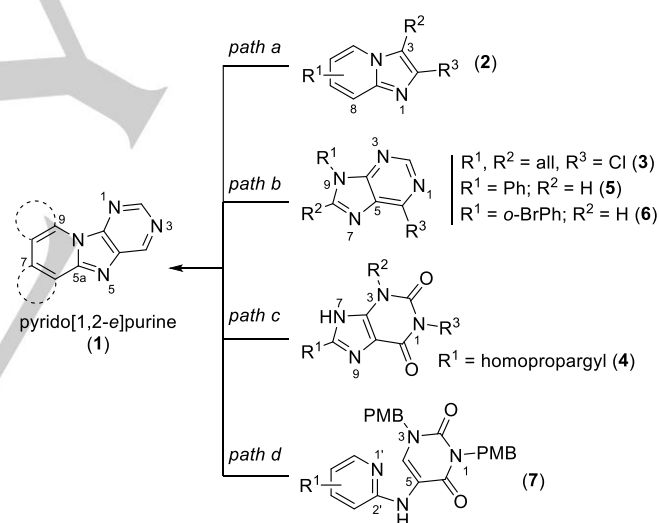
Purines are essential ubiquitous heterocyclic aromatic compounds that consist of a pyrimidine molecule fused to an imidazole ring. They are the most abundant nitrogen-containing heterocycles in nature,<sup>[1]</sup> and accordingly exhibit crucial roles. They display wide range of biological activities in various cellular processes involving DNA and RNA, ATP, GTP, cyclic AMP, NADH, and coenzyme A.<sup>[1-2]</sup>

Since the early 1900's,<sup>[3]</sup> the purine class of compounds have therefore spurred curiosity from the medicinal and organic synthetic chemistry community in generating analogs of variously substituted (heterocyclic) purines of biological interest.<sup>[4]</sup>

Noteworthy, for some specific pharmacological activities, purine derivatives have been found to be less potent, while their surrogates with an additional fused ring motif have been shown to possess better pharmacokinetic profiles, enhanced pharmacological activities and significant physicochemical properties.<sup>[5]</sup> The fused and extended imidazopyridines and their related compounds may indeed serve as valuable tools in

chemical biology, as many polycyclic nucleosides are fluorescent.<sup>[6]</sup> Moreover, important activities have been emphasized, such as antihypertension,<sup>[7]</sup> anti-inflammatory,<sup>[5a]</sup> human A3 adenosine receptor antagonism,<sup>[5b-e,8]</sup> and inhibition of PDE1/5 and tyrosine kinase EphB4.<sup>[9,5f]</sup>

Pyrido[1,2-*e*]purines of type 1 have hence recently gained attention in this direction. The new chemical entities have been shown to behave as powerful PDE5 inhibitors,<sup>[9b-d]</sup> of which some had a better selectivity over PDE6 and PDE1 than sildenafil,<sup>[9b]</sup> anticancer agents able to induce apoptosis of certain cancer cell lines or intercalating drugs to fit between base pairs of oligodeoxynucleotides.<sup>[5g,10]</sup>



**Figure 1.** Synthetic routes to pyrido[1,2-*e*]purines.

As illustrated in Fig. 1, the classical methods for the preparation of pyrido[1,2-*e*]purines commonly involve the formation of a suitably functionalized imidazo[1,2-*a*]pyridine system 2 (R<sup>2</sup> = NO, NO<sub>2</sub>, NH<sub>2</sub>; R<sup>3</sup> = C≡N, CO<sub>2</sub>R, CONH<sub>2</sub>),<sup>[11]</sup> followed by construction of the C2–C3 annulated pyrimidine ring (path a).<sup>[5g,9b,10b,12]</sup> Various chemical approaches have been used in this respect, to give 2 in moderate to good yields, from substituted 2-aminopyridines and Tschitschibabin condensations,<sup>[9b,13]</sup> or Strecker–Ugi type cascade reactions.<sup>[5g,12a]</sup> Ehrlich–Sachs type cyclizations of 2-nitrosopyridines were also used, albeit with much lower efficiencies.<sup>[10b,12b,14]</sup> The imidazo[1,2-*a*]pyridine derivatives 2 could then be reacted with guanidine, formamide, acetamide

[a] Zahira Tber, Nicolas G. Biteau, Dr. Cyril Nicolas, Dr. Vincent Roy, Prof. Dr. Luigi Agrofoglio, Institut de Chimie Organique et Analytique, UMR CNRS 7311, Université d'Orléans, Rue de Chartres - BP 6759, 45067 Orléans cedex 2, France. [vincent.roy@univ-orleans.fr](mailto:vincent.roy@univ-orleans.fr) and [luigi.agrofoglio@univ-orleans.fr](mailto:luigi.agrofoglio@univ-orleans.fr) <http://www.icoa.fr/fr/agrofoglio>

[b] Julien Cros, Stéphane Goffinont, Dr. Bertrand Castaing, Centre de Biophysique Moléculaire, UPR CNRS 4301, Rue Charles Sadron, 45072 Orléans, France.

Supporting information for this article is given via a link at the end of the document.

acetate, triethyl orthoformate, ammonium formate, or acyl chloride reagents to give, after few other reactions, the expected pyrido[1,2-*e*]purines of type **1**.

As miscellaneous, compounds **1** may also be readily available through few synthetic sequences and (i) ring-closing metathesis of 8,9-diallyl-6-chloro-purine **3** (path b),<sup>[10g]</sup> (ii) silver-catalyzed intramolecular hydroamination of terminal alkynes of type **4** (path c),<sup>[15]</sup> (iii) double C–H arylations of 9-phenylpurines **5**, or (iv) consecutive Suzuki-Miyaura and direct C–H arylation of 9-(2-bromophenyl)purines **6** (path b).<sup>[16]</sup> Intramolecular cyclization reactions of 1,3-bis(4-methoxybenzyl)-5-(pyridin-2-ylamino)pyrimidine-2,4(1*H*,3*H*)-diones **7** could be performed otherwise (path d).<sup>[17]</sup>

Worth noting, oxidatively damaged DNA, which result from the attack of sugar and base moieties by reactive oxygen species (ROS) are formed as byproducts of normal cell metabolism and during exposure to endogenous or exogenous chemical or physical agents. Guanine, having the lowest redox potential, is the DNA base the most susceptible to oxidation, yielding mutagenic 8-oxo-7,8-dihydroguanine (8-oxoG). In eukaryotic cells, 8-oxoG is primarily repaired by the base excision repair pathway (BER) initiated by the DNA *N*-glycosylase hOGG1.<sup>[18]</sup> Human molecular and epidemiological studies have shown that hOGG1 can affect significantly cancer proliferation and other diseases development, such as Neurodegenerative diseases (NDD).<sup>[19,20]</sup> hOGG1 is therefore considered as a pertinent pharmacological target.<sup>[20,21]</sup>

Along our ongoing research program directed at generating small molecule modulators of hOGG1, we were interested in the synthesis of pyrido[1,2-*e*]purine scaffolds that would feature a CF<sub>3</sub> substituent at C-2 and an aromatic functional group at C-4 that would possibly be connected via a rigid carbon–carbon (Csp<sup>2</sup>–Csp) bond. Surprisingly, there is no example of such derivatives in the literature so far.

Herein, we thus report our studies concerning the straightforward and efficient preparation of such compounds (i.e., **A**).

## Results and Discussion

### Synthesis

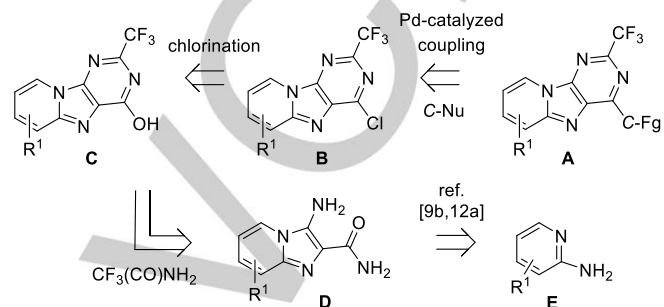
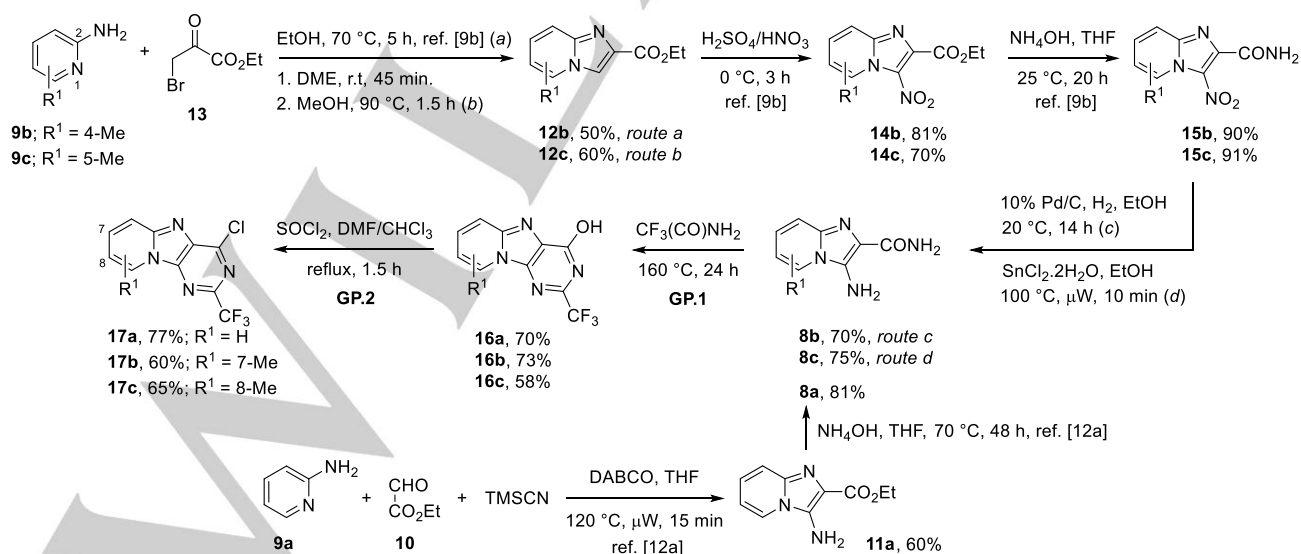


Figure 2. Retrosynthetic planning.

As depicted here above (Fig. 2), our retrosynthetic planning for the making of compounds **A** follows path a (e.g., Fig. 1). It requires novel 4-chloro-2-(trifluoromethyl)pyrido[1,2-*e*]purines **B** that would be derivatized through Pd-catalyzed cross-coupling chemistry. The synthesis of **B** would in turn, be achieved through dehydrochlorination of hitherto unknown 2-(trifluoromethyl)pyrido[1,2-*e*]purin-4-ol derivatives **C**, obtained from the original reactions of imidazo[1,2-*a*]pyridine-2-carboxamides **D** and 2,2,2-trifluoroacetamide (CF<sub>3</sub>(CO)NH<sub>2</sub>). Carboxamides **D** would be readily prepared, using known reaction sequences from commercial heterocyclic 2-amidines **E**.



Scheme 1. Synthesis of 4-chloro-2-(trifluoromethyl)pyrido[1,2-*e*]purine derivatives **17a–17c**.

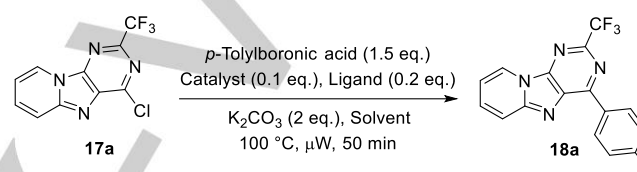
A set of aminoimidazo[1,2-*a*]pyridine-2-carboxamides **8a–8c** ( $R^1 = \text{H}$  (**a**), 4-Me (**b**), 5-Me (**c**)) were thus generated as model substrates (Scheme 1). Following a desilylative Strecker–Ugi type multicomponent reaction, the 2-aminopyridine **9a** was reacted with ethylglyoxalate **10** in the presence of TMSCN and 1,4-diazabicyclo[2.2.2]octane (DABCO) under microwave irradiation (120 °C) to give **11a** in moderate yield (60%).<sup>[5g,12a]</sup> **8a** was afforded by subsequent reaction with aqueous ammonia at 70 °C for 48 h (81%). Compounds **8b** and **8c** were prepared otherwise according to a Tschitschibabin type condensation protocol.<sup>[9b]</sup> Aminopyridines **9b** and **9c** were therefore converted into imidazo[1,2-*a*]pyridine-2-carboxylates **12b** (50%) and **12c** (60%) respectively, by refluxing in EtOH (route a) or MeOH (route b) with ethyl bromopyruvate **13**. The regioselective nitrations (e.g.,  $\text{H}_2\text{SO}_4/\text{HNO}_3$ ) of **12b–c** were then performed at 0 °C to provide the mono-nitro products **14b–c** in good yields (81 vs. 70%). Next, the nitroesters **14b–c** were stirred in a mixture of aqueous ammonia and THF at room temperature, to provide nitroamides **15b–c** in excellent yields (90 and 91%). Reductions of **15b–c** to the corresponding aminoamides **8b–c** were achieved by catalytic hydrogenation (10% Pd–C, rt, route c), or treatment with Tin(II) chloride in EtOH at 100 °C under  $\mu\text{W}$  irradiation (route d).<sup>[9b]</sup> From the pyridine-carboxamide intermediates **8a–8c**, annulation and chlorination reactions were then carried out by heating at 160 °C with  $\text{CF}_3(\text{CO})\text{NH}_2$  used as solvent (24 h) and treatment with an excess of  $\text{SOCl}_2$  under reflux (1.5 h). The 2-(trifluoromethyl)pyrido[1,2-*e*]purin-4-ol derivatives **16a–16c** (58–73%) and 4-chloro-2-(trifluoromethyl)pyrido[1,2-*e*]purines **17a–17c** were obtained in moderate to good yields (i.e., 60–77%).

Compounds **17a–17c** in hands we decided to investigate further post-modification of the pyrimidine substitution pattern. Easy post-decoration of 4-chloro-pyrido[1,2-*e*]purines through nucleophilic substitutions with (aryl)- amines, alcohols and thiol reagents has already been described;<sup>[5g,12a]</sup> but to the best of our knowledge, there is no mention of their transition-metal catalyzed cross-coupling reactions with C–Nu.

The Suzuki–Miyaura reaction is a cornerstone of modern organic synthesis. Unlike many cross-coupling strategies, it is a routine, versatile and benign reaction that is cost-effective, scalable and maybe amenable to green chemistry principles and industrial standards.<sup>[22]</sup> It was successfully applied to many different coupling partners, including nitrogen-containing heterocycles using catalytic amount of palladium(II) acetate (0.1 eq.), Xantphos (0.2 eq.) as ligand and potassium carbonate (2 equiv.) as base in toluene at elevated temperature. In addition, conventional thermal heating could be replaced by microwave irradiation in a sealed reactor with major improvement in terms of yields and reaction times.<sup>[23]</sup> These conditions were thus tested with *p*-tolylboronic acid and chloropurine **17a** as model substrate to give **18a** in good yield (85%) after 50 min of reaction at 100 °C (Table 1, entry 1). Triphenyl phosphine, and BINAP,<sup>[24]</sup> together with Xantphos,<sup>[25]</sup> have become the most often used ligands for palladium-catalyzed carbon–carbon and the more challenging carbon–nitrogen bond-forming reactions.<sup>[26,27]</sup> Thus, subsequent cross-coupling reactions were next conducted with  $\text{PPh}_3$  and BINAP, but a disappointing yield decrease was noticed (entries 2–3). Of note, in situ generation of

tetrakis(triphenylphosphine)palladium(0) through insertion of  $\text{Pd}(\text{OAc})_2$  and  $\text{PPh}_3$  (entry 2) vs. direct addition of  $\text{Pd}(\text{PPh}_3)_4$  (entry 4) did not produce any variation of the reaction yield (ca. 80%). When the influence of the solvent was assessed ( $\text{H}_2\text{O}$ ,  $\text{H}_2\text{O}/\text{DME}$ , 1,4-dioxane), slight to dramatic decrease of the catalytic efficiency was noted (entries 5–7). It was also the case when  $\text{Cs}_2\text{CO}_3$  was replaced by  $\text{K}_2\text{CO}_3$  as base (entry 8). Finally, reaction temperature was increased to 120 °C to give a satisfactory 84% yield after a period of reaction of 30 min (entry 9). Interestingly, there was no cross-coupling reaction without a catalyst (entry 10), which excludes an addition/elimination pathway.

**Table 1.** Optimization of the conditions for the Suzuki–Miyaura coupling reaction of *p*-tolylboronic acid and compound **17a**.<sup>[a]</sup>



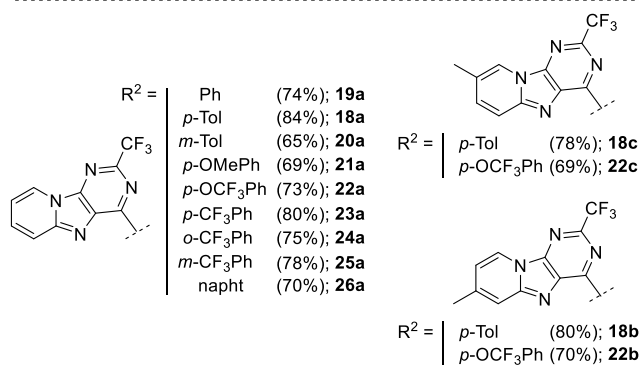
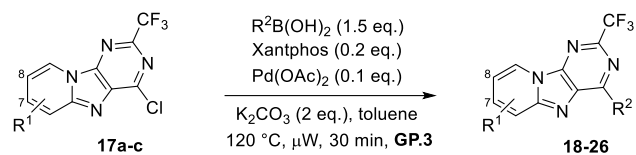
Entry	Catalyst	Ligand	Solvent	Yield (%) of <b>18a</b>
1	$\text{Pd}(\text{OAc})_2$	Xantphos	toluene	85
2	$\text{Pd}(\text{OAc})_2$	$\text{PPh}_3$	toluene	80
3	$\text{Pd}(\text{OAc})_2$	BINAP	toluene	60
4	$\text{Pd}(\text{PPh}_3)_4$	–	toluene	79
5	$\text{Pd}(\text{OAc})_2$	Xantphos	$\text{H}_2\text{O}$	50
6	$\text{Pd}(\text{OAc})_2$	Xantphos	$\text{H}_2\text{O}/\text{DME}$	40
7	$\text{Pd}(\text{OAc})_2$	Xantphos	1,4-dioxane	70
8	$\text{Pd}(\text{OAc})_2$	Xantphos	toluene	77 <sup>[b]</sup>
9	$\text{Pd}(\text{OAc})_2$	Xantphos	toluene	84 <sup>[c]</sup>
10	$\text{Pd}(\text{OAc})_2$	–	toluene	traces

[a] Typical reaction conditions: Ar atmosphere, compound **17a** (1 eq.), *p*-tolylboronic acid (1.5 eq.),  $\text{K}_2\text{CO}_3$  (2 eq.) as base, catalyst (0.1 eq.), additional ligand (0.2 eq.), heating at 100 °C under microwave irradiation for 50 min in a sealed reactor. [b]  $\text{Cs}_2\text{CO}_3$  (2 eq.) instead of  $\text{K}_2\text{CO}_3$  (2 eq.) were added. [c] Heating was performed at 120 °C for 30 min.

The scope of the reaction was then explored using various organoboronic acids under the optimized aforementioned conditions (entry 9). As depicted in Scheme 2, yields obtained were good for most products (e.g., 65–85%). It is worth noting that a better reactivity was observed for boronic acids substituted with a methyl or an electron-withdrawing group. The outcomes were also indicative of the influence of the substituent position on the reactivity of the boronic acid. Comparing the same moiety, the *p*-substituted phenylboronic acid showed better reactivity than the

## FULL PAPER

respective *m*- and *o*-substituted phenylboronic acids. Furthermore, substitution by a methyl group at the C-7 or C-8 position of compounds **17** did not change significantly the yield of the catalysis.

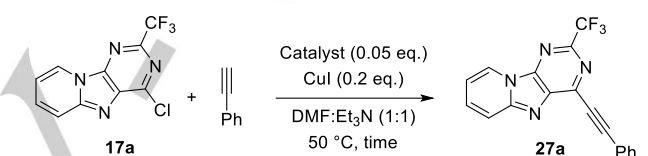


**Scheme 2.** Scope of the Suzuki–Miyaura Reaction.

Having successfully established the efficacy of the Suzuki–Miyaura in constructing trifluoro purines with aromatic substituents at C-4 with a Csp<sup>2</sup>–Csp<sup>2</sup> bond, we next turned our attention to a palladium–catalyzed process allowing construction of Csp<sup>2</sup>–Csp bonds. The Sonogashira reaction has found extensive use in this respect, in natural products synthesis and for the making of complex molecules.<sup>[28]</sup> Various solvents, palladium species, copper(I) salts and bases were tested. Remarkably, few examples have been reported on halogeno[1,2-*a*]pyridines,<sup>[29]</sup> due to their possible antiviral, anticancer, antiulcer, antifungal and antibacterial properties. The substituted [1,2-*a*]pyridine compounds may also find applications as calcium channel blockers, benzodiazepine receptor agonists, herbicides, GABA<sub>A</sub> receptor modulators, and cyclin-dependent kinase (CDK) inhibitors, etc.,<sup>[30]</sup> In some instances, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.05 eq.), Pd(OAc)<sub>2</sub> (0.05 eq.) and PPh<sub>3</sub> (0.1 eq.) or Pd(PPh<sub>3</sub>)<sub>4</sub> (0.05 eq.) as catalysts were used with Cul (0.2 eq.) as co-catalyst in a mixture of DMF/Et<sub>3</sub>N (1:1, v/v) at 50 °C.<sup>[29,31]</sup> These conditions were thus employed with **17a** and ethynylbenzene to give moderate to good yields (45–70%, Table 2, entries 1–3) of purine **27a** after 60 min of reaction. Total conversion was observed with 1.2 eq. of the alkyne reagent and 1 eq. of **17a**, as monitored by TLC analysis of the crude reaction mixtures. The amount of the copper(I) iodide salt proved to be crucial, as it was not amenable to a lower loading without loss of the catalysis efficiency (55% vs. 70%, entries 3–4). Heating under microwave irradiation was also studied in order to improve the yields and to decrease reaction times.<sup>[23a–b]</sup> Notable, a 65% yield was obtained over 5 min of reaction at 90 °C (entry 5), whereas a satisfactory 75% of product **27a** was afforded after

15 min at 70 °C (entry 5). The deprotonation of the acetylene may be an important step at the beginning of the cross-coupling reaction. However, the use of other bases (Cs<sub>2</sub>CO<sub>3</sub>, HN-*i*-Pr<sub>2</sub>, KOt-Bu, etc.,) was not explored. At that stage, we thought the conditions were acceptable to be evaluated with compounds **17a–c** and a range of variously substituted alkynyl (aromatic) reagents. Gratifyingly, yields of the coupled derivatives **27–34** were quite good for most products, as shown in Scheme 3. As expected, the stereoelectronic properties of the acetylenes were correlated with the performance in alkylation reactions. As a rule, the arylacetylene with the most 4-R electron-donating ability produces the best chemical yield (OMe > H > Me > F, see compounds **28a–30a**, **34a**). Interestingly, it is the opposite of Plenio investigations on electronic effects for Tolanes synthesis.<sup>[32]</sup>

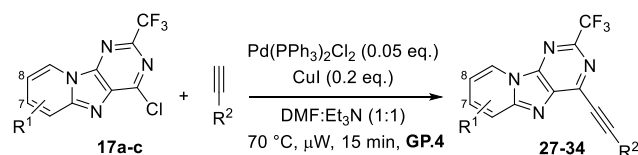
**Table 2.** Optimization of the conditions for the Sonogashira coupling reaction of ethynylbenzene and compound **17a**.<sup>[a]</sup>



Entry	Catalyst	Ligand	Time (min)	Yield (%) of <b>27a</b> <sup>[a]</sup>
1	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub>	60	45 <sup>[b]</sup>
2	Pd(PPh <sub>3</sub> ) <sub>4</sub>	–	60	62
3	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	–	60	70
4	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	–	60	55 <sup>[c]</sup>
5	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	–	5	65 <sup>[d]</sup>
6	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>	–	15	75 <sup>[e]</sup>

[a] Typical reaction conditions: Ar atmosphere, compound **17a** (1 eq.), ethynylbenzene (1.2 eq.), catalyst (0.05 eq.), copper(I) iodide (0.2 eq.), heating at 50 °C. [b] Pd(OAc)<sub>2</sub> (0.05 eq.) as catalyst and PPh<sub>3</sub> (0.1 eq.) as ligand were used. [c] Cul (0.1 eq.) was used as co-catalyst instead of Cul (0.2 eq.). [d] Heating was performed at 90 °C under μW irradiation. [e] Heating was performed at 70 °C under μW irradiation.

Comparing the same moiety, the *p*-substituted phenylalkynes showed enhanced product formation as regard to the *o*-derivatives. The *m*-substituted ones behave in the medium range with slightly similar overall yield than the *p*-substituted compounds (74% vs. 80% for **30a** (*o*-MeOPh) and **32a** (*p*-MeOPh)). Noteworthy, substitution by a methyl group at the C-7 position of compounds **17** did not affect significantly the yield of the cross-coupled products (see **28b** and **32b**) while substitution at C-8 (i.e., **17c**) gave no conversion. The starting materials were fully recovered when reactions were attempted with 3-ethynylanisole and 4-ethynyltoluene (e.g., **28c** and **32c**).



R<sup>1</sup> = H **a**, 7-Me **b**, 8-Me **c**

R <sup>1</sup> = H; R <sup>2</sup> =	Ph (75%); <b>27a</b>	R <sup>1</sup> = 7-Me
	<i>p</i> -Tol (70%); <b>28a</b>	R <sup>2</sup> =
	<i>p</i> -FPh (63%); <b>29a</b>	<i>p</i> -Tol (60%); <b>28b</b>
	<i>p</i> -OMePh (80%); <b>30a</b>	<i>m</i> -OMePh (69%); <b>32b</b>
	<i>o</i> -OMePh (52%); <b>31a</b>	
	<i>m</i> -OMePh (74%); <b>32a</b>	R <sup>1</sup> = 8-Me
	<i>t</i> -Bu (66%); <b>33a</b>	R <sup>2</sup> =
	4-F-3-MePh (60%); <b>34a</b>	<i>p</i> -Tol (nc); <b>28c</b>
		<i>m</i> -OMePh (nc); <b>32c</b>

**Scheme 3.** Scope of the Sonogashira Reaction.

## Conclusions

In conclusion, we have reported an efficient and easy way to provide novel pyrido[1,2-*e*]purine derivatives featuring a trifluoromethyl substituent at C-2 and an aromatic functional group at C-4. The valuable synthetic routes were developed through reaction sequences from commercial heterocyclic 2-amidines to give original 4-chloro-2-(trifluoromethyl)pyrido[1,2-*e*]purine intermediates **17a–c**. Compounds **17a–c** were then further functionalized by Suzuki–Miyaura and Sonogashira palladium(0) catalysis, under microwave irradiation to give compounds of type **18–26** and **27–34** in moderate to good yields. Of note, the cross-coupling reactions exhibited a high functional group tolerance, being reproducible for a wide range of arylboronic acids and (aryl) alkynyl reagents. In general, substitution at C-7 or C-8 position of the chloropurines (e.g., **17b–c**) could be tolerated albeit it was not the case for the alkylation reactions of compound **17c** and 3-ethynylanisole or 4-ethynyltoluene. Complementary studies to synthesize these important molecules are ongoing and biological evaluations on the 8-oxoguanine-DNA *N*-glycosylase hOGG1 isoform will be reported in due course.

## Experimental Section

**General Remarks.** Unless otherwise stated, all solvents and commercially available reagents were used as purchased. *N,N*-Dimethylformamide anhydrous, 99.8% was purchased from Sigma–Aldrich. Thionyl chloride (SOCl<sub>2</sub>) was distilled prior to use. Reactions were monitored by thin-layer chromatography (TLC) using Merck Silica Gel 60 F254 pre-coated plates. Visualization of the developed chromatogram was performed under ultraviolet light (254 nm) and on staining by immersion in aqueous, acidic ceric ammonium molybdate (CAM; 470 mL H<sub>2</sub>O, 28 mL H<sub>2</sub>SO<sub>4</sub>, 24 g ammonium molybdate, 0.5 g cerium ammonium nitrate) followed by heating on a hot plate. Normal phase flash chromatography was performed in air on Silica Gel 60 (230–400 mesh). Organic solutions were concentrated under reduced pressure with a Buchi rotary evaporator. Microwave activations were performed in sealed vessels using a Biotage Initiator system. The following settings were used: Normal absorption level, Fixed Hold Time: on. The internal temperature was measured by an IR-

sensor. NMR spectra were recorded at 298 K with a Bruker Avance III HD nanobay 400 MHz spectrometer equipped with a PABBO BBO probe, a Bruker Avance II and a Bruker DPX 250 MHz spectrometer. The nuclei-signal assignments were done with the aid of 1D [<sup>1</sup>H NMR, <sup>13</sup>C NMR, Distortionless Enhancement by Polarization Transfer (DEPT)] and 2D Correlation Spectroscopy [(<sup>1</sup>H–<sup>1</sup>H COSY and <sup>1</sup>H–<sup>13</sup>C Heteronuclear Single Quantum Coherence (HSQC)) experiments. When appropriate or in case of ambiguous proton and carbon, assignments were established using <sup>19</sup>F NMR and Heteronuclear Multiple-bond Correlation (HMBC). <sup>13</sup>C and <sup>19</sup>F spectra were acquired on a broad band decoupled mode. <sup>1</sup>H NMR (400 or 250 MHz) chemical shift values are listed in parts per million (ppm) downfield from TMS as the internal standard or relative to the corresponding non-deuterated solvent. Data are reported as follows: chemical shift (ppm on the δ scale), multiplicity (s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet and m = multiplet), coupling constant J (Hz), and integration. <sup>13</sup>C NMR (101 or 63 MHz) chemical shifts are given in ppm relative to the corresponding non-deuterated solvent or TMS as the internal standard. <sup>19</sup>F NMR (376 MHz) chemical shifts are given in ppm. High-resolution mass spectra were recorded with a MaXis ESI qTOF ultrahigh-resolution mass spectrometer (FR2708, Orléans). Melting points (m.p., °C) were determined using a Fisher Scientific Fisherbrand 9300 apparatus in open capillaries and are uncorrected. Infrared spectra were recorded neat with a Thermo Scientific Nicolet IS10 FTIR spectrometer using diamond ATR golden gate sampling and are reported in wave numbers (cm<sup>-1</sup>).

**General Procedure for the Synthesis of Compounds 16a–c From Carboxamide Derivatives 8a–c (GP.1).** A single-necked round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 2,2,2-trifluoroacetamide (10 equiv.) under argon atmosphere. The white solid was then heated at 110 °C until it melted and compound **8a–c** (1 equiv.) was added. The reaction mixture was heated at 160 °C for 24 h. Afterwards, the mixture was allowed to reach room temperature (20 °C) and the crude residue was purified through silica gel column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> : MeOH 95:5) to afford the desired product **16a–c** in moderate to good yield.

**General Procedure for the Dehydrochlorination of Pyrido[1,2-*e*]purin-4-ol Derivatives 16a–c (GP.2).** A single-necked round-bottomed flask equipped with a reflux condenser under argon atmosphere was charged with compound **16a–c** (1 equiv.) and CHCl<sub>3</sub> (3 mL) and the mixture was stirred under reflux for 10 minutes (flask A). In parallel, a single-necked round-bottomed flask under argon atmosphere was charged with SOCl<sub>2</sub> (5 equiv.) and anhydrous DMF (280 μL) at 0 °C (ice-water bath) and the mixture was stirred at the same temperature for 10 minutes (solution B). Solution B was then added to flask A, dropwise (syringe addition) and the reaction mixture was refluxed for 1.5 h under argon atmosphere. The reaction was poured into ice and water, the aqueous and organic layers were separated, and the organic phase was washed with water. The aqueous phase was then adjusted to pH 7 (sat. aq. NaHCO<sub>3</sub>) and extracted with Et<sub>2</sub>O. Afterwards, combined organic layers were dried (MgSO<sub>4</sub>), filtered through a cotton plug and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>) to provide the desired product in moderate to good yield.

**General Procedure for the Suzuki–Miyaura Cross-Coupling Reactions of Compounds 17a–c (GP.3).** A 2–5 mL microwave vial under argon atmosphere was charged with a given boronic acid (1.5 equiv.), compound **17a–c** (1 equiv.), K<sub>2</sub>CO<sub>3</sub> (2 equiv.) and anhydrous toluene (2 mL). The mixture was deoxygenated by passing a stream of argon through a syringe and Pd(OAc)<sub>2</sub> (0.1 equiv.) and Xantphos (0.2 equiv.) were added. The tube was closed with the cap and the reaction mixture was stirred at 120 °C

under microwave irradiation for 30 minutes. H<sub>2</sub>O (20 mL) was then added and the organic phase was extracted thrice with AcOEt (3 × 5 mL). Next, combined organic layers were dried (MgSO<sub>4</sub>), filtered through a cotton plug and concentrated under vacuum. The crude product was purified by column chromatography over silica gel.

**General Procedure for the Sonogashira Cross-coupling Reactions of Compounds 17a–c (GP.4).** A 2–5 mL microwave vial under argon atmosphere was charged with a given alkynyl derivative (1.2 equiv.), compound **17a–c** (1 equiv.), and 3 mL of Et<sub>3</sub>N–anhydrous DMF (1:1, v/v). The mixture was deoxygenated by passing a stream of argon through a syringe and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.05 equiv.) and CuI (0.2 equiv.) were added. The tube was closed with the cap and the reaction mixture was stirred at 70 °C under microwave irradiation for 15 minutes. H<sub>2</sub>O (20 mL) was then added and the organic phase was extracted thrice with AcOEt (3 × 5 mL). Next, combined organic layers were dried (MgSO<sub>4</sub>), filtered through a cotton plug and concentrated under vacuum. The crude product was purified by column chromatography over silica gel.

**Ethyl 3-aminoimidazo[1,2-*a*]pyridine-2-carboxylate (11a).** A 20-mL microwave vial under argon atmosphere was charged with 2-aminopyridine (200 mg, 2.12 mmol) and ethyl glyoxalate solution (50% in toluene) (420 μL, 2.12 mmol). The mixture was stirred for 2 min at rt (20 °C) and 1,4-Diazabicyclo[2.2.2]octane (DABCO, 238 mg, 2.12 mmol) and THF (4 mL) were added. The solution was then cooled to 0–5 °C (ice–water bath) and TMSCN (265 μL, 2.12 mmol) was added dropwise. The vial was capped and the reaction mixture was subsequently heated under microwave irradiation for 15 min at 120 °C. Next, sat. aq. K<sub>2</sub>CO<sub>3</sub> was added and the organic solvents were evaporated under reduced pressure (rotary evaporation). The aqueous phase was extracted thrice with AcOEt, combined organic phases dried over Na<sub>2</sub>SO<sub>4</sub>, filtered through a cotton plug and evaporated in vacuo. The crude titled compound was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>:MeOH 95:5) to afford **11a** as a yellow precipitate (261 mg, 60%). m.p.: 211–212 °C; IR (neat):  $\tilde{\nu}$  = 3419, 2084, 2987, 1677, 1638, 1573, 1268, 1183, 1026, 745, 509 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_H$  = 8.17 (d, *J* = 7.1 Hz, 1 H, *H*<sub>Ar</sub>), 7.33 (d, *J* = 9.3 Hz, 1 H, *H*<sub>Ar</sub>), 7.08 (dd, *J* = 9.3, 6.7, Hz, 1 H, *H*<sub>Ar</sub>), 6.81 (t, *J* = 6.7 Hz, 1 H, *H*<sub>Ar</sub>), 6.36 (s, 2 H, *NH*<sub>2</sub>), 4.27 (q, *J* = 7.1 Hz, 1 H, OCH<sub>2</sub>CH<sub>3</sub>), 1.31 (t, *J* = 7.1 Hz, 3 H, OCH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>):  $\delta_C$  = 164.4 (C, CO), 138.5 (C, C<sub>Ar</sub>), 137.5 (C, C<sub>Ar</sub>), 123.7 (CH, CH<sub>Ar</sub>), 123.2 (CH, CH<sub>Ar</sub>), 118.1 (CH, CH<sub>Ar</sub>), 112.6 (C, C<sub>Ar</sub>), 111.5 (CH, CH<sub>Ar</sub>), 59.2 (CH<sub>2</sub>, OCH<sub>2</sub>CH<sub>3</sub>), 14.5 (CH<sub>3</sub>, OCH<sub>2</sub>CH<sub>3</sub>) ppm.

**7-Methyl-3-nitroimidazo[1,2-*a*]pyridine-2-carboxamide (15b).** A single-necked round-bottomed flask equipped with a reflux condenser under argon atmosphere, was charged with 2-Amino-4-methylpyridine (2.16 g, 20 mmol) and EtOH absolute (50 mL) and the mixture was heated at 70 °C until complete dissolution. Ethyl bromopyruvate (2.76 mL, 22 mmol) was then added dropwise and the reaction mixture was refluxed for 5 h. After solvent removal (rotary evaporation), the crude material was purified through silica gel chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>:MeOH, 99:1) to afford ethyl 7-methylimidazo[1,2-*a*]pyridine-2-carboxylate **12b** as a beige solid (2.02 g, 50%). m.p.: 133–134 °C; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta_H$  = 8.09 (d, *J* = 0.8 Hz, 1 H, *H*<sub>Ar</sub>), 7.95–7.86 (m, 1 H, *H*<sub>Ar</sub>), 7.57 (d, *J* = 9.3 Hz, 1 H, *H*<sub>Ar</sub>), 7.08 (dd, *J* = 9.4, 1.7 Hz, 1 H, *H*<sub>Ar</sub>), 4.44 (q, *J* = 7.1 Hz, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 2.32 (s, 3 H, CH<sub>3</sub>), 1.50 (t, *J* = 7.1 Hz, 3 H, OCH<sub>2</sub>CH<sub>3</sub>) ppm.

A round-bottomed flask under argon atmosphere was charged with compound **12b** (3.5 g, 16.8 mmol) and the flask was cooled to 0–5 °C (ice–water bath). Concentrated sulphuric acid (H<sub>2</sub>SO<sub>4</sub> > 95%, 17 mL) was then added, followed by nitric acid (HNO<sub>3</sub> 65%, 2 mL) dropwise and the reaction mixture was stirred for 3 h at 0 °C. The mixture was carefully poured onto ice (250 g) and the yellow solid was filtered, rinsed with H<sub>2</sub>O (50 mL) and dried in vacuo. The crude residue was purified by column chromatography

(SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>) to give ethyl 7-methyl-3-nitroimidazo[1,2-*a*]pyridine-2-carboxylate **14b** as a yellow solid (3.4 g, 81%). m.p.: 145 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/TMS):  $\delta_H$  = 9.23 (d, *J* = 7.2 Hz, 1 H, *H*<sub>Ar</sub>), 7.60 (br s, 1 H, *H*<sub>Ar</sub>), 7.17 (dd, *J* = 7.2, 1.7 Hz, 1 H, *H*<sub>Ar</sub>), 4.54 (q, *J* = 7.2 Hz, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 2.56 (s, 3 H, CH<sub>3</sub>), 1.45 (t, *J* = 7.1 Hz, 3 H, OCH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C$  = 162.1 (C, CO), 145.4 (C, C<sub>Ar</sub>), 143.3 (C, C<sub>Ar</sub>), 143.3 (C, C<sub>Ar</sub>), 140.8 (C, C<sub>Ar</sub>), 126.6 (CH, CH<sub>Ar</sub>), 120.3 (CH, CH<sub>Ar</sub>), 118.0 (CH, CH<sub>Ar</sub>), 63.0 (CH<sub>2</sub>, OCH<sub>2</sub>CH<sub>3</sub>), 21.8 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>, OCH<sub>2</sub>CH<sub>3</sub>) ppm.

Thereafter, the product (3.3 g, 13.2 mmol) was inserted in a microwave vial under air atmosphere and a 28–30% aq. NH<sub>4</sub>OH solution (20 ml) and THF (1 ml) were added. The vial was capped and the mixture was subsequently stirred at room temperature for 20 h. The solvents were evaporated under vacuum and Methanol (50 mL) was added. The precipitate was filtered and washed further with a mixture of methanol and pentane (8:2) to provide compound **15b** as a yellow solid (2.61 g, 90%). m.p.: 295–296 °C (from MeOH); IR (neat):  $\tilde{\nu}$  = 3406, 3177, 2988, 1678, 1482, 1398, 1320, 1206, 1157, 765, 510 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_H$  = 9.22 (d, *J* = 7.1 Hz, 1 H, *H*<sub>Ar</sub>), 8.08 (s, 1 H, *NH*), 7.90 (s, 1 H, *NH*), 7.80 (s, 1 H, *H*<sub>Ar</sub>), 7.39 (d, *J* = 7.1 Hz, 1 H, *H*<sub>Ar</sub>), 2.52 (s, 3 H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>):  $\delta_C$  = 163.6 (C, CO), 145.2 (C, C<sub>Ar</sub>), 144.9 (C, C<sub>Ar</sub>), 143.6 (C, C<sub>Ar</sub>), 127.8 (C, C<sub>Ar</sub>), 127.0 (CH, CH<sub>Ar</sub>), 120.0 (CH, CH<sub>Ar</sub>), 116.8 (CH, CH<sub>Ar</sub>), 20.9 (CH<sub>3</sub>) ppm.

**6-Methyl-3-nitroimidazo[1,2-*a*]pyridine-2-carboxamide (15c).** A single-necked round-bottomed flask under argon atmosphere was charged with 2-amino-5-methylpyridine (5 g, 46 mmol) and 1,2-dimethoxyethane (DME, 50 mL). Ethyl bromopyruvate (5.77 mL, 46 mmol) was then added, dropwise and the reaction mixture was stirred for 45 minutes at room temperature. The precipitate was filtered, washed with Et<sub>2</sub>O and dried in vacuo to give a yellow solid. The solid was suspended in MeOH (50 mL) and the suspension was heated at 90 °C until complete dissolution (1.5 h). The solution was concentrated and neutralized to pH 7. The mixture was extracted thrice with CH<sub>2</sub>Cl<sub>2</sub>, combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered over a cotton plug and concentrated under vacuum. The residue was purified through silica gel chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> : MeOH 95:5) to provide ethyl 6-methylimidazo[1,2-*a*]pyridine-2-carboxylate **12c** as a yellow light solid (5.63 g, 60%).

Next, a round-bottomed flask under argon atmosphere was charged with compound **12c** (4.0 g, 19.6 mmol) and the flask was cooled to 0–5 °C (ice–water bath). Concentrated sulphuric acid (H<sub>2</sub>SO<sub>4</sub> > 95%, 20 mL) was added, followed by nitric acid (HNO<sub>3</sub> 65%, 2.4 mL) dropwise and the reaction mixture was stirred for 3 h at 0 °C. The mixture was carefully poured onto ice (250 g) and the yellow solid was filtered, rinsed with H<sub>2</sub>O (50 mL) and dried in vacuo. The crude residue was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>) to give ethyl 6-methyl-3-nitroimidazo[1,2-*a*]pyridine-2-carboxylate **14c** as a yellow solid (3.4 g, 70%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H$  = 9.17 (br s, 1 H, *H*<sub>Ar</sub>), 7.78 (d, *J* = 9.1 Hz, 1 H, *H*<sub>Ar</sub>), 7.53 (dd, *J* = 9.2, 1.7 Hz, 1 H, *H*<sub>Ar</sub>), 4.55 (q, *J* = 7.2 Hz, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 2.52 (s, 3 H, CH<sub>3</sub>), 1.45 (t, *J* = 7.1 Hz, 3 H, OCH<sub>2</sub>CH<sub>3</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C$  = 162.1 (C, CO), 143.8 (C, C<sub>Ar</sub>), 140.3 (C, C<sub>Ar</sub>), 134.0 (C, CH<sub>Ar</sub>), 128.5 (C, C<sub>Ar</sub>), 125.3 (C, CH<sub>Ar</sub>), 118.6 (C, CH<sub>Ar</sub>), 100.1 (C, C<sub>Ar</sub>), 63.0 (CH<sub>2</sub>, OCH<sub>2</sub>CH<sub>3</sub>), 18.9 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>, OCH<sub>2</sub>CH<sub>3</sub>) ppm.

Thereafter, the product (990 mg, 3.97 mmol) was inserted in a microwave vial under air atmosphere and 28–30% aq. NH<sub>4</sub>OH solution (4 ml) and THF (0.2 ml) were added. The vial was capped and the mixture was stirred at room temperature for 20 h. The solvents were evaporated under vacuum and methanol (10 mL) was added. The precipitate was filtered and washed further with a mixture of methanol and pentane (8:2) to afford compound **15c** as a yellow solid (800 mg, 91%). m.p.: 300 °C (from MeOH); IR (neat) ( $\nu_{\max}/\text{cm}^{-1}$ ): 3369, 3146, 1664, 1640, 1384, 1218, 1191, 834, 799, 510; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_H$  = 9.16 (s, 1 H, *H*<sub>Ar</sub>), 8.07 (s, 1 H, *NH*), 7.90

(s, 1 H,  $H_{Ar}$ ), 7.88 (s, 1 H,  $NH$ ), 7.72 (d,  $J = 9.0$  Hz, 1 H,  $H_{Ar}$ ), 2.47 (s, 3 H,  $CH_3$ ) ppm;  $^{13}C$  NMR (101 MHz, DMSO- $d_6$ ):  $\delta_C = 163.6$  (C, CO), 144.7 (C,  $C_{Ar}$ ), 143.4 (C,  $C_{Ar}$ ), 134.5 (C,  $CH_{Ar}$ ), 127.8 (C,  $C_{Ar}$ ), 125.4 (C,  $CH_{Ar}$ ), 117.5 (C,  $CH_{Ar}$ ), 17.9 ( $CH_3$ ) ppm.

**Aminoimidazo[1,2-*a*]pyridine-2-carboxamide (8a).** A microwave vial under air atmosphere was charged with imidazo[1,2-*a*]pyridine **11a** (550 mg, 2.44 mmol), 28–30% aq.  $NH_4OH$  solution (10 ml) and THF (0.5 ml). The vial was sealed and the mixture was stirred at 70 °C for 48 h (normal heating with an oil bath). The solvents were evaporated under vacuum and the residue was purified through neutral alumina column ( $Al_2O_3$ ,  $CH_2Cl_2$  : MeOH 9:1) to furnish compound **8a** as a yellow solid (342 mg, 81%). m.p.: 233–236 °C; IR (neat):  $\tilde{\nu} = 3381, 3309, 3108, 1660, 1600, 1498, 1323, 1246, 698, 617, 510$   $cm^{-1}$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_H = 8.13$  (d,  $J = 7.0$  Hz, 1 H,  $H_{Ar}$ ), 7.40 (br s, 1 H,  $NH$ ), 7.34 (d,  $J = 9.3$  Hz, 1 H,  $H_{Ar}$ ), 7.14 (br s, 1 H,  $NH$ ), 7.06 (dd,  $J = 12.3, 1.2$  Hz, 1 H,  $H_{Ar}$ ), 6.80 (t,  $J = 6.7$  Hz, 1 H,  $H_{Ar}$ ), 6.14 (s, 2 H,  $H_{Ar}$ ) ppm;  $^{13}C$  NMR (101 MHz, DMSO- $d_6$ ):  $\delta_C = 167.1$  (C, CO), 136.7 (C,  $C_{Ar}$ ), 135.4 (C,  $C_{Ar}$ ), 123.1 (C,  $CH_{Ar}$ ), 123.0 (C,  $CH_{Ar}$ ), 117.5 (C,  $CH_{Ar}$ ), 116.2 (C,  $C_{Ar}$ ), 111.3 (C,  $CH_{Ar}$ ) ppm.

**3-Amino-7-methylimidazo[1,2-*a*]pyridine-2-carboxamide (8b).** A single-necked round-bottomed flask under air atmosphere was charged with carboxamide **15b** (500 mg, 2.27 mmol), 10% Pd/C and EtOH ( $\geq 95\%$ ). The suspension was degassed under vacuum and the flask was filled with  $H_2$  ( $H_2$ -filled balloon) five times. The reaction mixture was stirred at 20 °C under hydrogen atmosphere (balloon of  $H_2$ ) for 14 h. Next, the mixture was filtered through celite and the filter residue was rinsed with MeOH. The solvents were evaporated (rotary evaporation) and the residue was purified by column chromatography ( $SiO_2$ ,  $CH_2Cl_2$  : MeOH 95:5) to provide the titled compound as an off white precipitate (302 mg, 70%). m.p. > 260 °C; IR (neat):  $\tilde{\nu} = 3674, 3390, 3270, 3106, 1656, 1614, 1456, 1409, 1245, 1066, 775, 521$   $cm^{-1}$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta_H = 8.04$  (d,  $J = 7.1$  Hz, 1 H,  $H_{Ar}$ ), 7.27 (br s, 1 H,  $NH$ ), 7.11 (s, 1 H,  $H_{Ar}$ ), 7.04 (br s, 1 H,  $NH$ ), 6.67 (d,  $J = 7.1$  Hz, 1 H,  $H_{Ar}$ ), 6.06 (s, 2 H,  $NH_2$ ), 2.31 (s, 3 H,  $CH_3$ ) ppm;  $^{13}C$  NMR (101 MHz, DMSO- $d_6$ ):  $\delta_C = 167.1$  (C, CO), 137.0 (C,  $C_{Ar}$ ), 135.1 (C,  $C_{Ar}$ ), 133.4 (C,  $C_{Ar}$ ), 122.2 (CH,  $CH_{Ar}$ ), 115.8 (C,  $C_{Ar}$ ), 115.3 (CH,  $CH_{Ar}$ ), 113.9 (CH,  $CH_{Ar}$ ), 20.9 ( $CH_3$ ) ppm.

**3-Amino-6-methylimidazo[1,2-*a*]pyridine-2-carboxamide (8c).** A microwave vial under argon atmosphere was charged with carboxamide **15c** (700 mg, 3.18 mmol), Tin (II) chloride dihydrate (3.56 g, 15.8 mmol) and EtOH ( $\geq 95\%$ ; 15 mL). The vial was sealed and the reaction mixture was heated under microwave irradiation at 100 °C for 10 min. After solvents removal (rotary evaporation) the crude residue was then diluted with EtOAc (50 mL) and the organic phase was washed successively with  $NaHCO_3$  (20 mL) and brine (30 mL). Next, the organic layer was dried ( $MgSO_4$ ), filtered through a cotton plug and evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel ( $CH_2Cl_2$  : MeOH 95:5) to give **8c** as a beige solid (452 mg, 75%). m.p.: 250–252 °C; IR (neat):  $\tilde{\nu} = 3674, 3390, 3270, 3106, 2987, 1656, 1614, 1409, 1305, 1245, 1066, 1014, 775, 706, 603$   $cm^{-1}$ ;  $^1H$  NMR (250 MHz, DMSO- $d_6$ ):  $\delta_H = 7.93$  (s, 1 H,  $H_{Ar}$ ), 7.26 (d, 2 H,  $J = 9.3$  Hz,  $H_{Ar} + NH$ ), 7.05 (br s, 1 H,  $NH$ ), 6.92 (dd,  $J = 9.4, 1.5$  Hz, 1 H,  $H_{Ar}$ ), 6.04 (s, 2 H,  $NH_2$ ), 2.23 (s, 3 H,  $CH_3$ ) ppm.  $^{13}C$  NMR (63 MHz, DMSO- $d_6$ ):  $\delta_C = 167.0$  (C, CO), 135.9 (C,  $C_{Ar}$ ), 135.0 (C,  $C_{Ar}$ ), 126.3 (C,  $CH_{Ar}$ ), 120.3 (C,  $C_{Ar}$ ), 120.0 (CH,  $CH_{Ar}$ ), 116.9 (CH,  $CH_{Ar}$ ), 116.4 (CH,  $CH_{Ar}$ ), 17.8 ( $CH_3$ ) ppm.

**2-(Trifluoromethyl)pyrido[1,2-*e*]purin-4-ol (16a).** According to GP1, the reaction was performed with carboxamide **8a** (200 mg, 1.13 mmol) and  $CF_3(CO)NH_2$  (1.28 g, 11.35 mmol) to furnish compound **17a** as a white solid (201 mg, 70%). m.p.: 310–312 °C; IR (neat):  $\tilde{\nu} = 3231, 2987, 2900, 1641, 1599, 1478, 1349, 1259, 1127, 755, 514$   $cm^{-1}$ ;  $^1H$  NMR (400 MHz, Methanol- $d_4$ ):  $\delta_H = 8.63$  (d,  $J = 6.8$  Hz, 1 H,  $H_{Ar}$ ), 7.62 (d,  $J = 9.3$  Hz, 1 H,  $H_{Ar}$ ), 7.51 (dd,  $J = 6.8, 9.3$  Hz, 1 H,  $H_{Ar}$ ), 7.02 (t,  $J = 6.8$  Hz, 1 H,  $H_{Ar}$ ) ppm;

$^{13}C$  NMR (101 MHz, Methanol- $d_4$ ):  $\delta_C = 169.0$  (C, CO), 150.3 (q = 34.6 Hz,  $C-CF_3$ ), 147.0 (C,  $C_{Ar}$ ), 144.3 (C,  $C_{Ar}$ ), 131.8 (CH,  $CH_{Ar}$ ), 127.5 (C,  $C_{Ar}$ ), 125.9 (CH,  $CH_{Ar}$ ), 124.2 (q,  $J = 274.3$  Hz,  $CF_3$ ), 118.8 (CH,  $CH_{Ar}$ ), 113.9 (CH,  $CH_{Ar}$ ) ppm;  $^{19}F$  NMR (376 MHz, Methanol- $d_4$ ):  $\delta_F = -70.7$  ppm; HRMS (ESI):  $m/z$  calcd. for  $C_{10}H_6F_3N_4O$  [ $M + H$ ] $^+$  255.0488; found 255.0488.

**7-Methyl-2-(trifluoromethyl)pyrido[1,2-*e*]purin-4-ol (16b).** According to GP1, the reaction was performed with carboxamide **8b** (300 mg, 1.58 mmol) and  $CF_3(CO)NH_2$  (1.78 g, 15.8 mmol) to furnish compound **16b** as a white solid (310 mg, 73%). m.p.: 253–255 °C; IR (neat):  $\tilde{\nu} = 3674, 2987, 1693, 1477, 1358, 1286, 1202, 1132, 997, 784$   $cm^{-1}$ ;  $^1H$  NMR (250 MHz, Methanol- $d_4$ ):  $\delta_H = 8.52$  (d,  $J = 7.1$  Hz, 1 H,  $H_{Ar}$ ), 7.37 (s, 1 H,  $H_{Ar}$ ), 6.91 (dd,  $J = 7.1, 1.5$  Hz, 1 H,  $H_{Ar}$ ), 2.43 (s, 3 H,  $CH_3$ ) ppm;  $^{19}F$  NMR (376 MHz, Methanol- $d_4$ ):  $\delta_F = -70.5$  ppm; HRMS (ESI):  $m/z$  calcd. for  $C_{11}H_8F_3N_4O$  [ $M + H$ ] $^+$  269.0645; found 269.0647.

**8-Methyl-2-(trifluoromethyl)pyrido[1,2-*e*]purin-4-ol (16c).** According to GP1, the reaction was performed with carboxamide **8c** (150 mg, 0.79 mmol) and  $CF_3(CO)NH_2$  (1.78 g, 7.9 mmol) to give compound **16c** as a white solid (122 mg, 58%). m.p.: 250–252 °C; IR (neat):  $\tilde{\nu} = 3674, 2987, 1651, 1601, 1478, 1384, 1262, 1131, 995, 806$   $cm^{-1}$ ;  $^1H$  NMR (400 MHz, Methanol- $d_4$ ):  $\delta_H = 8.44$  (s, 1 H,  $H_{Ar}$ ), 7.52 (d,  $J = 9.4$  Hz, 1 H,  $H_{Ar}$ ), 7.39 (d,  $J = 9.4$  Hz, 1 H,  $H_{Ar}$ ), 2.39 (s, 3 H,  $CH_3$ ) ppm;  $^{19}F$  NMR (376 MHz, Methanol- $d_4$ ):  $\delta_F = -70.6$  ppm; HRMS (ESI):  $m/z$  calcd. for  $C_{11}H_8F_3N_4O$  [ $M + H$ ] $^+$  269.0645; found 269.0648.

**4-Chloro-2-(trifluoromethyl)pyrido[1,2-*e*]purine (17a).** According to GP2, the reaction was accomplished with purine **16a** (150 mg, 0.59 mmol) and  $SOCl_2$  (214  $\mu$ L, 2.95 mmol) to give compound **17a** as a white solid (124 mg, 77%). m.p.: 210–211 °C; IR (neat):  $\tilde{\nu} = 3113, 3035, 1646, 1397, 1300, 1125, 911, 758$   $cm^{-1}$ ;  $^1H$  NMR (250 MHz,  $CDCl_3$ ):  $\delta_H = 8.86$  (dd,  $J = 6.8, 1.0$  Hz, 1 H,  $H_{Ar}$ ), 7.88 (d,  $J = 6.8$  Hz, 1 H,  $H_{Ar}$ ), 7.76 (td,  $J = 6.8, 1.0$  Hz, 1 H,  $H_{Ar}$ ), 7.18 (td,  $J = 6.8, 1.0$  Hz, 1 H,  $H_{Ar}$ ) ppm;  $^{13}C$  NMR (63 MHz,  $CDCl_3$ ):  $\delta_C = 151.7$  (C,  $C_{Ar}$ ), 150.9 (C,  $C_{Ar}$ ), 146.8 (q,  $J = 38.1$  Hz,  $C-CF_3$ ), 146.0 (C,  $C_{Ar}$ ), 134.6 (CH,  $CH_{Ar}$ ), 134.0 (C,  $C_{Ar}$ ), 125.7 (CH,  $CH_{Ar}$ ), 119.7 (q,  $J = 274.1$  Hz,  $CF_3$ ), 119.4 (CH,  $CH_{Ar}$ ), 113.8 (CH,  $CH_{Ar}$ ) ppm;  $^{19}F$  NMR (376 MHz,  $CDCl_3$ ):  $\delta_F = -68.0$  ppm; HRMS (ESI):  $m/z$  calcd. for  $C_{10}H_5ClF_3N_4$  [ $M + H$ ] $^+$  273.0149; found 273.014.

**4-Chloro-7-methyl-2-(trifluoromethyl)pyrido[1,2-*e*]purine (17b).** According to GP2, the reaction was accomplished with purine **16b** (220 mg, 0.82 mmol) and  $SOCl_2$  (298  $\mu$ L, 4.10 mmol) to give compound **17b** as a beige solid (141 mg, 60%). m.p.: 220–222 °C; IR (neat):  $\tilde{\nu} = 3051, 2928, 1650, 1555, 1497, 1356, 1435, 1374, 1257, 1199, 1130, 943, 890, 703$   $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H = 8.71$  (d,  $J = 7.1$  Hz, 1 H,  $H_{Ar}$ ), 7.60 (d,  $J = 1.8$  Hz, 1 H,  $H_{Ar}$ ), 7.00 (dd,  $J = 7.1, 1.8$  Hz, 1 H,  $H_{Ar}$ ), 2.58 (s, 3 H,  $CH_3$ ) ppm;  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta_C = 151.4$  (C,  $C_{Ar}$ ), 150.8 (C,  $C_{Ar}$ ), 147.1 (C,  $C_{Ar}$ ), 146.4 (q,  $J = 36.6$  Hz,  $C-CF_3$ ), 146.3 (C,  $C_{Ar}$ ), 134.3 (C,  $C_{Ar}$ ), 124.6 (CH,  $CH_{Ar}$ ), 119.7 (q,  $J = 274.1$  Hz,  $CF_3$ ), 117.2 (CH,  $CH_{Ar}$ ), 116.8 (CH,  $CH_{Ar}$ ), 22.6 ( $CH_3$ ) ppm;  $^{19}F$  NMR (376 MHz,  $CDCl_3$ ):  $\delta_F = -68.0$  ppm; HRMS (ESI):  $m/z$  calcd. for  $C_{11}H_7ClF_3N_4$  287.0306; found 287.0303.

**4-Chloro-8-methyl-2-(trifluoromethyl)pyrido[1,2-*e*]purine 17c.** According to GP2, the reaction was accomplished with purine **16c** (140 mg, 0.52 mmol) and  $SOCl_2$  (190  $\mu$ L, 2.6 mmol) to give compound **17c** as a beige solid (97 mg, 65%). m.p.: 196–198 °C; IR (neat):  $\tilde{\nu} = 3052, 2929, 1651, 1556, 1498, 1357, 1436, 1375, 1256, 1198, 1129, 1063, 943, 890, 794, 702$   $cm^{-1}$ ;  $^1H$  NMR (250 MHz,  $CDCl_3$ ):  $\delta_H = 8.70$ –8.60 (m, 1 H,  $H_{Ar}$ ), 7.79 (dd,  $J = 9.5, 1.2$  Hz, 1 H,  $H_{Ar}$ ), 7.62 (dd,  $J = 9.5, 1.8$  Hz, 1 H,  $H_{Ar}$ ), 2.50 (d,  $J = 1.2$  Hz, 3 H,  $CH_3$ ) ppm;  $^{13}C$  NMR (63 MHz,  $CDCl_3$ ):  $\delta_C = 151.4$  (C,  $C_{Ar}$ ), 150.2 (C,  $C_{Ar}$ ), 146.5 (q,  $J = 38.5$  Hz,  $C-CF_3$ ), 145.8 (C,  $C_{Ar}$ ), 138.1 (CH,  $CH_{Ar}$ ), 134.0 (C,  $C_{Ar}$ ), 124.1 (C,  $C_{Ar}$ ), 122.8 (CH,  $CH_{Ar}$ ), 119.7 (q,  $J = 276.8$  Hz,  $CF_3$ ), 118.6 (CH,  $CH_{Ar}$ ), 18.3 ( $CH_3$ ) ppm;  $^{19}F$  NMR (376 MHz,



CDCl<sub>3</sub>):  $\delta_F = -68.0$ ; HRMS (ESI):  $m/z$  calcd. for C<sub>11</sub>H<sub>7</sub>ClF<sub>3</sub>N<sub>4</sub> 287.0306; found 287.0306.

**4-(*p*-Tolyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (18a).** According to GP3, the reaction was performed with compound **17a** (50 mg, 183  $\mu$ mol) and *p*-tolylboronic acid. The crude product was purified by column chromatography (SiO<sub>2</sub>, petroleum ether : EtOAc 7:3) to give compound **18** as a yellow solid (51 mg, 85%). m.p.: 195–197 °C; IR (neat):  $\tilde{\nu} = 2918, 2854, 1637, 1574, 1396, 1264, 1178, 1127, 1049, 890, 764, 717, 510$  cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H = 8.96$  (d,  $J = 8.1$  Hz, 2 H, *H*<sub>Ar</sub> tol), 8.86 (d,  $J = 6.8$  Hz, 1 H, *H*<sub>Ar</sub>), 7.85 (d,  $J = 9.3$  Hz, 1 H, *H*<sub>Ar</sub>), 7.67 (ddd,  $J = 9.3, 6.8, 1.3$  Hz, 1 H, *H*<sub>Ar</sub>), 7.42 (d,  $J = 8.1$  Hz, 2 H, *H*<sub>Ar</sub> tol), 7.06 (t,  $J = 6.8$  Hz, 1 H, *H*<sub>Ar</sub>), 2.48 (s, 3 H, *CH*<sub>3</sub>) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C = 155.7$  (C, *C*<sub>Ar</sub>), 150.2 (C, *C*<sub>Ar</sub>), 147.3 (C, *C*<sub>Ar</sub>), 147.4 (q,  $J = 36.8$  Hz, C–CF<sub>3</sub>), 142.6 (C, *C*<sub>Ar</sub>), 133.4 (C, *CH*<sub>Ar</sub>), 133.0 (C, *C*<sub>Ar</sub>), 132.6 (C, *C*<sub>Ar</sub>), 130.5 (2 × CH, *CH*<sub>Ar</sub> tol), 129.8 (2 × CH, *CH*<sub>Ar</sub> tol), 125.4 (CH, *CH*<sub>Ar</sub>), 120.5 (q,  $J = 274.8$  Hz, CF<sub>3</sub>), 119.2 (CH, *CH*<sub>Ar</sub>), 112.7 (CH, *CH*<sub>Ar</sub>), 21.9 (CH<sub>3</sub>) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F = -68.2$  ppm; HRMS (ESI):  $m/z$  calcd. for C<sub>17</sub>H<sub>12</sub>F<sub>3</sub>N<sub>4</sub> [M+H]<sup>+</sup> 329.1009; found 329.1010.

**4-(4-Methoxyphenyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (21a).** According to GP3, the reaction was performed with compound **17a** (50 mg, 183  $\mu$ mol) and 4-methoxyphenylboronic acid. The crude product was purified by column chromatography (SiO<sub>2</sub>, petroleum ether : EtOAc 7:3) to give compound **21a** as a yellow solid (43 mg, 69%). m.p.: 216–217 °C; IR (neat):  $\tilde{\nu} = 2969, 1640, 1568, 1514, 1403, 1306, 1174, 1050, 715, 601$  cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H = 9.08$  (d,  $J = 8.6$  Hz, 2 H, *H*<sub>Ar</sub> tol), 8.84 (d,  $J = 6.8$  Hz, 1 H, *H*<sub>Ar</sub>), 7.82 (d,  $J = 9.3$  Hz, 1 H, *H*<sub>Ar</sub>), 7.66 (t,  $J = 6.8$  Hz, 1 H, *H*<sub>Ar</sub>), 7.13 (d,  $J = 8.6$  Hz, 2 H, *H*<sub>Ar</sub> tol), 7.06 (t,  $J = 6.8$  Hz, 1 H, *H*<sub>Ar</sub>), 3.93 (s, 3 H, OCH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C = 162.9$  (C, CO), 155.3 (C, *C*<sub>Ar</sub>), 149.9 (C, *C*<sub>Ar</sub>), 147.4 (q,  $J = 36.8$  Hz, C–CF<sub>3</sub>), 147.0 (C, *C*<sub>Ar</sub>), 133.3 (CH, *CH*<sub>Ar</sub>), 132.6 (C, *C*<sub>Ar</sub>), 132.4 (2 × CH, *CH*<sub>Ar</sub> anis), 128.1 (C, *C*<sub>Ar</sub>), 125.4 (CH, *CH*<sub>Ar</sub>), 119.5 (q,  $J = 276.6$  Hz, CF<sub>3</sub>), 119.1 (CH, *CH*<sub>Ar</sub>), 114.4 (2 × CH, *CH*<sub>Ar</sub> anis), 112.7 (CH, *CH*<sub>Ar</sub>), 55.6 (CH<sub>3</sub>, OCH<sub>3</sub>) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F = -68.3$  ppm; HRMS (ESI)  $m/z$  calcd. for C<sub>17</sub>H<sub>12</sub>F<sub>3</sub>N<sub>4</sub>O [M+H]<sup>+</sup> 345.0958; found 345.0964.

**4-(4-Trifluoromethoxyphenyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (22a).** According to GP3, the reaction was accomplished with compound **17a** (50 mg, 183  $\mu$ mol) and 4-(trifluoromethoxy)phenylboronic acid. The crude product was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> : petroleum ether 5:5) to give the titled compound as a yellow solid (53 mg, 73%). m.p.: 126–128 °C; IR (neat):  $\tilde{\nu} = 2918, 1641, 1582, 1510, 1386, 1343, 1248, 1050, 1019, 759, 717, 503, 643$  cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H = 9.10$  (d,  $J = 8.7$  Hz, 2 H, *H*<sub>Ar</sub>), 8.84 (d,  $J = 6.8$  Hz, 1 H, *H*<sub>Ar</sub>), 7.80 (d,  $J = 9.3$  Hz, 1 H, *H*<sub>Ar</sub>), 7.69 (t,  $J = 6.8$  Hz, 1 H, *H*<sub>Ar</sub>), 7.43 (d,  $J = 8.4$  Hz, 2 H, *H*<sub>Ar</sub>), 7.09 (t,  $J = 6.8$  Hz, 1 H, *H*<sub>Ar</sub>) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C = 153.7$  (C, *C*<sub>Ar</sub>), 151.9 (q,  $J = 1.8$  Hz, C–OCF<sub>3</sub>), 150.5 (C, *C*<sub>Ar</sub>), 147.5 (C, *C*<sub>Ar</sub>), 147.3 (q,  $J = 37.2$  Hz, C–CF<sub>3</sub>), 133.9 (CH, *CH*<sub>Ar</sub>), 133.7 (C, *C*<sub>Ar</sub>), 133.0 (C, *C*<sub>Ar</sub>), 132.2 (2 × CH, *CH*<sub>Ar</sub>), 125.4 (CH, *CH*<sub>Ar</sub>), 120.9 (CH, *CH*<sub>Ar</sub>), 120.6 (q,  $J = 258.2$  Hz, OCF<sub>3</sub>), 120.4 (q,  $J = 274.6$  Hz, C, CF<sub>3</sub>), 119.1 (CH, *CH*<sub>Ar</sub>), 113.0 (CH, *CH*<sub>Ar</sub>) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F = -57.5, -68.2$  ppm; HRMS (ESI):  $m/z$  calcd. for C<sub>17</sub>H<sub>9</sub>F<sub>6</sub>N<sub>4</sub>O [M+H]<sup>+</sup> 399.0675; found 399.0673.

**4-(4-Trifluoromethylphenyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (23a).** According to GP3, the reaction was accomplished with compound **17a** (50 mg, 183  $\mu$ mol) and 4-(trifluoromethyl)phenylboronic acid. The crude product was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> : petroleum ether 6:4) to give compound **23a** as a yellow solid (56 mg, 80%). m.p.: 164–165 °C; IR (neat):  $\tilde{\nu} = 2920, 1638, 1558, 1486, 1420, 1268, 1304, 1214, 1196, 1068, 1047, 891, 807, 719, 653$  cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H = 9.15$  (d,  $J = 8.1$  Hz, 2 H, *H*<sub>Ar</sub>), 8.86 (d,  $J = 6.8$  Hz, 1 H, *H*<sub>Ar</sub>), 7.84 (t,  $J = 8.1$  Hz, 2 H, *H*<sub>Ar</sub>), 7.72 (dd,  $J = 9.4, 6.6$  Hz, 1 H, *H*<sub>Ar</sub>), 7.11 (t,  $J = 6.8$  Hz, 1 H, *H*<sub>Ar</sub>) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C = 153.4$  (C, *C*<sub>Ar</sub>),

150.8 (C, *C*<sub>Ar</sub>), 147.8 (C, *C*<sub>Ar</sub>), 147.2 (q,  $J = 37.2$  Hz, C–CF<sub>3</sub>), 138.4 (q,  $J = 1.6$  Hz, C, *C*<sub>Ar</sub>), 134.2 (CH, *CH*<sub>Ar</sub>), 133.4 (C, *C*<sub>Ar</sub>), 133.1 (q,  $J = 32.6$  Hz, C–CF<sub>3</sub>), 130.6 (2 × CH, *CH*<sub>Ar</sub>), 125.8 (q,  $J = 3.74$  Hz, 2 × CH, *CH*<sub>Ar</sub>), 125.5 (CH, *CH*<sub>Ar</sub>), 124.1 (q,  $J = 272.5$  Hz, CF<sub>3</sub>), 120.4 (q,  $J = 274.6$  Hz, CF<sub>3</sub>), 119.2 (CH, *CH*<sub>Ar</sub>), 113.1 (CH, *CH*<sub>Ar</sub>) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F = -63.0, -68.2$  ppm; HRMS (ESI):  $m/z$  calcd. for C<sub>17</sub>H<sub>9</sub>F<sub>6</sub>N<sub>4</sub> [M+H]<sup>+</sup> 383.0726; found 383.0726.

**4-(3-(Trifluoromethylphenyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (25a).** According to GP3, the reaction was carried out with compound **17a** (50 mg, 183  $\mu$ mol) and 3-(trifluoromethyl)phenylboronic acid. The crude product was purified by column chromatography (SiO<sub>2</sub>, petroleum ether : EtOAc 5:5) to give compound **25a** as a yellow solid (54 mg, 78%). m.p.: 143–144 °C; IR (neat):  $\tilde{\nu} = 2921, 1642, 1581, 1498, 1260, 1094, 1075, 904, 759$  cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H = 9.34$  (s, 1 H, *H*<sub>Ar</sub>), 9.29 (d,  $J = 7.9$  Hz, 1 H, *H*<sub>Ar</sub>), 8.86 (dd,  $J = 6.8, 1.2$  Hz, 1 H, *H*<sub>Ar</sub>), 7.90–7.78 (m, 2 H, *H*<sub>Ar</sub>), 7.78–7.65 (m, 2 H, *H*<sub>Ar</sub>), 7.11 (t,  $J = 6.8$  Hz, 1 H, *H*<sub>Ar</sub>) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C = 154.0$  (C, *C*<sub>Ar</sub>), 150.7 (C, *C*<sub>Ar</sub>), 147.7 (C, *C*<sub>Ar</sub>), 147.2 (q,  $J = 37.3$  Hz, C–CF<sub>3</sub>), 136.0 (C, *C*<sub>Ar</sub>), 134.1 (CH, *CH*<sub>Ar</sub>), 133.6 (CH, *CH*<sub>Ar</sub>), 133.2 (C, *C*<sub>Ar</sub>), 131.4 (q,  $J = 32.5$  Hz, C–CF<sub>3</sub>), 129.5 (CH, *CH*<sub>Ar</sub>), 128.2 (q,  $J = 3.6$  Hz, CH, *CH*<sub>Ar</sub>), 127.1 (q,  $J = 4.0$  Hz, CH, *CH*<sub>Ar</sub>), 125.5 (CH, *CH*<sub>Ar</sub>), 124.3 (q,  $J = 272.4$  Hz, CF<sub>3</sub>), 120.9 (q,  $J = 258.4$  Hz, CF<sub>3</sub>), 119.2 (CH, *CH*<sub>Ar</sub>), 113.1 (CH, *CH*<sub>Ar</sub>) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F = -62.6, -68.1$  ppm; HRMS (ESI):  $m/z$  calcd. for C<sub>17</sub>H<sub>9</sub>F<sub>6</sub>N<sub>4</sub> [M+H]<sup>+</sup> 383.0726; found 383.0726.

**4-(3-Methylphenyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (20a).** According to GP3, the reaction was achieved with compound **17a** (40 mg, 147  $\mu$ mol) and 3-methoxyphenylboronic acid. The crude product was purified by column chromatography (SiO<sub>2</sub>, petroleum ether : EtOAc 7:3) to give compound **20a** as a yellow solid (39 mg, 65%). m.p.: 192–193 °C; IR (neat):  $\tilde{\nu} = 2923, 1639, 1573, 1392, 1273, 1221, 1179, 1142, 1054, 924, 793, 754, 649, 624$  cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta_H = 8.94$ – $8.72$  (m, 3 H, *H*<sub>Ar</sub>), 7.83 (d,  $J = 9.4$  Hz, 1 H, *H*<sub>Ar</sub>), 7.66 (ddd,  $J = 9.4, 6.8, 1.4$  Hz, 1 H, *H*<sub>Ar</sub>), 7.51 (t,  $J = 7.6$  Hz, 1 H, *H*<sub>Ar</sub>), 7.39 (d,  $J = 7.6$  Hz, 1 H, *H*<sub>Ar</sub>), 7.06 (td,  $J = 6.8, 1.1$  Hz, 1 H, *H*<sub>Ar</sub>), 2.54 (s, 3 H, *CH*<sub>3</sub>) ppm; <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>):  $\delta_C = 155.8$  (C, *C*<sub>Ar</sub>), 150.2 (C, *C*<sub>Ar</sub>), 147.5 (C, *C*<sub>Ar</sub>), 147.3 (q,  $J = 37.0$  Hz, C–CF<sub>3</sub>), 138.7 (C, *C*<sub>Ar</sub>), 135.2 (C, *C*<sub>Ar</sub>), 133.5 (CH, *CH*<sub>Ar</sub>), 133.1 (C, *C*<sub>Ar</sub>), 132.8 (CH, *CH*<sub>Ar</sub>), 130.6 (CH, *CH*<sub>Ar</sub>), 128.9 (CH, *CH*<sub>Ar</sub>), 127.9 (CH, *CH*<sub>Ar</sub>), 125.4 (CH, *CH*<sub>Ar</sub>), 120.5 (q,  $J = 274.6$  Hz, CF<sub>3</sub>), 119.2 (CH, *CH*<sub>Ar</sub>), 112.8 (CH, *CH*<sub>Ar</sub>), 21.8 (CH<sub>3</sub>) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F = -68.0$  ppm; HRMS (ESI):  $m/z$  calcd. for C<sub>17</sub>H<sub>12</sub>F<sub>3</sub>N<sub>4</sub> [M+H]<sup>+</sup> 329.1008; found 329.1009.

**2-(Trifluoromethyl)-4-(2-(trifluoromethyl)phenyl)pyrido[1,2-*e*]purine (24a).** According to GP3, the reaction was performed with compound **17a** (50 mg, 183  $\mu$ mol) and 2-(trifluoromethyl)phenylboronic acid. The crude product was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>) to give compound **24a** as a yellow solid (52.5 mg, 75%). m.p.: 115–116 °C; IR (neat):  $\tilde{\nu} = 2919, 2850, 1640, 1588, 1506, 1400, 1346, 1302, 1126, 1067, 908, 759, 657, 525$  cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta_H = 8.92$  (d,  $J = 6.9, 1.3$  Hz, 1 H, *H*<sub>Ar</sub>), 7.92 (br d,  $J = 6.9$  Hz, 2 H, *H*<sub>Ar</sub>), 7.80–7.60 (m, 4 H, *H*<sub>Ar</sub>), 7.13 (t,  $J = 6.7, 1.2$  Hz, 1 H, *H*<sub>Ar</sub>) ppm; <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>):  $\delta_C = 157.4$  (C, *C*<sub>Ar</sub>), 151.0 (C, *C*<sub>Ar</sub>), 146.9 (q,  $J = 37.4$  Hz, C–CF<sub>3</sub>), 146.9 (C, *C*<sub>Ar</sub>), 134.2 (CH, *CH*<sub>Ar</sub>), 133.7–133.5 (m, C, *C*<sub>Ar</sub>), 132.2 (CH, *CH*<sub>Ar</sub>), 131.8 (CH, *CH*<sub>Ar</sub>), 130.3 (CH, *CH*<sub>Ar</sub>), 129.7 (q,  $J = 31.8$  Hz, C–CF<sub>3</sub>), 127.7 (q,  $J = 5.0$  Hz, CH, *CH*<sub>Ar</sub>), 125.6 (CH, *CH*<sub>Ar</sub>), 123.9 (q,  $J = 274.0$  Hz, CF<sub>3</sub>), 120.3 (q,  $J = 272.5$  Hz, CF<sub>3</sub>), 119.3 (CH, *CH*<sub>Ar</sub>), 113.1 (C, *CH*<sub>Ar</sub>) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F = -57.2, -68.1$  ppm; HRMS (ESI):  $m/z$  calcd. for C<sub>17</sub>H<sub>9</sub>F<sub>6</sub>N<sub>4</sub> [M+H]<sup>+</sup> 383.0726; found 383.0726.

**4-Phenyl-2-(trifluoromethyl)pyrido[1,2-*e*]purine (19a).** According to GP3, the reaction was performed with compound **17a** (50 mg, 183  $\mu$ mol) and phenylboronic acid. The crude product was purified by column

chromatography (SiO<sub>2</sub>, petroleum ether : EtOAc 7:3) to give compound **19a** as a yellow solid (42 mg, 74%). m.p.: 191–192 °C; IR (neat):  $\tilde{\nu}$  = 2987, 1639, 1570, 1398, 1346, 1247, 11156, 1050, 908, 755, 717 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H$  = 9.04 (d, *J* = 7.8 Hz, 2 H, *H<sub>Ar</sub>*), 8.86 (d, *J* = 6.8 Hz, 1 H, *H<sub>Ar</sub>*), 7.84 (d, *J* = 9.3 Hz, 1 H, *H<sub>Ar</sub>*), 7.68 (dd, *J* = 9.3, 6.8 Hz, 1 H, *H<sub>Ar</sub>*), 7.61 (q, *J* = 9.5, 8.1 Hz, 3 H, *H<sub>Ar</sub>*), 7.07 (t, *J* = 6.8 Hz, 1 H, *H<sub>Ar</sub>*) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C$  = 155.6 (C, *C<sub>Ar</sub>*), 150.4 (C, *C<sub>Ar</sub>*), 147.4 (C, *C<sub>Ar</sub>*), 147.4 (q, *J* = 37.1 Hz, C–CF<sub>3</sub>), 135.3 (C, *C<sub>Ar</sub>*), 133.7 (CH, *CH<sub>Ar</sub>*), 133.2 (C, *C<sub>Ar</sub>*), 131.9 (CH, *CH<sub>Ar</sub>*), 130.5 (2 × CH, *CH<sub>Ar</sub>*), 129.0 (2 × CH, *CH<sub>Ar</sub>*), 125.4 (CH, *CH<sub>Ar</sub>*), 120.5 (q, *J* = 274.7 Hz, CF<sub>3</sub>), 119.2 (CH, *CH<sub>Ar</sub>*), 112.8 (CH, *CH<sub>Ar</sub>*) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F$  = –68.2 ppm; HRMS (ESI): *m/z* calcd. for C<sub>16</sub>H<sub>10</sub>F<sub>3</sub>N<sub>4</sub> [M+H]<sup>+</sup> 315.0852; found 315.0855.

#### 4-(Naphthalen-1-yl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (26a).

According to GP3, the reaction was accomplished with compound **17a** (50 mg, 183 μmol) and naphthalenyl-1-boronic acid. The crude product was purified by column chromatography (SiO<sub>2</sub>, petroleum ether : EtOAc 7:3) to give compound **26a** as a yellow solid (45 mg, 70%). m.p.: 216–218 °C; IR (neat):  $\tilde{\nu}$  = 3106, 2209, 1637, 1574, 1287, 1120, 1128, 954, 755, 686, 598 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H$  = 8.92 (d, *J* = 6.9 Hz, 1 H, *H<sub>Ar</sub>*), 8.48–8.40 (m, 1 H, *H<sub>Ar</sub>*), 8.33 (dd, *J* = 7.2, 1.3 Hz, 1 H, *H<sub>Ar</sub>*), 8.06 (d, *J* = 8.2 Hz, 1 H, *H<sub>Ar</sub>*), 7.99–7.90 (m, 1 H, *H<sub>Ar</sub>*), 7.80 (d, *J* = 9.4 Hz, 1H, *H<sub>Ar</sub>*), 7.74–7.63 (m, 2 H, *H<sub>Ar</sub>*), 7.61–7.48 (m, 2 H, *H<sub>Ar</sub>*), 7.10 (t, *J* = 6.7 Hz, 1 H, *H<sub>Ar</sub>*) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C$  = 159.0 (C, *C<sub>Ar</sub>*), 150.6 (C, *C<sub>Ar</sub>*), 147.2 (q, *J* = 37.1 Hz, C–CF<sub>3</sub>), 147.0 (C, *C<sub>Ar</sub>*), 134.7 (C, *C<sub>Ar</sub>*), 134.4 (C, *C<sub>Ar</sub>*), 133.8 (CH, *CH<sub>Ar</sub>*), 131.7 (C, *C<sub>Ar</sub>*), 131.7 (CH, *CH<sub>Ar</sub>*), 131.2 (C, *C<sub>Ar</sub>*), 131.2 (CH, *CH<sub>Ar</sub>*), 128.7 (CH, *CH<sub>Ar</sub>*), 127.3 (CH, *CH<sub>Ar</sub>*), 126.4 (CH, *CH<sub>Ar</sub>*), 125.7 (CH, *CH<sub>Ar</sub>*), 125.5 (CH, *CH<sub>Ar</sub>*), 125.3 (CH, *CH<sub>Ar</sub>*), 120.5 (q, *J* = 274.7 Hz, CF<sub>3</sub>), 119.3 (CH, *CH<sub>Ar</sub>*), 113.0 (CH, *CH<sub>Ar</sub>*) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F$  = –67.9 ppm; HRMS (ESI): *m/z* calcd. for C<sub>20</sub>H<sub>11</sub>F<sub>3</sub>N<sub>4</sub> [M+H]<sup>+</sup> 365.0952; found 355.0955.

#### 7-Methyl-4-(*p*-tolyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (18b).

According to GP3, the reaction was carried out with compound **17b** (52 mg, 183 μmol) and *p*-tolylboronic acid. The crude product was purified by column chromatography (SiO<sub>2</sub>, petroleum ether : EtOAc 8:2) to give compound **18b** as a yellow solid (50 mg, 80%). m.p.: 237–239 °C; IR (neat):  $\tilde{\nu}$  = 2923, 1647, 1568, 1513, 1298, 1204, 1047, 897, 788 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H$  = 8.91 (d, *J* = 8.0 Hz, 2 H, *H<sub>Ar</sub>* tol), 8.65 (d, *J* = 7.0 Hz, 1 H, *H<sub>Ar</sub>*), 7.51 (s, 1 H, *H<sub>Ar</sub>*), 7.40 (d, *J* = 8.0 Hz, 2 H, *H<sub>Ar</sub>* tol), 6.83 (dd, *J* = 7.0, 1.6 Hz, 1 H, *H<sub>Ar</sub>*), 2.51 (s, 3 H, *CH<sub>3</sub>*), 2.48 (s, 3 H, *CH<sub>3</sub>*) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C$  = 154.8 (C, *C<sub>Ar</sub>*), 150.6 (C, *C<sub>Ar</sub>*), 147.3 (C, *C<sub>Ar</sub>*), 146.8 (q, *J* = 36.9 Hz, C–CF<sub>3</sub>), 145.5 (C, *C<sub>Ar</sub>*), 142.3 (C, *C<sub>Ar</sub>*), 133.1 (C, *C<sub>Ar</sub>*), 132.7 (C, *C<sub>Ar</sub>*), 130.3 (2 × CH, *CH<sub>Ar</sub>* tol), 129.7 (2 × CH, *CH<sub>Ar</sub>* tol), 124.2 (CH, *CH<sub>Ar</sub>*), 120.6 (q, *J* = 274.5 Hz, CF<sub>3</sub>), 116.9 (CH, *CH<sub>Ar</sub>*), 115.6 (CH, *CH<sub>Ar</sub>*), 22.4 (CH<sub>3</sub>), 21.9 (CH<sub>3</sub>) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F$  = –68.1 ppm; HRMS (ESI): *m/z* calcd. for C<sub>18</sub>H<sub>14</sub>F<sub>3</sub>N<sub>4</sub> [M+H]<sup>+</sup> 343.1165; found 343.1165.

#### 8-Methyl-4-(*p*-tolyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (18c).

According to GP3, the reaction was accomplished with compound **17c** (20 mg, 70 μmol) and *p*-tolylboronic acid. The crude product was purified by column chromatography (SiO<sub>2</sub>, petroleum ether : EtOAc 8:2) to give compound **18c** as a yellow solid (19 mg, 78%). m.p.: 234–236 °C; IR (neat):  $\tilde{\nu}$  = 2920, 1640, 1570, 1516, 1299, 1200, 1048, 890, 784 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H$  = 8.93 (d, *J* = 8.2 Hz, 2 H, *H<sub>Ar</sub>* tol), 8.62 (s, 1 H, *H<sub>Ar</sub>*), 7.73 (d, *J* = 9.5 Hz, 1 H, *H<sub>Ar</sub>*), 7.50 (dd, *J* = 9.5, 1.8 Hz, 1 H, *H<sub>Ar</sub>*), 7.41 (d, *J* = 8.2 Hz, 2 H, *H<sub>Ar</sub>* tol), 2.48 (s, 3 H, *CH<sub>3</sub>*), 2.45 (d, *J* = 1.4 Hz, 3 H, *CH<sub>3</sub>*) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C$  = 155.4 (C, *C<sub>Ar</sub>*), 149.4 (C, *C<sub>Ar</sub>*), 146.9 (C, *C<sub>Ar</sub>*), 146.5 (q, *J* = 37.2 Hz, C–CF<sub>3</sub>), 142.4 (C, *C<sub>Ar</sub>*), 136.9 (CH, *CH<sub>Ar</sub>*), 133.0 (C, *C<sub>Ar</sub>*), 132.7 (C, *C<sub>Ar</sub>*), 130.4 (2 × CH, *CH<sub>Ar</sub>* tol), 129.7 (2 × CH, *CH<sub>Ar</sub>* tol), 122.8 (C, *C<sub>Ar</sub>*), 122.5 (CH, *CH<sub>Ar</sub>*), 120.6 (q, *J* = 274.7 Hz, CF<sub>3</sub>), 118.3 (CH, *CH<sub>Ar</sub>*), 21.9 (CH<sub>3</sub>), 18.2 (CH<sub>3</sub>) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):

$\delta_F$  = –68.2 ppm; HRMS (ESI): *m/z* calcd. for C<sub>18</sub>H<sub>14</sub>F<sub>3</sub>N<sub>4</sub> [M+H]<sup>+</sup> 343.1165; found 343.1165.

#### 7-Methyl-4-(4-(trifluoromethoxy)phenyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (22b).

According to GP3, the reaction was accomplished with compound **17b** (52 mg, 183 μmol) and 4-(trifluoromethoxy)phenylboronic acid. The crude product was purified by column chromatography (SiO<sub>2</sub>, petroleum ether : EtOAc 7:3) to give compound **22b** as a yellow solid (52 mg, 70%). m.p.: 149–150 °C; IR (neat):  $\tilde{\nu}$  = 2917, 1651, 1402, 1252, 1140, 1049, 1018, 673, 629, 509 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H$  = 9.06 (d, *J* = 8.9 Hz, 2 H, *H<sub>Ar</sub>*), 8.66 (d, *J* = 7.1 Hz, 1 H, *H<sub>Ar</sub>*), 7.50 (s, 1 H, *H<sub>Ar</sub>*), 7.42 (br d, *J* = 8.9 Hz, 2 H, *H<sub>Ar</sub>*), 6.87 (br d, *J* = 7.1 Hz, 1 H, *H<sub>Ar</sub>*), 2.52 (s, 3 H, *CH<sub>3</sub>*) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C$  = 152.9 (C, *C<sub>Ar</sub>*), 151.7 (q, *J* = 1.8 Hz, C–OCF<sub>3</sub>), 151.0 (C, *C<sub>Ar</sub>*), 147.6 (C, *C<sub>Ar</sub>*), 146.7 (q, *J* = 37.2 Hz, C–CF<sub>3</sub>), 146.2 (C, *C<sub>Ar</sub>*), 133.8 (C, *C<sub>Ar</sub>*), 133.3 (C, *C<sub>Ar</sub>*), 132.1 (2 × CH, *CH<sub>Ar</sub>*), 124.5 (CH, *CH<sub>Ar</sub>*), 120.8 (CH, *CH<sub>Ar</sub>*), 120.6 (q, *J* = 258.2 Hz, OCF<sub>3</sub>), 120.4 (q, *J* = 274.5 Hz, CF<sub>3</sub>), 116.9 (CH, *CH<sub>Ar</sub>*), 115.9 (CH, *CH<sub>Ar</sub>*), 22.5 (CH<sub>3</sub>) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F$  = –57.5, –68.2 ppm; HRMS (ESI): *m/z* calcd. for C<sub>18</sub>H<sub>11</sub>F<sub>6</sub>N<sub>4</sub>O [M+H]<sup>+</sup> 413.0832; found 413.0829.

#### 8-Methyl-4-(4-(trifluoromethoxy)phenyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (22c).

According to GP3, the reaction was carried out with compound **17c** (20 mg, 69 μmol) and 4-(trifluoromethoxy)phenylboronic acid. The crude product was purified by column chromatography (SiO<sub>2</sub>, petroleum ether : EtOAc 8:2) to give compound **22c** as a yellow solid (20 mg, 70%). m.p.: 139–140 °C; IR (neat):  $\tilde{\nu}$  = 2918, 2649, 1652, 1577, 1422, 1197, 1046, 937, 852, 708 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H$  = 9.13–9.08 (m, 2 H, *H<sub>Ar</sub>*), 8.68–8.65 (m, 1 H, *H<sub>Ar</sub>*), 7.75 (d, *J* = 9.4 Hz, 1 H, *H<sub>Ar</sub>*), 7.56 (dd, *J* = 9.4, 1.8 Hz, 1 H, *H<sub>Ar</sub>*), 7.44 (bd, *J* = 8.2, 2 H, *H<sub>Ar</sub>*), 2.48 (bs, 3 H, *CH<sub>3</sub>*) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C$  = 153.7 (C, *C<sub>Ar</sub>*), 151.8 (q, *J* = 2.1 Hz, C–OCF<sub>3</sub>), 149.9 (C, *C<sub>Ar</sub>*), 147.3 (C, *C<sub>Ar</sub>*), 137.5 (CH, *CH<sub>Ar</sub>*), 133.8 (C, *C<sub>Ar</sub>*), 133.2 (C, *C<sub>Ar</sub>*), 132.2 (2 × CH, *CH<sub>Ar</sub>*), 123.2 (C, *C<sub>Ar</sub>*), 122.7 (CH, *CH<sub>Ar</sub>*), 120.9 (2 × CH, *CH<sub>Ar</sub>*), 122.5 (q, *J* = 138.1 Hz, OCF<sub>3</sub>), 119.7 (q, *J* = 146.5 Hz, CF<sub>3</sub>), 118.4 (CH, *CH<sub>Ar</sub>*), 18.3 (CH<sub>3</sub>) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F$  = –57.5, –68.2 ppm; HRMS (ESI): *m/z* calcd. for C<sub>18</sub>H<sub>11</sub>F<sub>6</sub>N<sub>4</sub>O [M+H]<sup>+</sup> 413.0832; found 413.0829.

#### 4-(Phenyl)ethynyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (27a).

According to GP4, the reaction was accomplished with compound **17a** (52 mg, 183 μmol) and phenylacetylene. The crude product was purified by column chromatography (SiO<sub>2</sub>, petroleum ether : CH<sub>2</sub>Cl<sub>2</sub> 4:6) to give compound **27a** as a yellow solid (65 mg, 75%). m.p.: 216–218 °C; IR (neat):  $\tilde{\nu}$  = 3106, 2209, 1637, 1574, 1287, 1120, 1128, 954, 755, 686, 598 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta_H$  = 8.87 (d, *J* = 6.9 Hz, 1 H, *H<sub>Ar</sub>*), 7.89 (d, *J* = 9.4 Hz, 1 H, *H<sub>Ar</sub>*), 7.81 (d, *J* = 7.2 Hz, 2 H, *H<sub>Ar</sub>*), 7.73 (t, *J* = 7.9 Hz, 1 H, *H<sub>Ar</sub>*), 7.55–7.35 (m, 3 H, *H<sub>Ar</sub>*), 7.14 (t, *J* = 6.7 Hz, 1 H, *H<sub>Ar</sub>*) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta_C$  = 151.0 (C, *C<sub>Ar</sub>*), 147.6 (q, *J* = 37.4 Hz, C–CF<sub>3</sub>), 146.6 (C, *C<sub>Ar</sub>*), 142.4 (C, *C<sub>Ar</sub>*), 136.3 (C, *C<sub>Ar</sub>*), 134.5 (CH, *CH<sub>Ar</sub>*), 133.0 (2 × CH, *CH<sub>Ar</sub>*), 130.4 (CH, *CH<sub>Ar</sub>*), 128.6 (2 × CH, *CH<sub>Ar</sub>*), 125.6 (CH, *CH<sub>Ar</sub>*), 121.3 (C, *C<sub>Ar</sub>*), 120.1 (q, *J* = 274.6 Hz, CF<sub>3</sub>), 119.3 (CH, *CH<sub>Ar</sub>*), 113.3 (CH, *CH<sub>Ar</sub>*), 101.3 (C, ≡C), 84.5 (C, ≡C) ppm; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):  $\delta_F$  = –68.0 ppm; HRMS (ESI): *m/z* calcd. for C<sub>18</sub>H<sub>9</sub>F<sub>3</sub>N<sub>4</sub> [M+H]<sup>+</sup> 339.0852; found 339.0849.

#### 4-((4-Methylphenyl)ethynyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (28a).

According to GP4, the reaction was accomplished with compound **17a** (52 mg, 183 μmol) and 4-ethynyltoluene. The crude product was purified by column chromatography (SiO<sub>2</sub>, petroleum ether : EtOAc 5:5) to give compound **28a** as a yellow solid (45 mg, 70%). m.p.: 236–237 °C; IR (neat):  $\tilde{\nu}$  = 3455, 3015, 2946, 2205, 1739, 1367, 1407, 1216, 1149, 1128, 1087, 952, 817, 766 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/TMS):  $\delta_H$  = 8.85 (br d, *J* = 6.9 Hz, 1 H, *H<sub>Ar</sub>*), 7.87 (d, *J* = 9.4 Hz, 1 H, *H<sub>Ar</sub>*), 7.80–7.60 (m, 3 H,

$H_{Ar}$ , 7.23 (br d,  $J = 7.7$  Hz, 2 H,  $H_{Ar}$ ), 7.12 (br t,  $J = 6.0$  Hz, 1 H,  $H_{Ar}$ ), 2.41 (s, 3 H,  $CH_3$ ) ppm;  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta_C = 150.9$  (C,  $C_{Ar}$ ), 147.5 (q,  $J = 37.3$  Hz,  $C-CF_3$ ), 146.5 (C,  $C_{Ar}$ ), 142.6 (C,  $C_{Ar}$ ), 141.1 (C,  $C_{Ar}$ ), 136.2 (C,  $C_{Ar}$ ), 134.3 (CH,  $CH_{Ar}$ ), 133.0 (2  $\times$  CH,  $CH_{Ar}$ ), 129.4 (2  $\times$  CH,  $CH_{Ar}$ ), 125.6 (CH,  $CH_{Ar}$ ), 120.1 (q,  $J = 274.9$  Hz,  $CF_3$ ), 119.3 (CH,  $CH_{Ar}$ ), 118.2 (C,  $C_{Ar}$ ), 113.3 (CH,  $CH_{Ar}$ ), 102.0 (C,  $\equiv C$ ), 84.2 (C,  $C\equiv$ ), 21.9 ( $CH_3$ ) ppm;  $^{19}F$  NMR (376 MHz,  $CDCl_3$ ):  $\delta_F = -68.0$  ppm; HRMS (ESI):  $m/z$  calcd. for  $C_{19}H_{12}F_3N_4$   $[M+H]^+$  353.1009; found 353.1007.

**4-((4-Fluorophenyl)ethynyl)-2-(trifluoromethyl) pyrido[1,2-*e*]purine (29a).** According to GP4, the reaction was accomplished with compound **17a** (52 mg, 183  $\mu$ mol) and 1-ethynyl-4-fluorobenzene. The crude product was purified by column chromatography ( $SiO_2$ , petroleum ether : EtOAc 4:6) to give compound **29a** as a yellow solid (41 mg, 63%). m.p.: 194–195 °C; IR (neat):  $\tilde{\nu} = 3851, 3127, 2921, 2850, 2213, 1969, 1509, 1223, 1142, 802$   $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H = 8.86$  (d,  $J = 7.0$  Hz, 1 H,  $H_{Ar}$ ), 7.88 (br d,  $J = 9.4$  Hz, 1 H,  $H_{Ar}$ ), 7.84–7.77 (m, 2 H,  $H_{Ar}$ ), 7.74 (ddd,  $J = 9.4, 6.7, 1.4$  Hz, 1 H,  $H_{Ar}$ ), 7.20–7.07 (m, 3 H,  $H_{Ar}$ ) ppm;  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta_C = 163.9$  (d,  $^1J = 253.1$  Hz, C,  $C-F$ ), 151.0 (C,  $C_{Ar}$ ), 147.6 (q,  $^2J = 37.6$  Hz,  $C-CF_3$ ), 146.6 (C,  $C_{Ar}$ ), 142.2 (C,  $C_{Ar}$ ), 136.2 (C,  $C_{Ar}$ ), 135.2 (d,  $^3J = 8.8$  Hz, CH,  $CH=C-C-F$ ), 134.6 (CH,  $CH_{Ar}$ ), 125.6 (CH,  $CH_{Ar}$ ), 120.1 (q,  $^1J = 274.8$  Hz,  $CF_3$ ), 119.3 (CH,  $CH_{Ar}$ ), 117.4 (d,  $^4J = 3.6$  Hz, C,  $C-C=C-C-F$ ), 116.1 (d,  $^2J = 22.3$  Hz, CH,  $CH-C-F$ ), 113.3 (CH,  $CH_{Ar}$ ), 100.1 (C,  $\equiv C$ ), 84.3 (C,  $C\equiv$ ) ppm;  $^{19}F$  NMR (376 MHz,  $CDCl_3$ ):  $\delta_F = -68.0, -107.1$ ; HRMS (ESI):  $m/z$  calcd. for  $C_{18}H_9F_4N_4$   $[M+H]^+$  357.0758; found 357.0759.

**4-((4-Methoxyphenyl)ethynyl)-2-(trifluoromethyl) pyrido[1,2-*e*]purine (30a).** According to GP4, the reaction was performed with compound **17a** (46.6 mg, 171  $\mu$ mol) and 4-ethynylanisole. The crude product was purified by column chromatography ( $SiO_2$ , petroleum ether : EtOAc 5:5) to give compound **30a** as a yellow solid (54 mg, 86%). m.p.: 208–210 °C; IR (neat):  $\tilde{\nu} = 3456, 3015, 2945, 2195, 1738, 1572, 1365, 1251, 1295, 1365, 1216, 1125, 1086, 954, 829, 763$   $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H = 8.85$  (br d,  $J = 6.5$  Hz, 1 H,  $H_{Ar}$ ), 7.87 (d,  $J = 9.2$  Hz, 1 H,  $H_{Ar}$ ), 7.76 (d,  $J = 8.3$  Hz, 2 H,  $H_{Ar}$  anis), 7.72 (t,  $J = 6.5$  Hz, 1 H,  $H_{Ar}$ ), 7.12 (br t,  $J = 6.5$  Hz, 1 H,  $H_{Ar}$ ), 6.94 (d,  $J = 8.3$  Hz, 2 H,  $H_{Ar}$  anis), 3.87 (s, 3 H,  $OCH_3$ ) ppm;  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta_C = 161.5$  (C, CO), 150.8 (C,  $C_{Ar}$ ), 147.6 (q,  $J = 37.2$  Hz,  $C-CF_3$ ), 146.4 (C,  $C_{Ar}$ ), 142.9 (C,  $C_{Ar}$ ), 136.0 (C,  $C_{Ar}$ ), 134.9 (2  $\times$  CH,  $CH_{Ar}$ ), 134.2 (CH,  $CH_{Ar}$ ), 125.6 (CH,  $CH_{Ar}$ ), 120.2 (q,  $J = 274.9$  Hz,  $CF_3$ ), 119.3 (CH,  $CH_{Ar}$ ), 114.3 (2  $\times$  CH,  $CH_{Ar}$ ), 113.2 (CH,  $CH_{Ar}$ ), 102.3 (C,  $\equiv C$ ), 84.1 (C,  $C\equiv$ ), 55.6 ( $CH_3, OCH_3$ ) ppm;  $^{19}F$  NMR (376 MHz,  $CDCl_3$ ):  $\delta_F = -68.0$ ; HRMS (ESI):  $m/z$  calcd. for  $C_{19}H_{12}F_3N_4O$   $[M+H]^+$  369.0958; found 369.0957.

**4-[2-(3-Methoxyphenyl)ethynyl]-2-(trifluoromethyl)pyrido[1,2-*e*]purine (32a).** According to GP4, the reaction was achieved with compound **17a** (52 mg, 183  $\mu$ mol) and 3-ethynylanisole. The crude product was purified by column chromatography ( $SiO_2$ , petroleum ether : EtOAc 5:5) to give compound **32a** as a yellow solid (49.5 mg, 73%). m.p.: 194–195 °C; IR (neat):  $\tilde{\nu} = 3456, 3015, 2969, 2220, 1739, 1640, 1365, 1269, 1216, 1135, 1034, 907, 852$   $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H = 8.87$  (d,  $J = 6.9$  Hz, 1 H,  $H_{Ar}$ ), 7.89 (d,  $J = 9.3$  Hz, 1 H,  $H_{Ar}$ ), 7.78–7.69 (m, 1 H,  $H_{Ar}$ ), 7.41 (d,  $J = 7.5$  Hz, 1 H,  $H_{Ar}$ ), 7.34 (t,  $J = 6.7$  Hz, 2 H,  $H_{Ar}$ ), 7.14 (t,  $J = 6.7$  Hz, 1 H,  $H_{Ar}$ ), 7.03 (d,  $J = 8.0$  Hz, 1 H,  $H_{Ar}$ ), 3.86 (s, 3 H,  $OCH_3$ ) ppm;  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta_C = 159.5$  (C, CO), 151.0 (C,  $C_{Ar}$ ), 147.6 (q,  $J = 38.1$  Hz,  $C-CF_3$ ), 146.6 (C,  $C_{Ar}$ ), 142.4 (C,  $C_{Ar}$ ), 136.3 (C,  $C_{Ar}$ ), 134.5 (CH,  $CH_{Ar}$ ), 129.7 (CH,  $CH_{Ar}$ ), 125.7 (CH,  $CH_{Ar}$ ), 125.6 (CH,  $CH_{Ar}$ ), 122.2 (C,  $C_{Ar}$ ), 120.1 (q,  $J = 274.8$  Hz,  $CF_3$ ), 119.3 (CH,  $CH_{Ar}$ ), 117.6 (CH,  $CH_{Ar}$ ), 117.2 (CH,  $CH_{Ar}$ ), 113.3 (CH,  $CH_{Ar}$ ), 101.3 (C,  $\equiv C$ ), 84.3 (C,  $C\equiv$ ), 55.7 ( $CH_3, OCH_3$ ) ppm;  $^{19}F$  NMR (376 MHz,  $CDCl_3$ ):  $\delta_F = -68.0$  ppm; HRMS (ESI):  $m/z$  calcd. for  $C_{19}H_{12}F_3N_4O$   $[M+H]^+$  369.0958; found 369.0956.

**4-((2-Methoxyphenyl)ethynyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (31a).** According to GP4, the reaction was carried out with compound **17a** (52 mg, 183  $\mu$ mol) and 2-ethynylanisole. The crude product was purified by column chromatography ( $SiO_2$ , petroleum ether : EtOAc 5:5) to give compound **31a** as a yellow solid (35 mg, 52%). m.p.: 204–205 °C; IR (neat):  $\tilde{\nu} = 3455, 3015, 2922, 2200, 1738, 1637, 1409, 1216, 905, 503$   $cm^{-1}$ ;  $^1H$  NMR (250 MHz,  $CDCl_3$ ):  $\delta_H = 8.84$  (d,  $J = 6.9$  Hz, 1 H,  $H_{Ar}$ ), 7.86 (d,  $J = 9.3$  Hz, 1 H,  $H_{Ar}$ ), 7.76–7.67 (m, 2 H,  $H_{Ar}$ ), 7.51–7.36 (m, 1 H,  $H_{Ar}$ ), 7.11 (t,  $J = 6.7$  Hz, 1 H,  $H_{Ar}$ ), 7.04–6.90 (m, 2 H,  $H_{Ar}$ ), 4.00 (s, 3 H,  $OCH_3$ ) ppm;  $^{13}C$  NMR (63 MHz,  $CDCl_3$ ):  $\delta_C = 161.3$  (C, CO), 150.9 (C,  $C_{Ar}$ ), 147.6 (q,  $J = 37.4$  Hz,  $C-CF_3$ ), 146.4 (C,  $C_{Ar}$ ), 142.7 (C,  $C_{Ar}$ ), 136.2 (C,  $C_{Ar}$ ), 134.8 (CH,  $CH_{Ar}$ ), 134.3 (CH,  $CH_{Ar}$ ), 132.2 (CH,  $CH_{Ar}$ ), 125.6 (CH,  $CH_{Ar}$ ), 120.6 (CH,  $CH_{Ar}$ ), 120.1 (q,  $J = 274.8$  Hz,  $CF_3$ ), 119.3 (CH,  $CH_{Ar}$ ), 113.2 (CH,  $CH_{Ar}$ ), 110.9 (CH,  $CH_{Ar}$ ), 110.6 (C,  $C_{Ar}$ ), 98.6 (C,  $\equiv C$ ), 88.4 (C,  $C\equiv$ ), 56.1 ( $CH_3, OCH_3$ ) ppm;  $^{19}F$  NMR (235 MHz,  $CDCl_3$ ):  $\delta_F = -68.0$  ppm; HRMS (ESI):  $m/z$  calcd. for  $C_{19}H_{12}F_3N_4O$   $[M+H]^+$  369.2958; found 369.0958.

**4-((4-Fluoro-3-methylphenyl)ethynyl)-2-(trifluoromethyl) pyrido[1,2-*e*]purine (34a).** According to GP4, the reaction was performed with compound **17a** (52 mg, 183  $\mu$ mol) and 4-ethynyl-1-fluoro-2-methylbenzene. The crude product was purified by column chromatography ( $SiO_2$ , petroleum ether : EtOAc 5:5) to give compound **34a** as a yellow solid (41 mg, 60%). m.p.: 192–193 °C; IR (neat):  $\tilde{\nu} = 3120, 2920, 2849, 2210, 1968, 1510, 1222, 1142, 800, 803$   $cm^{-1}$ ;  $^1H$  NMR (250 MHz,  $CDCl_3$ ):  $\delta_H = 8.86$  (dt,  $J = 6.9, 1.2$  Hz, 1 H,  $H_{Ar}$ ), 7.89 (dt,  $J = 9.4, 1.2$  Hz, 1 H,  $H_{Ar}$ ), 7.78–7.57 (m, 3 H,  $H_{Ar}$ ), 7.13 (td,  $J = 6.9, 1.2$  Hz, 1 H,  $H_{Ar}$ ), 7.06 (t,  $J = 9.4$  Hz, 1 H,  $H_{Ar}$ ), 2.32 (d,  $J = 2.0$  Hz, 3 H  $CH_3$ ) ppm;  $^{13}C$  NMR (63 MHz,  $CDCl_3$ ):  $\delta_C = 162.6$  (d,  $^1J = 251.7$  Hz, C,  $C-F$ ), 151.0 (C,  $C_{Ar}$ ), 147.6 (q,  $^2J = 37.3$  Hz,  $C-CF_3$ ), 146.5 (C,  $C_{Ar}$ ), 142.4 (C,  $C_{Ar}$ ), 136.5 (d,  $^3J = 6.0$  Hz, CH,  $CH=C-C-F$ ), 136.2 (C,  $C_{Ar}$ ), 134.5 (CH,  $CH_{Ar}$ ), 132.5 (d,  $^3J = 6.0$  Hz, CH,  $CH=C-C-F$ ), 125.9 (d,  $^2J = 18.3$  Hz, C,  $CH_3-C-C-F$ ), 125.6 (CH,  $CH_{Ar}$ ), 120.1 (q,  $^1J = 274.7$  Hz,  $CF_3$ ), 119.3 (CH,  $CH_{Ar}$ ), 117.0 (d,  $^4J = 3.8$  Hz, C,  $C-C=C-C-F$ ), 115.7 (d,  $^2J = 23.3$  Hz, CH,  $CH-C-F$ ), 113.3 (CH,  $CH_{Ar}$ ), 100.7 (C,  $\equiv C$ ), 84.1 (C,  $C\equiv$ ), 14.5 (d,  $^3J = 3.5$  Hz,  $F-CH_3$ ) ppm;  $^{19}F$  NMR (235 MHz,  $CDCl_3$ ):  $\delta_F = -68.0, -111.5$  ppm; HRMS (ESI):  $m/z$  calcd. for  $C_{19}H_{11}F_4N_4$   $[M+H]^+$  371.0914; found 371.0914.

**4-(3,3-Dimethylbut-1-yn-1-yl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (33a).** According to GP4, the reaction was performed with compound **17a** (52 mg, 183  $\mu$ mol) and *tert*-butylacetylene. The crude product was purified by column chromatography ( $SiO_2$ , petroleum ether : EtOAc 6:4) to give compound **33a** as a yellow solid (38 mg, 65%). m.p.: 228–229 °C; IR (neat):  $\tilde{\nu} = 3458, 2925, 2852, 2220, 1738, 1640, 1488, 1365, 1270, 1153, 900, 762, 762, 743$   $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H = 8.83$  (d,  $J = 6.8$  Hz, 1 H,  $H_{Ar}$ ), 7.86 (d,  $J = 9.4$  Hz, 1 H,  $H_{Ar}$ ), 7.78–7.64 (m, 1 H,  $H_{Ar}$ ), 7.10 (t,  $J = 6.8$  Hz, 1 H,  $H_{Ar}$ ), 1.49 (s, 9 H) ppm;  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta_C = 150.8$  (C,  $C_{Ar}$ ), 147.5 (q,  $J = 37.2$  Hz,  $C-CF_3$ ), 146.3 (C,  $C_{Ar}$ ), 143.3 (C,  $C_{Ar}$ ), 136.3 (C,  $C_{Ar}$ ), 134.1 (CH,  $CH_{Ar}$ ), 125.5 (CH,  $CH_{Ar}$ ), 120.1 (q,  $J = 274.7$  Hz,  $CF_3$ ), 119.3 (CH,  $CH_{Ar}$ ), 113.1 (CH,  $CH_{Ar}$ ), 112.0 (C,  $\equiv C$ ), 75.3 (C,  $C\equiv$ ), 30.6 ( $CH_3$ ), 28.9 (C,  $C(CH_3)_3$ ) ppm;  $^{19}F$  NMR (376 MHz,  $CDCl_3$ ):  $\delta_F = -68.0$  ppm; HRMS (ESI):  $m/z$  calcd. for  $C_{16}H_{13}F_3N_4$   $[M+H]^+$  319, 1165; found 319.1164.

**7-Methyl-4-(*p*-tolylethynyl)-2-(trifluoromethyl)pyrido[1,2-*e*]purine (28b).** According to GP4, the reaction was performed with compound **17b** (52 mg, 183  $\mu$ mol) and 4-ethynyltoluene. The crude product was purified by column chromatography ( $SiO_2$ , petroleum ether : EtOAc 7:3) to give compound **28b** as a yellow solid (40 mg, 60%). m.p.: 198–200 °C; IR (neat):  $\tilde{\nu} = 3455, 3015, 2946, 2205, 1739, 1367, 1407, 1216, 1149, 1128, 1087, 952, 817, 766$   $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H = 8.69$  (d,  $J = 7.0$  Hz, 1 H,  $H_{Ar}$ ), 7.68 (d,  $J = 8.0$  Hz, 2 H,  $H_{Ar}$ ), 7.57 (s, 1 H,  $H_{Ar}$ ), 7.21 (d,  $J = 7.9$  Hz, 2 H,  $H_{Ar}$ ), 6.93 (d,  $J = 7.9$  Hz, 1 H,  $H_{Ar}$ ), 2.55 (s, 3 H,  $CH_3$ ), 2.40 (s, 3 H,  $CH_3$ ) ppm;  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta_C = 151.4$  (C,  $C_{Ar}$ ), 147.1 (q,  $J = 37.5$  Hz,  $C-CF_3$ ), 146.7 (C,  $C_{Ar}$ ), 146.6 (C,  $C_{Ar}$ ), 141.7 (C,  $C_{Ar}$ ), 140.9 (C,

$C_{Ar}$ , 136.5 (C,  $C_{Ar}$ ), 132.9 (2 × CH,  $CH_{Ar}$ ), 129.4 (2 × CH,  $CH_{Ar}$ ), 124.4 (CH,  $CH_{Ar}$ ), 120.1 (q,  $J = 274.7$  Hz,  $CF_3$ ), 118.2 (C,  $C_{Ar}$ ), 117.0 (CH,  $CH_{Ar}$ ), 116.2 (CH,  $CH_{Ar}$ ), 101.4 (C,  $\equiv C$ ), 84.2 (C,  $C\equiv$ ), 22.6 (CH<sub>3</sub>), 21.9 (CH<sub>3</sub>) ppm;  $^{19}F$  NMR (376 MHz,  $CDCl_3$ ):  $\delta_F = -68.0$  ppm; HRMS (ESI):  $m/z$  calcd. for  $C_{20}H_{14}F_3N_4$  [M+H]<sup>+</sup> 367.1165; found 367.1161.

**4-((3-Methoxyphenyl)ethynyl)-7-methyl-2-(trifluoromethyl)pyrido[1,2-e]purine (32b).** According to GP4, the reaction was achieved with compound **17b** (52 mg, 183  $\mu$ mol) and 3-ethynylanisole. The crude product was purified by column chromatography ( $SiO_2$ , petroleum ether : EtOAc 6:4) to give compound **32b** as a yellow solid (48 mg, 69%). m.p.: 193–194 °C; IR (neat):  $\tilde{\nu} = 3455, 3015, 2945, 2202, 1739, 1650, 1571, 1365, 1249, 1216, 1161, 1092, 789$   $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta_H = 8.71$  (d,  $J = 7.0$  Hz, 1 H,  $H_{Ar}$ ), 7.61–7.59 (m, 1 H,  $H_{Ar}$ ), 7.40 (dt,  $J = 7.6, 1.3$  Hz, 1 H,  $H_{Ar}$ ), 7.33 (d,  $J = 8.1$  Hz, 1 H,  $H_{Ar}$ ), 7.31–7.29 (m, 1 H,  $H_{Ar}$ ), 7.01 (ddd,  $J = 8.6, 2.7, 1.5$  Hz, 1 H,  $H_{Ar}$ ), 6.95 (dd,  $J = 7.0, 1.5$  Hz, 1 H,  $H_{Ar}$ ), 3.85 (s, 3 H, OCH<sub>3</sub>), 2.57 (s, 3 H, CH<sub>3</sub>) ppm;  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta_C = 159.4$  (C, CO), 151.5 (C,  $C_{Ar}$ ), 147.1 (q,  $J = 37.6$  Hz, C- $CF_3$ ), 146.9 (C,  $C_{Ar}$ ), 146.8 (C,  $C_{Ar}$ ), 141.4 (C,  $C_{Ar}$ ), 136.6 (C,  $C_{Ar}$ ), 129.7 (CH,  $CH_{Ar}$ ), 125.7 (CH,  $CH_{Ar}$ ), 124.5 (CH,  $CH_{Ar}$ ), 122.3 (C,  $C_{Ar}$ ), 120.1 (q,  $J = 274.8$  Hz,  $CF_3$ ), 117.5 (CH,  $CH_{Ar}$ ), 117.2 (CH,  $CH_{Ar}$ ), 117.1 (CH,  $CH_{Ar}$ ), 116.3 (CH,  $CH_{Ar}$ ), 100.7 (C,  $\equiv C$ ), 84.3 (C,  $C\equiv$ ), 55.6 (CH<sub>3</sub>, OCH<sub>3</sub>), 22.6 (CH<sub>3</sub>) ppm;  $^{19}F$  NMR (376 MHz,  $CDCl_3$ ):  $\delta_F = -67.9$  ppm; HRMS (ESI):  $m/z$  calcd. for  $C_{20}H_{14}F_3N_4O$  [M+H]<sup>+</sup> 383.1114; found 383.1114.

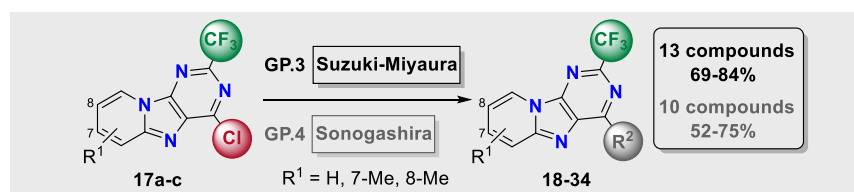
## Acknowledgments

The authors are grateful for financial support from Centre National de la Recherche Scientifique (CNRS), Labex SynOrg (ANR-11-LABX-0029), the Ligue nationale contre le cancer (Projects CSIRGO 2017 & 2018, thesis salary of JC) and the Région Centre-Val de Loire (Projects n°2013-00082978 & n°2017-00117252).

**Keywords:** Nitrogen heterocycles • Fused-ring systems • Cross-coupling • C–C coupling • Base excision repair

- [1] H. Rosemeyer, *Chem. Biodivers.* **2004**, *1*, 361–401.
- [2] a) M. Legraverend, D. S. Grierson, *Bioorg. Med. Chem.* **2006**, *14*, 3987–4006; b) A. P. Schmidt, D. R. Lara, D. O. Souza, *Pharmacol. Ther.* **2007**, *116*, 401–416.
- [3] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2550–2574.
- [4] For recent reviews on synthetic methods for the preparation of purines and analogs as privileged scaffolds in medicinal chemistry see: a) M. Legraverend, *Tetrahedron*, **2008**, *64*, 8585–8603; b) A. Conejo-Garcia, O. Cruz-Lopez, V. Gomez-Perez, F. Morales, M. E. Garcia-Rubino, M. Kimatrai, M. C. Nunez, J. M. Campos, *Curr. Org. Chem.* **2010**, *14*, 2463–2482; c) M. Chauhan, R. Kumar, *Bioorg. Med. Chem.* **2013**, *21*, 5657–5668; d) A. Manvar, A. Shah, *Tetrahedron* **2013**, *69*, 8105–8127; e) F. Phei Lin Lim, A. V. Dolzhenko, *Eur. J. Med. Chem.* **2014**, *85*, 371–390; Z. Jahnz-Wechmann, G. Framski, P. Januszczczyk, J. Boryski, *Eur. J. Med. Chem.* **2015**, *95*, 388–396; M. Abdoli, Z. Mirjafary, H. Saeidian, A. Kakanejadifard, *RSC Adv.* **2015**, *5*, 44371–44389; f) V. L. Rusinov, V. N. Charushin, O. N. Chupakhin, *Russ. Chem. Bull., Int. Ed.* **2018**, *67*, 573–599; E. M. H. Ali, M. S. Abdel-Maksoud, C.-H. Oh, *Bioorg. Med. Chem.* **2019**, *27*, 1159–1194.
- [5] For a few selected papers see: a) D. J. Blythin, J. J. Kaminski, M. S. Domalski, J. Spittler, D. M. Solomon, D. J. Conn, S. C. Wong, L. L. Verbiar, L. A. Bober, *J. Med. Chem.* **1986**, *29*, 1099–1113; b) E.-M. Priego, J. V. F. D. Kuenzel, A. P. IJerman, M.-J. Camarasa, M.-J. Pérez-Pérez, *J. Med. Chem.* **2002**, *45*, 3337–3344; c) C. E. Müller, M. Thorand, R. Qurishi, M. Diekmann, K. A. Jacobson, W. L. Padgett, J. W. Daly, *J. Med. Chem.* **2002**, *45*, 3440–3450; d) P. G. Baraldi, D. Preti, M. A. Tabrizi, F. Fruttarolo, R. Romagnoli, N. A. Zaid, A. R. Moorman, S. Merighi, K. Varani, P. A. Borea, *J. Med. Chem.* **2005**, *48*, 4697–4701; e) O. Lenzi, V. Colotta, D. Catarzi, F. Varano, G. Filacchioni, C. Martini, L. Trincavelli, O. Ciampi, K. Varani, F. Marighetti, E. Morizzo, S. Moro, *J. Med. Chem.* **2006**, *49*, 3916–3925; f) K. Lafleur, D. Huang, T. Zhou, A. Caffisch, C. Nevado, *J. Med. Chem.* **2009**, *52*, 6433–6446; g) V. Chaudhary, S. Das, A. Nayak, S. K. Guchhait, C. N. Kundu, *RSC Adv.* **2015**, *5*, 26051–26060.
- [6] S. S. Bag, I. Saito, In *Fluorescent Analogues of Biomolecular Building Blocks: Design and Applications* (Eds.: Y. Tor, M. Wilhelmsson), John Wiley & Sons, Chichester, West Sussex, UK, **2016**, pp. 137–173.
- [7] a) H.-S. Ahn, A. Bercovici, G. Boykow, A. Bronnenkant, S. Chackalamannil, J. Chow, R. Cleven, J. Cook, M. Czarniecki, C. Domalski, A. Fawzi, M. Green, A. Gündes, G. Ho, M. Laudicina, N. Lindo, K. Ma, M. Manna, B. McKittrick, B. Mirzai, T. Nechuta, B. Neustadt, C. Puchalski, K. Pula, L. Silverman, E. Smith, A. Stamford, R. P. Tedesco, H. Tsai, D. Tulshian, H. Vaccaro, R. W. Watkins, X. Weng, J. T. Witkowski, Y. Xia and H. Zhang, *J. Med. Chem.* **1997**, *40*, 2196–2210.
- [8] T. Okamura, Y. Kurogi, K. Hashimoto, H. Nishikawa, Y. Nagao, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2443–2446.
- [9] a) C. D. Boyle, R. Xu, T. Asberom, S. Chackalamannil, J. W. Clader, W. J. Greenlee, H. Guzik, Y. Hu, Z. Hu, C. M. Lankin, D. A. Pissarnitski, A. W. Stamford, Y. Wang, J. Skell, S. Kurowski, S. Vemulapalli, J. Palamanda, M. Chintala, P. Wu, J. Myers, P. Wang, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2365–2369; b) G. Xia, J. Li, A. Peng, S. Lai, S. Zhang, J. Shen, Z. Liu, X. Chen and R. Ji, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2790–2794; c) G. X. Xia, J. F. Li, S. A. Lai, A. M. Peng, S. J. Zhang, X. H. Wei, X. J. Chen, J. S. Shen, R. Y. Ji, *Chin. Chem. Lett.* **2005**, *16*, 1283–1286; d) P. Srivani, E. Srinivas, R. Raghu, G. N. Sastry, *J. Mol. Graph. Modell.* **2007**, *26*, 378–390.
- [10] a) J. C. Debouzy, A. Gueiffier, F. Fauvelle, H. Viols, E. Dejean, V. Neirinck, A. Peinnequin, C. Bachelet, B. Perly, J. P. Chapat, *J. Pharm. Sci.* **1996**, *85*, 200–205; b) A. Gueiffier, O. Chavignon, S. Mavel, J. M. Chezal, J. C. Teulade, Y. Blache, J. P. Chapat, *Heterocycl. Commun.* **1996**, *2*, 241–246; c) J. C. Debouzy, S. Crouzy, V. Dabouis, A. Gueiffier, B. Brasme, C. Bachelet, A. Favier, J. P. Simorre, L. Mazet, A. Peinnequin, *Arch. Biochem. Biophys.* **1999**, *367*, 202–215; d) F. Pinguet, S. Mavel, C. Galtier, A. Gueiffier, *Pharmazie* **1999**, *54*, 876–878; e) J. C. Debouzy, V. Dabouis, S. Crouzy, C. Bachelet, A. Peinnequin, A. Gueiffier, *Pharmazie* **2001**, *56*, 125–132; f) A. Favier, M. Blackledge, J. P. Simorre, S. Crouzy, V. Dabouis, A. Gueiffier, D. Marion, J. C. Debouzy, *Biochemistry* **2001**, *40*, 8717–8726; g) V. H. R. Marzouk, M. Hennem, L.-L. Gundersen, *Tetrahedron Lett.* **2013**, *54*, 3437–3439.
- [11] For a review on the recent developments in the synthesis of imidazo[1,2-*a*]pyridines see: K. Pericherla, P. Kaswan, K. Pandey, A. Kumar, *Synthesis* **2015**, *47*, A–Z.
- [12] a) S. K. Guchhait, V. Chaudhary, *Org. Biomol. Chem.* **2014**, *12*, 6694–6705; b) H. Salgado-Zamora, E. C. Taylor, *Heterocycl. Commun.* **2006**, *12*, 307–312.
- [13] A. E. Tschitschibabin, *Chem. Ber.* **1925**, *58*, 1704–1706.
- [14] P. Ehrlich, F. Sachs, *Chem. Ber.* **1899**, *32*, 2341–2346.
- [15] D. Ye, X. Zhang, Y. Zhou, D. Zhang, L. Zhang, H. Wang, H. Jiang, H. Liu, *Adv. Synth. Catal.* **2009**, *351*, 2770–2778.
- [16] I. Čerňa, R. Pohl, B. Klepetářová, M. Hocek, *J. Org. Chem.* **2010**, *75*, 2302–2308.
- [17] J. Maes, T. R. M. Rauws, B. U. W. Maes, *Chem. Eur. J.* **2013**, *19*, 9137–9141.
- [18] S. Boiteux, F. Coste, B. Castaing, *Free radical biology & medicine* **2017**, *107*, 179–201.
- [19] Z. M. Ramdzan, V. Ginjala, J.B. Pinder, D. Chung, C.M. Donovan, S. Kaur, L. Leduy, G. Dellaire, S. Ganesan, A. Nepveu, *Oncotarget* **2015**, *6*, 3613–3626.
- [20] T. H. Massey, L. Jones, *Disease Models & Mechanisms* **2018**, *11*, dmm031930.

- [21] T. Visnes, M. Grube, B. M. F. Hanna, C. Benitez-Buelga, A. Cázares-Körner, T. Helleday, *DNA repair* **2018**, *71*, 118–126.
- [22] a) H. C. Shen, in *Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective* (Eds.: M. J. Crawley, B. M. Trost), Wiley: Hoboken, NJ, USA, **2012**; pp. 25–95; b) I. Maluenda, O. Navarro, *Molecules* **2015**, *20*, 7528–7557 and references cited therein; c) J. P. G. Rygus, C. M. J. Crudden, *J. Am. Chem. Soc.* **2017**, *139*, 18124–18137; d) A. T. Kal Koshvandi, M. M. Heravi, T. Momeni, *Appl. Organometal. Chem.* **2018**, *32*, e4210.
- [23] a) C. O. Kappe, *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284; b) P. Nilsson, K. Olofsson, M. Larhed in *Topics in Current Chemistry: Microwave Methods in Organic Synthesis, Vol. 266* (Eds.: M. Larhed, K. Olofsson) Springer, Heidelberg, **2006**, pp. 103–144; c) V. P. Mehta, E. V. D. Eycken, *Chem. Soc. Rev.* **2011**, *40*, 4925–4936 and references therein.
- [24] a) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805–818; b) J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1144–1157.
- [25] Yin J.; Buchwald S. L. *Org. Lett.* **2000**, *2*, 1101–1104; b) Artamkina G. A.; Sergeev A. G.; Beletskaya I. P. *Tetrahedron Lett.* **2001**, *42*, 4381–4384.
- [26] M. Beller, A. Varela-Fernandez, J. G. Vries, S. Man Wong, C. Ming So, F. Y. Kwong, in *Applied Homogeneous Catalysis with Organometallic Compounds* (Eds.: B. Cornils), Wiley-VCH, Weinheim, Germany, **2018**, pp. 411–464.
- [27] a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50; b) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649.
- [28] a) M. Heravi, M. Ghanbarian, N. Ghalavand, N. Nazari, *Curr. Org. Chem.* **2018**, *22*, 1420–1457; b) K. Semba, Y. Nakao, *Tetrahedron* **2019**, *75*, 709–719.
- [29] J. Koubachi, S. E. Kazzouli, M. Bousmina, G. Guillaumet, *Eur. J. Org. Chem.* **2014**, 5119–5138.
- [30] a) see references 5–36 cited in ref. [28]; b) L. Dymińska, *Bioorg. Med. Chem.* **2015**, *23*, 6087–6099.
- [31] A. El Akkaoui, I. Bassoude, J. Koubachi, S. Berteina-Raboin, A. Mouaddib, G. Guillaumet, *Tetrahedron* **2011**, *67*, 7128–7138.
- [32] M. Schilz, H. Plenio, *J. Org. Chem.* **2012**, *77*, 2798–2807.



The convenient preparation of novel 4-chloro-2-(trifluoromethyl)pyrido[1,2-*e*]purines by way of the original reactions of imidazo[1,2-*a*]pyridine-2-carboxamides and 2,2,2-trifluoroacetamide is reported. The derivatives were then efficiently cross-coupled through Suzuki–Miyaura and Sonogashira catalysis to give the related C-4 substituted pyrido[1,2-*e*]purines of biological interest in good yields.

### Nitrogen heterocycles, Cross-coupling

Zahira Tber,<sup>[a]</sup> Nicolas G. Biteau,<sup>[a]</sup> Luigi Agrofoglio,<sup>\*,[a]</sup> Julien Cros,<sup>[b]</sup> Stéphane Goffinont,<sup>[b]</sup> Bertrand Castaing,<sup>[b]</sup> Cyril Nicolas,<sup>[a]</sup> and Vincent Roy<sup>\*,[a]</sup>

### Microwave-Assisted Suzuki–Miyaura and Sonogashira Coupling of 4-Chloro-2-(trifluoromethyl)pyrido[1,2-*e*]purine Derivatives