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Original 2-(3-Alkoxy-1*H*-pyrazol-1-yl)azines Inhibitors of Human Dihydroorotate Dehydrogenase (DHODH)

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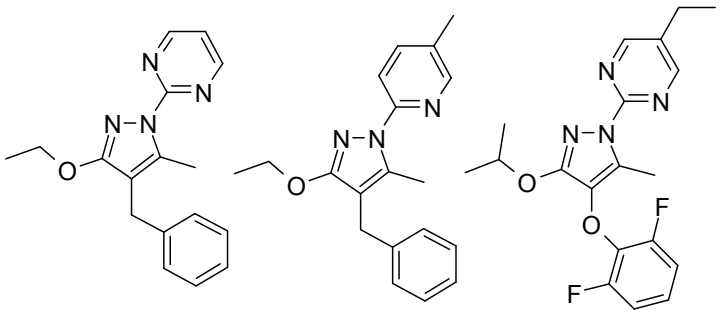
Abstract

Following our discovery of human dihydroorotate dehydrogenase (DHODH) inhibition by 2-(3-alkoxy-1*H*-pyrazol-1-yl)pyrimidine derivatives as well as 2-(4-benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-methylpyridine, we describe here the syntheses and evaluation of an array of azine-bearing analogues. As in our previous report, the structure-activity study of this series of human DHODH inhibitors was based on a phenotypic assay measuring measles virus replication. Among other inhibitors, this round of syntheses and biological evaluation iteration led to the highly active 5-cyclopropyl-2-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-3-fluoropyridine. Inhibition of DHODH by this compound was confirmed in an array of *in vitro* assays, including enzymatic tests and cell-based assays for viral replication and cellular growth. This molecule was found to be more active than the known inhibitors of DHODH brequinar and teriflunomide, thus opening perspectives for its use as a tool or for the design of an original series of immunosuppressive agent. Moreover, since other series of inhibitors of human DHODH have been found to also affect *Plasmodium falciparum* DHODH, all the compounds were assayed for their effect on *P. falciparum* growth. However, the modest *in vitro* inhibition solely observed for two compounds did not correlate with their inhibition of *P. falciparum* DHODH.

As explained in more details in our previous report,[1] in the course of a screening campaign of new chemical entities[2-11] against infectious agents, compounds **1** and **2** were found active on our whole cell measles virus replication assay.[12] An initial structure-activity study led to confirm the potential of this original chemotype and to greatly improved antiviral compounds, including the 2-(3-isopropyloxy-1*H*-pyrazol-1-yl)pyrimidine derivative **3**, which displayed a subnanomolar MIC_{50} on this measles virus replication assay. Moreover, a search for the

biochemical mechanism of action of this series pointed out that, as for other recently reported compounds,[13-18] the inhibition of the cellular dihydroorotate dehydrogenase (DHODH) is at the origin of the antiviral effect.[1]



1 (MIC_{50} = 2.7 μM) **2** (MIC_{50} = 0.65 μM) **3** (MIC_{50} = 0.66 nM)

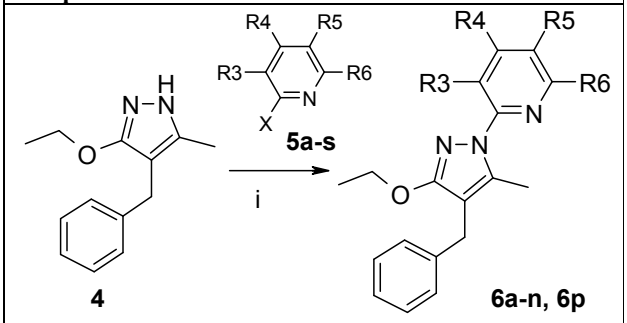
Figure 1. Structures of Compounds **1-3**.

From these results, in order to increase the chemical diversity possible in this series, we initially replaced the pyrimidine ring by a pyridine moiety since its additional carbon would provide another position for structure-activity studies. Accordingly, as in our first report,[1] we are describing here a succession of synthesis campaigns followed by comments on the antiviral effect obtained. Most of these results are presented in Tables in which the first result column (%) provides the yield of the reaction depicted and the second column describes the observed antiviral effect expressed as $pMIC_{50}$ values.[19] This corresponds to the negative log of the minimum compound concentration required to inhibit viral growth by 50% when using a recombinant measles virus strain expressing a luciferase as a reporter.[20] We first undertook the preparation of the 2-pyridyl derivatives **6a-t** depicted in Table 1. As compound **2**, these analogues were prepared from the 3-ethoxypyrazole **4**[10] and commercially available 2-halogenopyridines **5a-p**. From 2-halogenopyridines featuring electron-attracting substituents, the use of cesium carbonate in dry dimethylformamide or acetonitrile and heating at 150 °C

with a microwave oven for 1 h efficiently gave the N-pyridyl derivatives. On the other hand, from 2-fluoropyridines featuring electron donating substituents, a temperature of 180 °C (under pressure) was found necessary and, because of its decomposition into dimethylamine, dimethylformamide was replaced by acetonitrile. For the preparation of compound **6a**[7] or **6p**, we used 2-bromopyridine **5a** or **5p** and Taillefer and Cristau copper-catalyzed arylation conditions.[21] Moreover, as for compound **1**, the regioselectivity of these reactions was unambiguously checked in a couple of instances.[7] The 5-cyclopropyl bearing derivative **6q** was prepared in 48 % yield via a Suzuki-Miyaura reaction between cyclopropyl boronic acid and the 5-bromo derivatives **6j**. Alternatively, as described in the Experimental section, the 2-fluoropyridines **5q-s** were prepared via Suzuki-Miyaura reactions between cyclopropyl boronic acid and the corresponding 5-bromo precursors. From them, the analogues **6q-s** were then obtained by N-arylation of **4**. The N-arylation of compound **4** with 2-(6-fluoropyridin-3-yl)propan-2-ol (**5t**) gave the hydroxylated analogue **6t** and a reduction of its alcohol function led to the 5-isopropyl derivative **6u**. Interestingly, the palladium-catalyzed hydrogenation at room temperature of **6t** was mostly inefficient. To avoid the use of high hydrogen pressure, which would probably have also resulted in the hydrogenation of the pyridine ring,[7] we used triethylsilane in the presence of trifluoromethane sulfonic acid and achieved its hydrogenation into **6u** in an unoptimized 24 % yield. Concerning the antiviral effects, as seen in Table 1, the "methyl scan" leading to compounds **2** and **6b-d**, pointed out the importance of occupying the position 5 of the pyridine ring for a tangible antiviral effect ($pMIC_{50}$ = 6.2 for compound **2**). The lack of substituents or the introduction of a small fluorine atom seen in **6a**, **6e** and **6f** also gave almost inactive compounds although some improvement can be observed when comparing the antiviral effect of compound **6a** ($pMIC_{50}$ < 5) and the 3-fluorinated derivative **6e** ($pMIC_{50}$ = 5.2). The recourse to a trifluoromethyl (compounds **6g**) or a chlorine atom (compound **6i**) on position 5 gave slightly more active analogues (both $pMIC_{50}$ of 5.5) but the

bigger bromine present in compound **6j** did not improve this further ($pMIC_{50}$ = 5.3). On the other hand, the combination of the 3-fluoro and 5-bromo substituents seen in compound **6k** appeared to be the cause of slight synergic effect ($pMIC_{50}$ = 5.9) when considering the $pMIC_{50}$ of the parent mono-substituted compounds **6e** and **6j** (respectively 5.2 and 5.3). In contrast to a fluorine group, the 3-methyl substituent of 5-brominated derivative **6l** led only to a weak antiviral effect. A loss of effect was also seen for the three derivatives **6m**, **6n** and **6o** featuring respectively a cyano, an ester or a methyl ketone on position 5. To a lesser extent, a similar phenomenon was observed with the methoxy of compound **6p** ($pMIC_{50}$ = 5.5). It is only the introduction of the cyclopropyl group featured by compound **6q** that led to an improved inhibition of the virus replication ($pMIC_{50}$ = 7.0 nM). Combination of this group with the fluorine of compound **6r** led to an unchanged antiviral effect ($pMIC_{50}$ 7.0), whereas the nitrile of compound **6s** replacing this fluorine caused a loss ($pMIC_{50}$ = 6.6). Interestingly, the branched isopropyl derivative **6u** turns out to be an order of magnitude less active ($pMIC_{50}$ = 5.9) than the cyclopropyl analogue **6q**. Finally, the polar hydroxyl moiety of compound **6t** ($pMIC_{50}$ 5.3) led to an even bigger loss of effect in comparison with the hydrogen-bearing isopropyl group of compound **6u**.

Table 1. Preparation and Antiviral Effect of Compounds 6a-u.



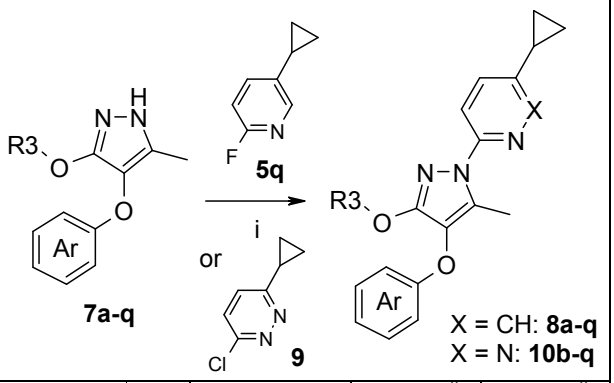
compd	R3	R4	R5	R6	%	$pMIC_{50}$ [ii]
6a	H	H	H	H	66[iii]	< 5
6b	H	Me	H	H	57	5.4
6c	Me	H	H	H	39	< 5
6d	H	H	H	Me	39	< 5
6e	F	H	H	H	74	5.2
6f	H	H	H	F	62	< 5
6g	H	H	CF_3	H	47	5.5
6h	H	H	H	CF_3	89	< 5
6i	H	H	Cl	H	40	5.5
6j	H	H	Br	H	44	5.3
6k	F	H	Br	H	33	5.9
6l	Me	H	Br	H	62	< 5
6m	H	H	CN	H	47	< 5
6n	H	H	CO_2Me	H	19	< 5
6o	H	H	COMe	H	15	< 5
6p	H	H	OMe	H	53[iv]	5.5
6q	H	H	*c*-Pr	H	48[v]	7.0
6r	F	H	*c*-Pr	H	17	7.0
6s	CN	H	*c*-Pr	H	18	6.6
6t	H	H	$COHMe_2$	H	67	5.3
6u	H	H	*i*-Pr	H	24[vi]	5.9

i: Cs_2CO_3, DMF/MeCN, microwave 150-180 °C.
ii: -log(MIC_{50}), MIC_{50} in mol/L, standard deviation < 2%.
iii: Using 2-bromopyridine and a copper catalyst.[7]
iv: Using 2-bromo-5-methoxypyridine and a copper catalyst see text and Experimental section.
v: From **6j**, see text and Experimental section.
vi: From **6t**, see text and Experimental section.

As for the pyrimidine-containing series,[1] by arylation of the 4-aryloxypyrazoles **7a-q** with the 2-fluoropyridine **5q**, we prepared the 4-aryloxy derivatives **8a-q** depicted in Table 2. Later on, we also prepared the corresponding pyridazine homologues **10b-q** from 3-chloro-6-cyclopropylpyridazine (**9**). For comparison purposes, Table 2 provides the pMIC50 for these two series. With few variations, the pattern of antiviral effect for analogues **8a-q** featuring a

5-cyclopylpyridine is somehow mirroring the one seen for the 5-ethylpyrimidyl bearing homologues.[1] In comparison with the phenoxy-bearing compound **8a** ($pMIC_{50}$ = 7.0), ortho-substitution with a fluorine, a chlorine of a bromine atom improved the antiviral effect ($pMIC_{50}$ of respectively 7.7, 7.9 and 7.8). A trifluoromethyl group instead of these halogens had a lesser effect (compound **8e**, $pMIC_{50}$ = 7.3). Shifting this trifluoromethyl group on the meta position of the phenoxy ring did not alter much the antiviral effect ($pMIC_{50}$ = 7.1 for **8f**) whereas placing this group on the para position led to a substantial loss ($pMIC_{50}$ = 5.3 for **8g**). A similar trend is observed with the fluorine atom of compounds **8k-m**, the ortho-fluoro derivative **8k** being the most active ($pMIC_{50}$ = 7.4) and the para fluorinated analogue **8m** far less effective ($pMIC_{50}$ = 5.9). Trends in the polyhalogenated derivatives are somehow less clear-cut although ortho-substituted derivatives are the most active but, as in the pyrimidine series,[1] with a $pMIC_{50}$ of 9.0 the 2,6-diflurophenoxy derivative **8q** is the best antiviral of this group of analogues. Very similar comments can be made on the antiviral effects of compounds **10b-q** and the differences between any given pair of analogues is always less than an order of magnitude.

Table 2. Preparation and Antiviral Effect of Compounds 8a-q and 10b-q.



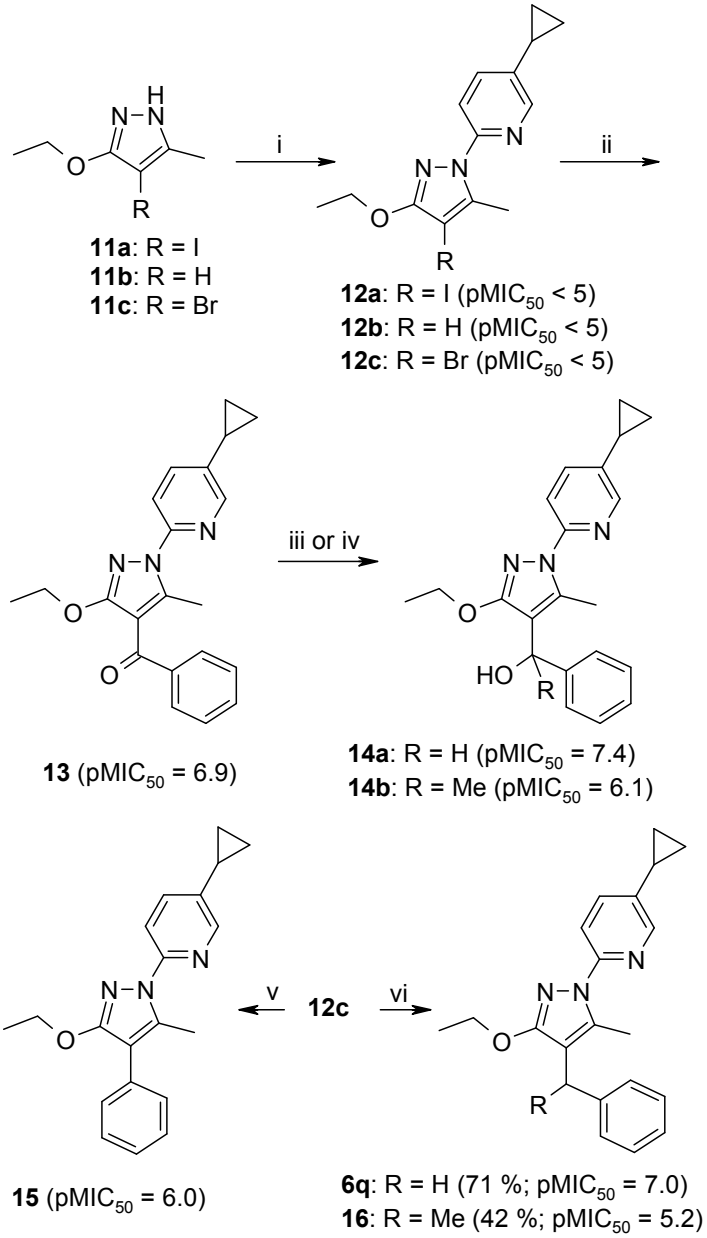
compd	R3	Ar	pMIC$_{50}$[ii] 8a-q	pMIC$_{50}$[ii] 10b-q
8a/10a	Et	C_6H_5	7.0	-
8b/10b	Et	2-FC_6H_4	7.7	7.7
8c/10c	Et	2-ClC_6H_4	7.9	7.1
8d/10d	Et	2-BrC_6H_4	7.8	7.2
8e/10e	Et	2-$CF_3C_6H_4$	7.3	6.8
8f/10f	Et	3-$CF_3C_6H_4$	7.1	6.4
8g/10g	Et	4-$CF_3C_6H_4$	5.3	5.2
8h/10h	Et	2,3-$Cl_2C_6H_3$	7.9	7.4
8i/10i	Et	2,5-$Cl_2C_6H_3$	7.1	6.9
8j/10j	Et	3,5-$Cl_2C_6H_3$	6.9	6.2
8k/10k	*i*-Pr	2-FC_6H_4	7.4	7.4
8l/10l	*i*-Pr	3-FC_6H_4	6.8	6.4
8m/10m	*i*-Pr	4-FC_6H_4	5.9	5.6
8n/10n	*i*-Pr	2,3-$F_2C_6H_3$	7.4	7.4
8o/10o	*i*-Pr	2,4-$F_2C_6H_3$	6.5	6.4
8p/10p	*i*-Pr	2,5-$F_2C_6H_3$	7.4	7.0
8q/10q	*i*-Pr	2,6-$F_2C_6H_3$	9.0	8.7

i: Cs_2CO_3, MeCN, microwave 180 °C 6h or 2h.
ii: -log(MIC_{50}), MIC_{50} in mol/L, standard deviation < 2%.

As depicted in Scheme 1, we also explored the preparation and use of precursors featuring a 5-cyclopropylpyridine moiety to which additional chemistry would allow the introduction of various group on the carbon 4 of the pyrazole ring. The N-arylation of the 4-iodopyrazole **11a**[5] with 5-cyclopropyl-2-fluoropyridine (**5q**) had to be conducted at 180 °C for up to 12 h and only led to a rather small amount (13 %) of the 4-iodinated target compound **12a** along with some (9 %) of the reduced derivative **12b**. This is quite in contrast with the 55 % yield we reported for the N-arylation of compound **11a** with 2-fluoropyridine at the same temperature for 3 h.[7] Extensive analysis of the reaction mixture pointed out the presence of

large amount of 3-ethoxy-5-methylpyrazole (**11b**) resulting from the reduction of the 4-iodopyrazole **11a** under this long reaction time. Although an explanation for this reduction is not obvious (a carbene occurrence?), we suggest that the much decreased reactivity of the electron rich 5-cyclopropyl-2-fluoropyridine (**5q**) toward nucleophilic reaction in comparison with 2-fluoropyridine is allowing the necessary time for this side reaction to proceed to a large extent. Somehow related to such behavior is the quick evolution of iodine, or iodochloride, upon heating 3-ethoxy-4-iodopyrazole in hydrochloric acid.[5] In any case, the iodinated target compound **12b** was treated with butyllithium followed by the addition of benzoylchloride to give the 4-benzoyl derivative **13** in 44 % yield. In an attempt to improve these results, we undertook the N-arylation of the 4-bromopyrazole **11c**. Under similar conditions, we could obtain the 4-brominated precursor **12c** in a much improved 48 % yield. The sodium borohydride reduction of ketone **13** led to the secondary alcohol **14a** whereas the addition of methyl lithium to ketone **13** provided an access to the tertiary alcohol **14b**. From compound **12c**, palladium-catalyzed reactions allowed the preparation of few analogues. A Suzuki-Miyaura reaction with phenylboronic acid gave 33 % of compound **15** whereas Negishi reactions with benzylzinc bromide or (1-phenylethyl)zinc chloride gave compounds **6q** and **16** in respectively 71 and 42 %. Of note in this part is an optimization of the preparation of 1-phenylethylzinc chloride using the lithium chloride, dibromoethane and trimethysilylchloride-based protocol[22-24] as well as the use of CPhos instead of XPhos in an attempt to lessen the extent of β-elimination possible with (1-phenylethyl)zinc chloride.[25] Concerning the antiviral effects of these compound, as for the pyrimidine-containing series,[1] the benzoyl derivative **13** ($pMIC_{50}$ = 6.9) was slightly less effective than the corresponding methylene analogue **6q** ($pMIC_{50}$ = 7.0). On the other hand, the alcohol **14a**, retained a more sizable antiviral effect ($pMIC_{50}$ = 7.4) but the gain is far from what we could observe in the case of the pyrimidine-containing series.[1] Introducing an additional methyl on this carbon led the tertiary alcohol **14b**

and to a much reduced antiviral activity ($pMIC_{50}$ = 6.1). A similar pattern was seen when adding a methyl to compound **6q** ($pMIC_{50}$ = 7.0) leading to the much less effective analogue **16** ($pMIC_{50}$ = 5.2). Finally, the low antiviral effect of the 4-phenyl derivative **15** ($pMIC_{50}$ = 6.0) pointed out the importance of a bridge between the pyrazole and the aromatic ring.



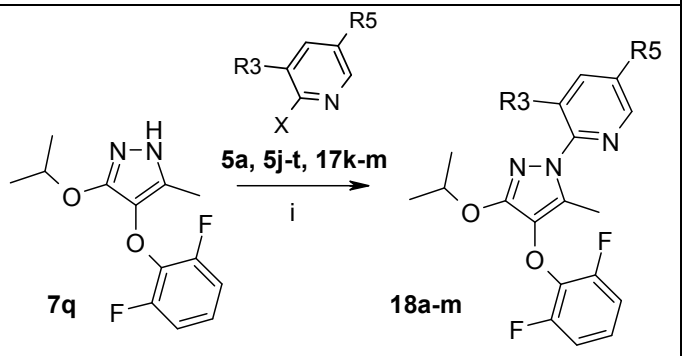
Scheme 1. 5-cyclopropyl-2-fluoropyridine (**5q**), MeCN, microwave 180 °C 12h. ii: a) BuLi, THF, -78 °C, b) PhCOCl, -78 ->20 °C. iii: $NaBH_4$, EtOH. iv: MeLi; THF, 20 °C. v:

PhB(OH)$_2$, Pddppf, Cs_2CO_3, PrOH/H_2O. vi: $PhCH_2ZnBr$, XPhos or PhCHMeZnCl, CPhos, $Pd(OAc)_2$, THF, 50 °C.

As depicted in Table 3, we then retained the 2,6-difluorophenoxy component of compound **8q** and prepared the 2-pyridyl derivatives **18a-s**. Analogues **18a-n** were obtained by the N-arylation of the pyrazole **7q** by the corresponding 2-halogenopyridines **5a**, **5g**, **5j-o**, **5q-t** and the 2-fluoropyridines **17l-n** (prepared as described in the Experimental section). In the case of the methoxy-bearing analogue **18p**, we used again the 2-bromo-5-methoxypyridine (**5p**) and Taillefer-Cristau copper-catalyzed arylation conditions.[21] The volatile 2-bromo-5-(1,1-difluoroethyl)pyridine (**17n**) was obtained from 2-bromo-5-acetylpyridine (**5o**). The following N-arylation of compound **7q** with this 2-bromopyridine **17n** had to be conducted at a relatively lower temperature to avoid extensive decomposition and the pure difluoromethylene-bearing analogue **18n** was thus obtained in a modest 12 % yield. A rather slow catalytic hydrogenation of the cyclopropyl ring of compound **18d** enabled an access to the propyl analogue **18o** in a 30 % yield. The preparation of analogues **18p-r** turned out to be possible as, under basic conditions, the fluorine atom on the pyridine ring of **18d** could be displaced by methanol, dimethylamine or benzylalcohol using high temperature and a micro-wave oven. In the last case, the catalytic hydrogenation of the resulting 3-benzyloxyderivative **18r** led to the 3-hydroxypyridinyl derivative **18s**. Unexpectedly, despite few trials, the direct hydrolysis of compound **18d** into **18s**, using sodium hydroxide in THF, was not successful. As seen in Table 3, with these compounds we could assess the effect of varying the pyridine substituents while retaining a 2,6-difluorophenoxy moiety. Going from the hydrogen of the N-pyridine derivative **18a** ($pMIC_{50}$ = 4.9) to the 5-methyl homolog **18b** ($pMIC_{50}$ = 7.6), a 400 fold improvement of the antiviral effect was observed. From then, the 5-cyclopropyl group of compound **8q** ($pMIC_{50}$ = 9) provided another order of magnitude. On the other hand, the ethyl

group of compound **18l** ($pMIC_{50}$ = 7.1) caused a loss of antiviral effect. This is actually reminiscent of what was observed for the 5-isopropyl bearing compound **6u** ($pMIC_{50}$ = 5.9) in comparison with the 5-cyclopropyl bearing analogue **6q** ($pMIC_{50}$ = 7.0) described above. Moreover, it is contrasting with what we previously reported for the 5-ethyl and 5-cyclopropyl pyrimidine analogues which had mostly the same antiviral effect ($pMIC_{50}$ = 9.2 and 8.9).[1] Replacement of the methyl group of compound **18b** ($pMIC_{50}$ = 7.6) by the trifluoromethyl of compound **18c** ($pMIC_{50}$ = 6.5) led to more than a 10 fold loss. If adding a fluorine atom on carbon 3 of the pyridine ring has very little effect when comparing the 5-ethyl bearing analogues **18l** and **18m** ($pMIC_{50}$ both of 7.1), a two fold loss was seen in comparison with the 5-cyclopropyl pair **8q** and **18d** ($pMIC_{50}$ = 9 and 8.6). On the other hand, as for the pair of analogues **6j** and **6k**, a fluorine on the same position is improving the antiviral effect when comparing the activity of the 5-bromo derivatives **18f** and **18g** ($pMIC_{50}$ = 6.3 and 6.9). Attempts to introduce various polar groups on carbon 5 of the pyridine ring such as the one seen in compound **18i-k** did not improve the antiviral effect and the two fluorine atoms of compound **18n** ($pMIC_{50}$ = 7.1) had no effect in comparison with the 5-ethyl analogue **18l** ($pMIC_{50}$ = 7.1). Only relatively small losses were observed for the bis-substitued derivatives **18p-s** featuring a cyclopropyl group. Interestingly, the influence of the methoxy moiety of compound **18p** ($pMIC_{50}$ = 7.5) is comparable to the dimethylaminated derivative **18q** ($pMIC_{50}$ = 7.5) whereas the hydroxyl-bearing analogue **18o** ($pMIC_{50}$ = 8.1) displayed a relative stronger activity. Somehow unexpectedly, the larger benzyloxy group of compound **18r** ($pMIC_{50}$ = 7) only caused a relatively small loss of antiviral effect. In any case, none of the analogues described in Table 3 displayed an antiviral effect better than the nanomolar level of compound **8q**.

Table 3. Preparation and Antiviral Effect of Compounds 18a-s.



compd	R3	R5	%	pMIC$_{50}$[ii]
18a	H	H	66	< 5.0
18b	H	Me	34	7.6
18c	H	CF_3	64	6.5
18d	F	*c*-Pr	46	8.6
18e	CN	*c*-Pr	96	8.1
18f	H	Br	79	6.3
18g	F	Br	73	6.9
18h	Me	Br	84	5.9
18i	H	OMe	64[iii]	7.3
18j	H	$COCH_3$	52	6.6
18k	H	$COHMe_2$	68	6.7
18l	H	Et	49	7.1
18m	F	Et	34	7.1
18n	H	CF_2CH_3	12	7.1
18o	F	*n*-Pr	30[iv]	6.7
18p	MeO	*c*-Pr	70[v]	7.5
18q	NMe_2	*c*-Pr	62[v]	7.5
18r	BnO	*c*-Pr	29[v]	7.0
18s	HO	*c*-Pr	72[vi]	8.1

i: Cs_2CO_3, DMF/MeCN, microwave, 130-180 °C.
ii: -log(MIC$_{50}$), MIC$_{50}$ in mol/L, standard deviation < 2%.
iii: Using 2-bromo-5-methoxypyridine and a copper catalyst, see text and Experimental section
iv: By catalytic reduction of **18d**.
v: From **18d**, see text and Experimental section.
vi: Reduction of **18r**, see text and Experimental section.

As depicted in Figure 2 and fully described in the Experimental section, from the 2,6-difluorophenoxy pyrazole **7q**, some other possible azines-bearing compounds such as 3-pyridyl, 5-pyrimidyl, the 2-pyrazinyl and the 1,2,4-triazine derivatives were also prepared. The 3-pyridyl bearing compounds **19a-c** were made by the Taillefer-Cristau[21] copper catalyzed N-arylation of **7q** with the commercially available 5-bromo-2-methyl, 5-bromo-2-ethyl and 5-bromo-2-methoxypyridines. The 5-pyrimidyl derivative **20a** was also made with

the copper catalyzed reaction between **7q** and 5-bromo-2-tert-butylpyrimidine. For the preparation of the 5-cyclopropyl analogue **20b** we had recourse to the N-arylation of compound **7q** with a small sample of 2-cyclopropylpyrimidin-5-ylboronic acid using Lam and Chan reaction conditions.[26] The N-arylation of 2,6-difluorophenoxy pyrazole **7q** with 2,5-dibromopyrazine led to the 5-bromopyrazine analogue **21a**. Similarly, from 2-chloro-5-(trifluoromethyl)pyrazine, the 5-trifluoromethyl analogue **21b** was obtained. The methoxy-bearing analogue **21c** was then made from **21a** by displacement of the bromine atom with methanol under basic conditions. As described in the Experimental section, the preparation of 2-bromo-5-cyclopropylpyrazine allowed the synthesis of the cyclopropyl-bearing analogue **21d** by N-arylation. In similar ways, the pyridazine-bearing analogues **10q** and **22a-b** were prepared from the corresponding chloropyridazines. The methoxy or ethoxy-bearing analogues **22c-d** were made by displacement of the chlorine atom of compound **22b** with the corresponding alcohols since an N-arylation trials using 3-chloro-6-methoxypyridazine led to extensive side reactions; including, as seen by LC/MS, a methylation of compound **7q**. The 1,2,4-triazine-bearing analogue **23** was prepared in a modest 10 % yield by the N-arylation of compound **7q** with 6-ethyl-3-(methylthio)-1,2,4-triazin-5-ol (preparation given) at 200 °C. Finally, as fully described in the Experimental section we also prepared the N-ethyl imidazole-bearing analogs **24** by the copper catalyzed N-arylation of compound **7q** with 1-ethyl-4-iodo-1*H*-imidazole. In view of the antiviral effect of the azine-bearing analogues **8q**, **10q**, **19b**, **21d**, one fact clearly stands out. As for the 2-pyrimidyl analogues previously studied, an ethyl or a cyclopropyl group *para* to the pyrazole ring often provides a low nanomolar antiviral effect. However, this is not true for the 2-cyclopropylpyrimidine derivative **20b** ($pMIC_{50}$ = 6.8) or the triazine **23** ($pMIC_{50}$ = 7.6) which is in this case featuring an additional hydroxyl group. Attempt to replace such alkyl groups by side chains of similar size but featuring more polar groups mostly failed as seen for the 2-methoxypyridine

derivative **19c** ($pMIC_{50}$ = 6.0), the 2-methoxypyrazine **21c** ($pMIC_{50}$ = 6.1) or the 3-methoxypyridazine **22c** ($pMIC_{50}$ = 7.1). The same trend was observed for the halogen-bearing analogues **21a-b** ($pMIC_{50}$ = 5.5 and 5.3) or **22b** ($pMIC_{50}$ = 6.8). Finally, the relatively low antiviral effect of the N-ethylimidazole derivative **23** may be another example of the trend which points at a detrimental effect of polar atoms (a nitrogen in this case) in the vicinity of this alkyl side chain.

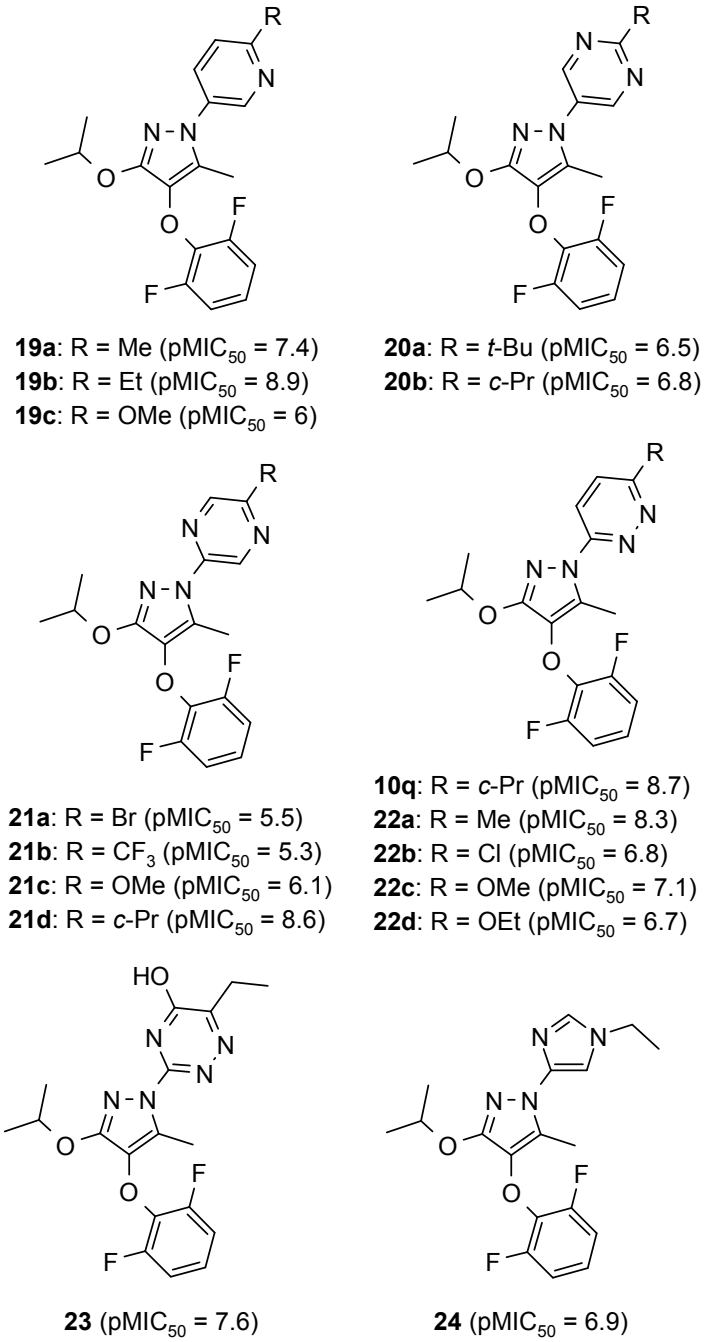


Figure 2. Structure and Antiviral Effect of Compounds **10q** and **19-24**.

The elucidation[1] of the biochemical target of our series has led us to publish a survey of all the reported inhibitors of DHODH along with their uses.[27] This review pointed out that teriflunomide (**25**) depicted in Figure 3, is the only human DHODH inhibitor used in

medicine against autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. Interestingly, in our cellular assay, teriflunomide (**25**) displayed an antiviral effect with an MIC_{50} of 5 μM which is reflected in the previously reported IC_{50} of 1 μM on recombinant human DHODH.[28,29] This relatively modest effect of teriflunomide (**25**) on the enzyme had actually triggered the search and the discovery of some off-target inhibitions in the past.[30-32] This value can also be compared to the enzymatic IC_{50} of 10 nM reported for brequinar (**26**),[29] a stronger inhibitor of DHODH which underwent disappointing phase II trials against solid tumors.[33-37]

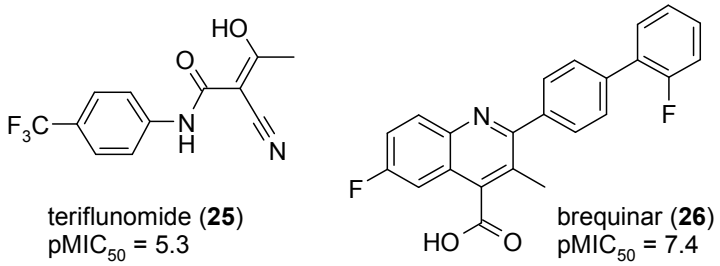


Figure 3. Structure and antiviral effect[1] of teriflunomide (**25**) and brequinar (**26**).

In order to assess the potential of our series in comparison with these compounds we undertook an array of biological assays using compound **18d**. *In cellulo*, as depicted in Figure 4, we could point out that compound **18d** is affecting pyrimidine nucleoside biosynthesis. Indeed, while adding **18d** at concentration varying from 4 to 100 nM blocked the measles virus replication in cells, the addition of the pyrimidine-containing nucleoside uridine at 10 μg/mL (Figure 4A) restored its replication. On the other hand, the addition of the purine-containing nucleoside guanosine at 10 μg/mL did not restore this (Figure 4B). Moreover, a restored virus replication was seen with the addition of orotic acid at 3 mM (Figure 4C) while, as seen in Figure 4D, dihydroorotic acid at 3 mM had no such effect. These last results thus narrowed down the biochemical target of compound **18d** to DHODH. Accordingly as

reported,[1] we produced recombinant human DHODH and compound **18d** was indeed found to be an inhibitor of this enzyme with an IC_{50} of 25 ± 5 nM.

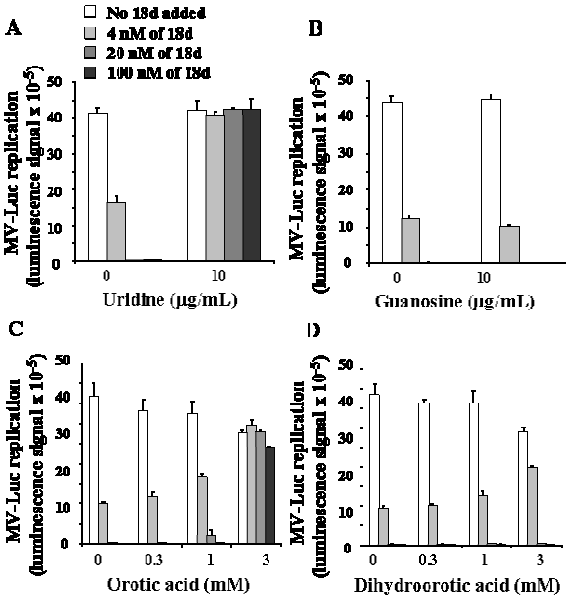


Figure 4. Compound **18d** is an inhibitor of pyrimidine biosynthesis pathway. HEK-293T cells were infected with recombinant MV strain expressing luciferase (multiplicity of infection = 0.1), incubated with DMSO alone or **18d** at 4, 20 or 100 nM, and culture medium was supplemented with uridine (A), guanosine (B), orotate (C) or dihydroorotate (D). After 24 h, luciferase expression was determined. Experiment was performed in triplicate, and data represent means ± SD.

By using a metabolite analysis protocol,[38] the HEK-293 T cells content in adenosine triphosphate (ATP), guanosine triphosphate (GTP), cytidine triphosphate (CTP) and uridine triphosphate (UTP) treated for 24 h with various concentration of compound **18d** could be determined. As seen in Table 4, intracellular concentrations of uridine and cytidine collapsed in cells treated with **18d**, whereas purine nucleotides concentrations were slightly increased likely as a consequence of the control loops connecting purine and pyrimidine metabolic

pathways. This strongly demonstrates in cell cultures the inhibition of *de novo* pyrimidine biosynthesis by **18d**.

Table 4. Normalized Cellular Nucleotides Content (%) in the Presence of Compound 18d at 0.016, 0.8, 4, 20 and 100 nM.

	DMSO	0.016	0.8	4	20	100
ATP	100 ± 13	65 ± 5	118 ± 20	115 ± 13	213 ± 18	110 ± 9
GTP	100 ± 6	68 ± 8	116 ± 34	115 ± 9	246 ± 15	118 ± 5
CTP	100 ± 13	66 ± 3	27 ± 3	5 ± 2	4 ± 0	4 ± 1
UTP	100 ± 8	64 ± 7	41 ± 2	26 ± 2	5 ± 1	7 ± 1

We recently reported that the inhibition of pyrimidine biosynthesis amplifies cellular response to pathogen-associated molecular patterns such as exogenous RNA molecules.[17] When transfecting cells with small synthetic RNA molecules (ssRNA) that mimic viral RNA genomes or transcripts, activation of the interferon-stimulated response element (ISRE) that drives innate immunity genes was enhanced by DHODH inhibition. As depicted in Figure 5, we thus monitored that compound **18d** increased the expression of an ISRE-luciferase reporter gene when transfecting cells with ssRNA molecules. This adds to the panel of cellular assays that support the inhibition of pyrimidine biosynthesis by compound **18d**.

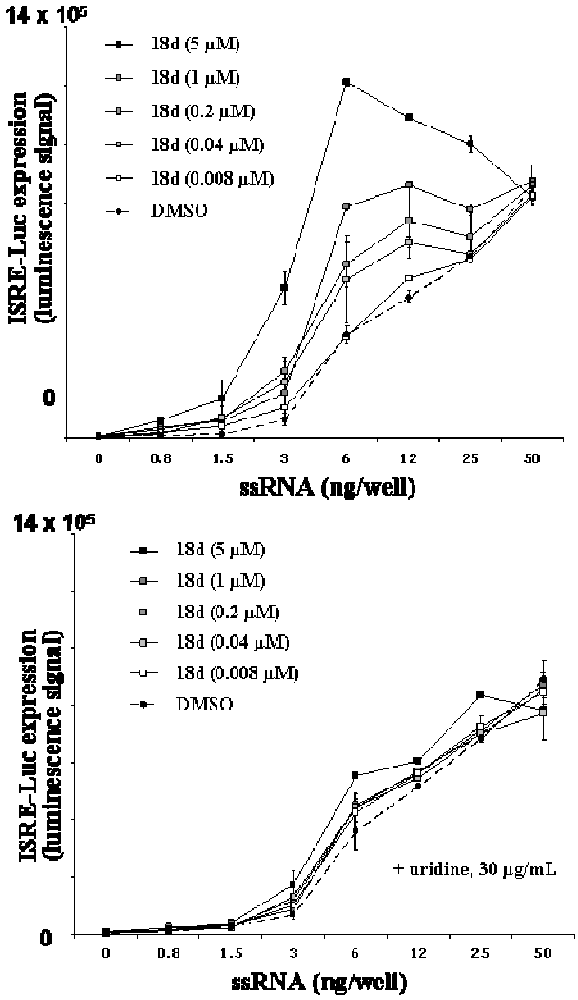


Figure 5. Compound **18d** amplifies cellular response to ssRNA molecules. **(Top)** HEK-293 T cells with the ISRE-luciferase reporter gene (STING-37 cells) were transfected with increasing doses of synthetic 5'-triphosphate RNA molecules (ssRNA), and incubated in the presence of compound **18d** or DMSO alone in 96-well cultures plates. After 24 h, luciferase expression was determined. **(Bottom)** Same experiment was performed in the presence of uridine at 30 µg/mL. Both experiments were performed in duplicate, and the data represents means ± SD.

Aside from their antiviral effect, pyrimidine biosynthesis inhibitors are also well known for blocking the proliferation of lymphocytes, and this probably accounts for their

immunosuppressive property *in vivo*.[39] Accordingly, we also determined the effect of compound **18d** on the growth of Jurkat T lymphocyte cell line, which has been demonstrated to be sensitive to DHODH inhibitors.[40,41] As shown in Figure 6, compound **18d** strongly inhibited Jurkat cells proliferation (IC_{50}= 0.02 μM), and its level of inhibition compared favorably with brequinar (IC_{50} = 0.2 μM) or teriflunomide (IC_{50} close to 60 μM, data not shown).

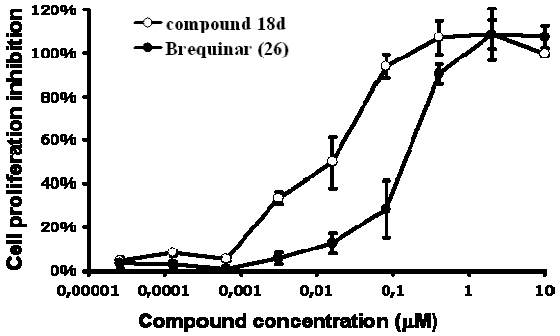


Figure 6. Inhibition (%) of Jurkat cells proliferation by compound **18d** and brequinar (**26**). Jurkat cells were incubated with increasing doses of **18d** or brequinar. As a control, cells were treated with DMSO alone. At t = 0 and after 72 h of culture, the number of living cells was determined using the CellTiter-Glo reagent. The inhibition of cellular proliferation is expressed as a percentage relative to DMSO-treated control wells. The results presented correspond to the mean ± SD of two independent experiments.

Also of much interest is the recent demonstration that *Plasmodium falciparum* DHODH is a valid target for the treatment of Malaria[42-46] and that a dual inhibition of human and *P. falciparum* DHODH was noticed for some series.[47-50] Accordingly, we screened all these antiviral compounds for a potential inhibition of *P. falciparum* growth. No growth inhibition was seen in a cellular assay at the concentration of 8.66 μg/mL (data not shown) for all the compounds aside from a modest effect for the pyridazine-bearing analogues **10q** and **22a**

(IC_{50} of 0.33 and 0.47 μM). Of course, these values led us to prepare many more pyridazine-bearing analogues, including compound **10b-p**, but all of them turned out to be at least an order of magnitude less effective on the parasite growth. Just in case, compound **10q** and **22a** were also assayed for their eventual inhibition of recombinant *P. falciparum* DHODH but they turned out to be completely devoid of effect on this biochemical assay.

In conclusion, along with our previous report,[1] this study made good use of the alkoxypyrazole chemistry we previously reported,[2-11] which somehow cleared a sort of "chemical blind spot" existing in pyrazole chemistry. The ensuing screenings of the resulting new chemical entities led us to extensively explore the structure-activity relationship of a new series of human DHODH inhibitors. Of note is a cellular antiviral assay which greatly simplified the evaluation of the compounds prepared and probably filtered out analogues of low cell membrane permeability. Concerning the potential of this series of inhibitors against immune diseases, the current success of teriflunomide (**25**)[51,52] has led to renewed interest in the search for better inhibitors of human DHODH. Quite a few strong acid-bearing human DHODH inhibitors have thus emerged and are currently at various stage of clinical development for the treatments of autoimmune diseases or graft rejection.[41,53-61] Since all these compounds, as well as brequinar (**26**), are featuring a carboxylic acid function, we are currently working on the selection of compounds displaying optimal preclinical properties in order to secure a proof of effect on an animal model of autoimmune disease. This endeavor is based on the reasonable assumption that our carboxylic acid-free series of inhibitors could display a different and beneficial pharmacological profile in comparison with the inhibitors currently in preclinical or clinical studies. However, so far our best inhibitors can be only considered as tools as a too short microsomal stability has been a recurrent feature for this series. Indeed, low half life values were observed for compounds such as **8k** ($t_{1/2}$ = 4 mn) or **8q** ($t_{1/2}$ = 6 mn) on human microsomes and only modest improvements were seen for the

"fluorine-protected" compound **18d** ($t_{1/2}$ = 27-41 mn), the "hydroxy-protected" compound **18s** ($t_{1/2}$ = 38 mn) or the less active analogues **22c** ($t_{1/2}$ = 22 mn) and **18g** ($t_{1/2}$ = 60 mn). Related to this aspect is a report mentioning similar difficulties for another type of N-arylated pyrazoles.[62] Accordingly, additional work will be required to improve this and the X-ray based determination of the binding mode of this series of inhibitors to human DHODH could be very useful in this regard. Finally, these results are probably an illustration of the interest of designing whole cell/phenotypic assays of sufficient sensitivity (a bioluminescent virus in the present case).[12] This led us to detect an unexpected biological effect and provided a simple biological mean not only to undertake further structure-activity study but also to find the mode of action of this series of compounds.

Experimental section

Measles Virus Inhibition Assay. HEK-293T cells (ATCC) were maintained in Dulbecco's modified Eagle's medium (DMEM; Gibco-Invitrogen) containing 10% fetal calf serum (FCS), penicillin, and streptomycin at 37°C and 5% CO_2. Antiviral activity of compounds was determined using a recombinant vaccine strain of measles virus expressing firefly luciferase (rMV2/Luc) from an additional transcription unit.[20] To determine the MIC_{50}, HEK-293T cells were infected with rMV2/Luc (MOI = 0.1), and incubated in 96-well culture plates at $3x10^{+4}$ cells/well with increasing concentrations of compounds or DMSO alone. After 24 h, luciferase expression was determined. The MIC_{50} corresponds to the concentration of a compound inhibiting luciferase activity by 50%.

***P. falciparum* Growth Assay.** Compounds were screened against *P. falciparum* 3D7 strain parasites with a starting parasitemia of 0.8% at 2% hematocrit in 96-well plates. Compound concentrations were 8.66 μg/mL final in the assay. Parasite growth and proliferation was measured using SYBR Green I.[63]

***P. falciparum* DHODHs.** This enzyme was expressed as recombinant proteins in *E. coli* and purified as previously described.[44,64] Steady-state kinetic analysis was performed using the 2,5-dichloroindophenol (DCIP)-based spectrophotometric method as described.[44] Enzyme and substrate concentrations were: DHODH (E = 5-10nM), substrates (0.2mM L-dihydroorotate and 0.02mM CoQd). The 100 x compound stock solutions were made in DMSO covering a 3-fold dilution series such that final concentrations in the assay for inhibition ranged from 0.001 – 100 μM.

Metabolite Analyses. HEK-293T cells were plated in 6-well plates (10^6 cells per well). One day later, culture medium was supplemented with increasing doses of compound **18d** or DMSO alone. After an additional 24 h of culture, cells were harvested, carefully counted and monitored for viability by trypan blue exclusion. Cellular nucleotides were quantified as previously described.[17]

ISRE-Luciferase Reporter Assay. STING-37 cell line was previously described, and corresponds to HEK-293 T cells that express luciferase under control of five interferon-stimulated response elements (ISRE).[17] Cells were transfected with increasing amounts of ssRNA molecules using JetPrime PEI reagents (Polyplus transfection), and dispensed in 96-well plates at 35,000 cells/well in 100 μl of Dulbecco's modified Eagle's medium (DMEM; Gibco-Invitrogen) containing 10% fetal calf serum (FCS), penicillin, and streptomycin. DMSO or compound **18d** was added to culture medium and after mixing, cells were cultured for 24 h at 37°C and 5% CO_2. Finally, firefly luciferase activity was determined using the Bright-Glo reagent following manufacturer's recommendations (Promega).

Inhibition of Jurkat Cells Proliferation. Jurkat cells were cultured in at $5x10^4$ cells per well in flat-bottom 96-well culture dishes. Cells were maintained at 37°C and 5% CO_2 in RPMI (Gibco-Invitrogen) containing 10% fetal calf serum (FCS), pyruvate sodium, non-essential amino acids, penicillin, and streptomycin. Number of living cells was determined by

quantification of adenosine triphosphate (ATP) in culture wells using the CellTiter-Glo Assay (Promega) following manufacturer's recommendations. This luciferase-based assay evaluates by ATP quantification the number of metabolically active cells in culture wells.

Human microsome stability. The microsomal stability assessments were subcontracted to Oroxcell, Romainville, France.

Chemistry. A Biotage initiator 2 microwave oven was used for reactions mentioning such heating method. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, respectively. Shifts (δ) are given in ppm with respect to the TMS signal and coupling constants (J) are given in Hertz. Column chromatography were performed either on Merck silica gel 60 (0.035 - 0.070 mm) or neutral alumina containing 1.5 % of added water using a solvent pump and an automated collecting system driven by a UV detector set to 254 nm unless required otherwise. Sample deposition was carried out by adsorption of the mixture to be purified on a small amount of the solid phase followed by its deposition of the top of the column. The low resolution mass spectra were obtained on an Agilent 1100 series LC/MSD system using an atmospheric electrospray ionization system and the high resolution mass spectra (HRMS) were obtained using a Waters Micromass Q-Tof with an electrospray ion source. Unless stated otherwise, a purity of at least 95 % was obtained for all the compounds by means of chromatography, recrystallisation or distillation and this level of purity was established by TLC, LC/MS and NMR spectroscopy

Preparations of all the commercially unavailable halogenoazines used in this work.

5-Cyclopropyl-2-fluoropyridine (5q). Under an inert atmosphere, 5-bromo-2-fluoropyridine (**5j**) (17 g, 0.096 mol) and cesium carbonate (114 g, 0.35 mol) were dispersed in a 95/5 vv mixture of toluene and water (500 mL). This was degassed by gently bubbling argon in the reaction and cyclopropyl boronic acid (10 g, 0.11 mol) and [1,1'-bis(diphenyl phosphino)ferrocene] dichloropalladium complexed with dichloromethane (1.45 g, 0.0018

mol) was added. The flask was heated to reflux for 40 minutes, upon cooling the suspension was diluted in ethyl acetate, the filtered organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a distillation at ambient pressure ($E_{760\ mm}$ = 206 °C) to give a volatile oil (8.06 g, 62 %). A lesser pure fraction (about 7 %) was also collected. ^{1}H ($CDCl_3$): 0.68 (m, 2H); 1.02 (m, 2H); 1.91 (m, 1H); 6.81 (m, 1H); 7.42 (m, 1H); 8.02 (m, 1H). ^{13}C ($CDCl_3$): 8.6; 12.2; 108.9 (38 Hz); 136.7 (4 Hz); 138.1 (7 Hz); 145.5 (14 Hz); 162.2 (236 Hz). HRMS: too volatile for analysis.

5-Cyclopropyl-2,3-difluoropyridine (5r). By using the procedure described for the preparation of 5-cyclopropyl-2-fluoropyridine (**5q**), this compound was obtained from 5-bromo-2,3-difluoropyrimidine (**5k**) in 63 % yield, as a volatile oil, after a chromatography over silica gel (cyclohexane – dichloromethane 2/1). ^{1}H ($CDCl_3$): 0.71 (m, 2H); 1.06 (m, 2H); 1.94 (m, 1H); 7.18 (m, 1H); 7.78 (m, 1H). ^{13}C ($CDCl_3$): 9.0; 12.2; 123.5 (3 and 15 Hz); 139.3; 139.4 (5 and 13 Hz); 145.4 (29 and 260 Hz); 150.4 (15 and 236 Hz). HRMS: too volatile for analysis.

2-Chloro-5-cyclopropylnicotinonitrile (5s). By using the procedure described for the preparation of 5-cyclopropyl-2-fluoropyridine (**5q**), this compound was obtained from 5-bromo-2-chloronicotinonitrile in 53 % yield, as a solid, after a chromatography over silica gel (cyclohexane – dichloromethane 1/1). ^{1}H ($CDCl_3$): 0.79 (m, 2H); 1.17 (m, 2H); 1.97 (m, 1H); 7.59 (d, 1H, J = 2.5); 8.38 (d, 1H, J = 2.5). ^{13}C ($CDCl_3$): 9.8; 12.3; 110.2; 114.8; 139.1; 139.3; 149.4. 151.3. HRMS calcd for $C_9H_7BrN_2$ + H: 222.9871. Found: 222.9840.

2-(6-Fluoropyridin-3-yl)propan-2-ol (5t). Under an inert atmosphere, 5-bromo-2-fluoropyridine (**5j**) (3.12 g, 17.7 mmol) was dissolved in dry ether (100 mL) and the solution cooled to -78 °C. Butyl lithium (9.3 mL, 18.6 mmol, 2N in cyclohexane) was added. The resulting precipitate was stirred at -78 °C for 15 mn, acetone (0.4 mL, 90 mmol, dried over 4

Å molecular sieves) was added and the reaction was allowed to warm back to room temperature for 30 mn. This was diluted with a saturated solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed with a saturated solution of ammonium chloride, brine, dried over magnesium sulfate and concentrated to dryness. The residue was further purified by a chromatography over silica gel (dichloromethane – ethanol 98.5/1.5) to yield compound **5t** as an oil (0.57 g, 20 %). ^{1}H ($CDCl_3$, slight differences with the reported one[65]): 1.63 (s, 6H); 1.89 (s, 1H); 6.91 (dd, 1H, *J* = 2.8 and 8.4); 7.94 (m, 1H); 8.33 (m, 1H). ^{13}C ($CDCl_3$): 31.8; 71.1; 108.8 (37 Hz); 138.0 (8 Hz); 142.0 (4 Hz); 144.0 (14 Hz); 162.6 (238 Hz). HRMS calcd for $C_8H_{10}FNO$ + H: 156.0825. Found: 156.0791.

2-Fluoro-5-ethylpyridine (17l). Under an inert atmosphere, 5-bromo-2-fluoropyridine (**5j**) (5.35 g, 30.39 mmol), potassium carbonate (16.8 g, 121.59 mmol) were dissolved in dry dimethylformamide (75 mL, dried over 4 Å molecular sieves). Oxygen was removed from this solution by a slow stream of argon and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium complexed with dichloromethane (0.62 g, 1.52 mmol) was added, followed by a 1M solution of triethylborane (40 mL, 40.4 mmol) which was slowly added with a syringe. This darkening suspension was heated at 85 °C for 4 h using an oil bath. The resulting black suspension was diluted in diethyl ether and water, the organic layer was washed with water 5 times, brine, dried over magnesium sulfate and cautiously concentrated to dryness to take into account the volatility of the reaction product. The residue was purified by a chromatography over silica gel (cyclohexane – dichloromethane from 2/3 to 1/4) to yield the 5-ethyl derivative **17l** as a volatile oil (1.52 g, 40 %). ^{1}H ($CDCl_3$): 1.25 (t, 3H, *J* = 7.6); 2.65 (q, 2H, *J* = 7.6); 6.84 (dd, 1H, *J* = 3.0 and 8.4); 7.61 (m, 1H); 8.03 (m, 1H). ^{13}C ($CDCl_3$): 15.3; 25.1; 108.9 (37 Hz); 136.7 (4 Hz); 140.5 (8 Hz); 145.6 (14 Hz); 162.2 (236 Hz). HRMS: too volatile for analysis.

2,3-Difluoro-5-ethylpyridine (**17k**). By using the protocol described for the synthesis of 2-fluoro-5-ethylpyridine (**17l**), compound **17k** was obtained in 17 % yield from 5-bromo-2,3-difluoropyridine (**5q**) as a volatile oil after a chromatography over silica gel (cyclohexane – dichloromethane from 1/1 to 1/4). ^{1}H ($CDCl_3$): 1.27 (t, 3H, *J* = 7.6); 2.68 (q, 2H, *J* = 7.6); 7.40 (m, 1H); 7.80 (m, 1H). ^{13}C ($CDCl_3$): 15.1; 25.0; 125.9 (3 and 14 Hz); 138.9 (4 Hz); 140.3 (5 and 12 Hz); 145.2 (28 and 260 Hz); 150.4 (14 and 235 Hz). HRMS: too volatile for analysis. Another fraction of this chromatography led, after a recrystallisation in cyclohexane, to 5,5',6,6'-tetrafluoro-3,3'-bipyridine in a 25 % yield as fine needles. ^{1}H ($CDCl_3$): 7.75 (m, 2H); 8.18 (m, 2H). ^{13}C ($CDCl_3$): 125.2 (4 and 16 Hz); 131.1 (5 Hz); 139.7 (6 and 13 Hz); 145.7 (29 and 264 Hz); 152.2 (14 and 242 Hz). HRMS: does not ionizes. Anal. Calcd for $C_{10}H_4F_4N_2$: C, 52.64; H, 1.77; N, 12.28. Found: C, 52.44; H, 1.84; N, 12.26.

2-Bromo-5-(1,1-difluoroethyl)pyridine (17n). In a closed teflon flask, 1-(6-bromopyridin-3-yl)ethanone (**5o**) (0.95 g, 4.75 mmol) and bis(2-methoxyethyl)aminosulfur trifluoride (3.6 g, 11.4 mmol) were stirred for seven days (as only a 78 % conversion was monitored by ^{1}HNMR, a longer reaction time may lead to an even better yield). This was diluted in water, solid calcium chloride was added and the solution was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to dryness (not for too long, this compound is volatile). The residue was purified by a chromatography over silica gel (cyclohexane –dichloromethane 1/1) to yield the difluorinated pyridine **17n** as a colorless and volatile oil (0.57 g, 54 %). ^{1}H ($CDCl_3$): 1.96 (t, 3H, *J* = 18); 7.57 (d, 1H, *J* = 8.3); 7.69 (dd, 1H, *J* = 2.3 and 8.3); 8.20 (m, 1H). ^{13}C ($CDCl_3$): 25.7 (29 Hz); 120.5 (240 Hz); 128.0; 133.2 (27 Hz); 135.0 (5 Hz); 143.7 (2 Hz); 146.9 (6 Hz). HRMS calcd for $C_7H_6BrF_2N$ + H: 221.9730. Found: 221.9667.

2-Bromo-5-cyclopropylpyrazine: Under an inert atmosphere, 2,5-dibromopyrazine (0.21 g, 0.88 mmol) and cesium carbonate (1.12 g, 3.43 mmol) were dispersed in a 95/5 vv mixture of

toluene and water (5 mL). Note: potassium carbonate works as well. This was degassed by gently bubbling argon in the reaction and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium complexed with dichloromethane (0.018 g, 0.022 mmol) and cyclopropyl boronic acid (0.098 g, 1. 14mmol) were added. The flask was heated to reflux for 30 minutes, upon cooling the suspension was diluted in ethyl acetate, the filtered organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to dryness. This was residue was purified by a chromatography over silica gel (cyclohexane – ethyl acetate 97/3 -> 9/1 to yield the 2-bromo-5-cyclopropylpyrazine (0.08 g, 45 %) as a solid. ^{1}H ($CDCl_3$): 1.09 (m, 4H); 2.03 (m, 1H); 8.26 (d, 1H, *J* = 1.4); 8.48 (d, 1H, *J* = 1.4). ^{13}C ($CDCl_3$): 10.6; 14.1; 136.8; 143.0; 146.5. 157.3. HRMS calcd for $C_7H_7BrN_2$ + H: 198.9871. Found: 198.9784.

3-Chloro-6-cyclopropylpyridazine (**9**). By using the same procedure used for the preparation of 2-bromo-5-cyclopropylpyrazine, this compound was obtained in 40 % yield as a solid (on a much larger scale), from 3,6-dichloropyridazine, by two consecutive chromatography processes over silica gel (dichloromethane – ethanol 99/1) and the second using only dichloromethane to yield the 2-bromo-5-cyclopropylpyrazine. ^{1}H ($CDCl_3$): 1.20 (m, 4H); 2.15 (m, 1H); 7.21 (d, 1H, *J* = 8.8); 7.35 (d, 1H, *J* = 8.8). ^{13}C ($CDCl_3$): 10.9; 15.4; 127.0; 127.6; 154.2; 164.0. HRMS calcd for $C_7H_7ClN_2$ + H: 155.0376. Found: 155.0354.

6-Ethyl-3-(methylthio)-1,2,4-triazin-5-ol: First step, preparation of 2-(2-carbamothioylhydrazono)butanoic acid: as previously described,[66] 2-oxObutyric acid (3.15 g, 0.0308 mol) and thiosemicarbazide (2.81 g, 0.0308 mol) were stirred in water (60 mL) at 70 °C for 10 minutes. This was left to cool and the precipitate was filtered washed with water and dried at 50 °C under vacuum to give the hydrazone (4.47 g, 82 %) as 4/17 mixture of isomers. ^{1}H NMR (DMSO-*d6*): (major isomer) 0.93 (t, 3H, *J* = 7.5); 2.65 (q, 2H, *J* = 7.5); 8.59 (s, 1H); 8.68 (s, 1H); 10.85 (s, 1H); (minor isomer) 1.08 (t, 3H, *J* = 7.4); 2.44 (q, 2H, *J* =

7.4); 8.01 (s, 1H); 8.65 (s, 1H); 12.15 (s, 1H). ^{13}C NMR (DMSO-*d6*) major isomer: 10.8; 18.7; 143.3; 164.8; 180.4, minor isomer: 11.6; 26.8; 139.0; 164.4; 179.1. Second step, preparation of 6-ethyl-3-mercapto-1,2,4-triazin-5-ol: as previously described,[66] the hydrazone (4.24 g, 0.0269 mol) and sodium carbonate (2.56 g, 0.0269 mol) were heated to reflux in water (300 mL) for 3 h. The solution was made acid with acetic acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to dryness to yield the 1,2,4-triazin-5-ol as a white powder (3.09 g, 86 %). ^{1}H NMR (DMSO-*d6*): 1.07 (t, 3H, *J* = 7.6); 2.50 (q, 2H, *J* = 7.6); 12.99 (s, 1H); 13.28 (s, 1H). ^{13}C NMR (DMSO-*d6*): 10.3; 23.0; 152.1; 153.5; 173.7. Third and last step, methylation of this compound: in water (30 mL) sodium hydroxide (1.25 g, 0.031 mol) was dissolved and after cooling, the 1,2,4-triazin-5-ol (2.46 g, 0.015 mol) was dissolved. Methyl iodide (1.07 mL, 0.017 mmol), diluted in and tetrahydrofuran (2 mL), was then slowly added. The solution was stirred at room temperature for 4 h; this was diluted with water, made acid with acetic acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated to dryness to yield the pure thioether as a white powder (2.28 g, 85 %). ^{1}H (DMSO-d_6): 1.07 (t, 3H, *J* = 7.6); 2.50 (q, 2H, *J* = 7.6); 12.99 (s, H); 13.28 (s, 1H). ^{13}C (DMSO-d_6): 10.5; 12.5; 23.6; 153.6; 160.7; 164.4. HRMS calcd for $C_6H_9N_3OS$ + H: 172.0545. Found: 172.0488.

1-Ethyl-4-iodo-1*H*-imidazole: Step 1: Under a moisture-protected atmosphere, a 50/50 mixture of 4,5-diiodo-1*H*-imidazole and 2,4,5-triiodo-1*H*-imidazole, obtained when iodinating imidazole using the described procedure,[67] ethyl iodide (2.14 g, 0.0137 mol) and potassium carbonate (3.97 g, 0.0286 mol) were stirred in dimethylformamide (50 ml, dried over 4A molecular sieve) for 22 h. This was diluted in water, extracted with ethyl acetate, the organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (dichloromethane –

ethanol 99/1 to 97/3) to give the 1-ethyl-4,5-diiodo-1*H*-imidazole (1.79 g, 37 % from imidazole). ^{1}H ($CDCl_3$): 1.43 (t, 3H, *J* = 7.3); 4.03 (q, 2H, *J* = 7.3); 7.64 (s, 1H). ^{13}C ($CDCl_3$): 16.1; 44.9; 81.8; 95.8, 140.2. *Note*: the 1-ethyl-2,4,5-triiodo-1*H*-imidazole also obtained in this step (1.90 g, 29 % from imidazole) can be selectively and completely reduced back to the 1-ethyl-4,5-diiodo-1*H*-imidazole by refluxing it with an excess of sodium sulfite in a 1/1 mixture of water and ethanol for 30 mn. Step 2: Under argon, 1-ethyl-4,5-diiodo-1*H*-imidazole (1.8 g, 0.0051 mol) was dissolved in dry tetrahydrofuran (20 mL). The solution was cooled to 0°C and ethyl magnesium (1.8 mL, 0.0054 mol, 3M solution in ether) was added. The resulting suspension was stirred for 30 minutes, quenched with an excess of ammonium chloride in water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (dichloromethane – ethanol 98/2) to give the 1-ethyl-4-iodo-1*H*-imidazole (0.78 g, 68 %) as an oil. ^{1}H ($CDCl_3$): 1.45 (t, 3H, *J* = 7.3); 3.98 (q, 2H, *J* = 7.3); 7.01 (d, 1H, *J* = 1.3); 7.38 (d, 1H, *J* = 1.3). ^{13}C ($CDCl_3$): 16.1; 42.2; 81.6; 124.0, 138.1.

N-arylation of 3-alkoxypyrazoles without copper catalyst, general method: In a reaction vial designed for microwave heating, the considered alkoxypyrazole (2 mmol), the considered halogenated heteroaryl (2.2 mmol) and cesium carbonate (2.8 mmol) were stirred in dimethylformamide or acetonitrile (3 mL) as specified. This was heated using a microwave at a temperature between 120 °C and 180 °C for the specified duration. The resulting suspension was diluted in water, extracted with ethyl acetate and the organic layer was washed with brine, dried over magnesium sulfate and concentrated to dryness. The residue was further purified as specified below.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-4-methylpyridine (6b). Obtained in 57 % yield as an oil using 2-fluoro-4-methylpyridine in acetonitrile at 180 °C for 2 h and a chromatography over silica gel (dichloromethane). ^{1}H NMR ($CDCl_3$): 1.41 (t, 3H, *J* = 7.0);

2.41 (s, 3H); 2.56 (s, 3H); 3.75 (s, 2H); 4.36 (q, 2H, *J* = 7.0); 6.90 (m, 1H); 7.18 (m, 1H); 7.28 (m, 4H); 7.59 (m, 1H); 8.22 (m, 1H). ^{13}C NMR ($CDCl_3$): 13.2; 14.9; 21.2; 27.8; 64.2; 106.7; 115.6; 121.0; 125.7; 128.2; 128.3; 139.5; 141.0; 147.0; 149.3; 154.0; 162.3. HRMS calcd for $C_{19}H_{21}N_3O$ + H: 308.1763. Found: 308.1718.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-3-methylpyridine (6c). Obtained in 39 % yield as an oil using 2-fluoro-3-methylpyridine in acetonitrile at 180 °C for 2 h and a chromatography over silica gel (dichloromethane). ^{1}H NMR ($CDCl_3$): 1.41 (t, 3H, *J* = 7.0); 2.52 (s, 3H); 2.59 (s, 3H); 3.76 (s, 2H); 4.35 (q, 2H, *J* = 7.0); 6.92 (m, 1H); 7.19 (m, 1H); 7.28 (m, 4H); 7.59 (m, 2H). ^{13}C NMR ($CDCl_3$): 13.3; 14.9; 24.1; 27.8; 64.2; 106.6; 111.8; 118.9; 125.7; 128.2; 128.3; 138.2; 139.4; 141.1; 153.3; 156.4; 162.2. HRMS calcd for $C_{19}H_{21}N_3O$ + H: 308.1763. Found: 308.1747.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-6-methylpyridine (6d). Obtained in 39 % yield using 2-fluoro-6-methylpyridine in acetonitrile at 180 °C for 2 h and a chromatography over silica gel (dichloromethane) as a wax. ^{1}H NMR ($CDCl_3$): 1.38 (t, 3H, *J* = 7.0); 2.11 (s, 3H); 2.30 (s, 3H); 3.77 (s, 2H); 4.29 (q, 2H, *J* = 7.0); 7.19 (m, 2H); 7.28 (m, 4H); 7.66 (m, 1H); 8.38 (m, 1H). ^{13}C NMR ($CDCl_3$): 10.6; 14.9; 17.9; 28.0; 64.2; 103.9; 123.1; 125.7; 128.2; 128.3; 130.7; 138.8; 140.3; 141.1; 146.1; 151.3; 161.9. HRMS calcd for $C_{19}H_{21}N_3O$ + H: 308.1763. Found: 308.1772.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-3-fluoropyridine (6e). Obtained in 74 % yield as an oil, using 2,3-difluoropyridine in acetonitrile at 180 °C for 2 h and a chromatography over silica gel (dichloromethane – ethanol from 100/0 to 98/2). ^{1}H NMR ($CDCl_3$): 1.40 (t, 3H, *J* = 7.1); 2.20 (s, 3H); 3.77 (s, 2H); 4.35 (q, 2H, *J* = 7.1); 7.19 (m, 1H); 7.28 (m, 5H); 7.57 (m, 1H); 8.37 (m, 1H). ^{13}C NMR ($CDCl_3$): 10.7; 14.9; 27.9; 64.3; 105.6; 123.7; 125.5 (J = 18 Hz); 125.8; 128.3; 128.32; 139.5; 140.7; 141.1; 144.1; 152.8 (J = 273 Hz); 163.1. HRMS calcd for $C_{18}H_{18}FN_3O$ + H: 312.1512. Found: 312.1503.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-6-fluoropyridine (6f). Obtained in 62 % yield as a solid, using 2,6-difluoropyridine in acetonitrile at 180 °C for 2 h and a chromatography over silica gel (cyclohexane – dichloromethane 2/1). ^{1}H NMR ($CDCl_3$): 1.41 (t, 3H, *J* = 7.0); 2.62 (s, 3H); 3.74 (s, 2H); 4.35 (q, 2H, *J* = 7.0); 6.64 (m, 1H); 7.20 (m, 1H); 7.27 (m, 4H); 7.66 (m, 1H); 7.80 (m, 1H). ^{13}C NMR ($CDCl_3$): 13.5; 14.8; 27.7; 64.2; 103.4 (J = 36 Hz); 107.9; 110.6; 125.9; 128.2; 128.3; 104.0; 140.6; 142.3; 152.3; 161.5 (J = 237 Hz); 162.7. HRMS calcd for $C_{18}H_{18}FN_3O$ + H: 312.1512. Found: 312.1502.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-(trifluoromethyl)pyridine (6g). Obtained in 47 % yield as a white powder, using 2-chloro-5-(trifluoromethyl)pyridine in acetonitrile at 180 °C for 2 h and a chromatography over silica gel (cyclohexane – dichloromethane 4/1 to 2/1). ^{1}H NMR ($CDCl_3$): 1.43 (t, 3H, *J* = 7.1); 2.65 (s, 3H); 3.75 (s, 2H); 4.37 (q, 2H, *J* = 7.1); 7.22 (m, 1H); 7.28 (m, 4H); 7.93 (m, 2H); 8.61 (m, 1H). ^{13}C NMR ($CDCl_3$): 13.9; 14.8; 27.6; 64.3; 108.7; 113.6; 121.7 (J = 33 Hz); 123.9 (J = 271 Hz); 125.9; 128.2; 128.4; 135.0; 140.4; 140.5; 144.6; 156.2; 163.0. HRMS calcd for $C_{19}H_{18}F_3N_3O$ + H: 362.1480. Found: 362.1449.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-6-(trifluoromethyl)pyridine (6h). Obtained in 89 % yield as an oil, using 2-fluoro-6-(trifluoromethyl)pyridine in acetonitrile at 180 °C for 2 h and a chromatography over silica gel (cyclohexane – dichloromethane 5/1). ^{1}H NMR ($CDCl_3$): 1.42 (t, 3H, *J* = 7.1); 2.65 (s, 3H); 3.74 (s, 2H); 4.35 (q, 2H, *J* = 7.1); 7.19 (m, 5H); 7.39 (d, 1H, *J* = 8.4); 7.86 (t, 1H, *J* = 8.4); 8.03 (d, 1H, *J* = 8.4). ^{13}C NMR ($CDCl_3$): 8.9; 10.0; 22.9; 59.5; 103.6; 110.4; 116.6 (273 Hz); 121.1; 123.4; 123.6; 134.4; 134.7; 135.7; 135.9; 140.8 (36 Hz); 149.1; 158.0. HRMS calcd for $C_{19}H_{18}F_3N_3O$ + H: 362.1480. Found: 362.1457.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-chloropyridine (6i). Obtained in 40 % yield as a white powder using 2,5-dichloropyridine in acetonitrile at 180 °C for 2 h and a

chromatography over silica gel (cyclohexane – dichloromethane 4/1). ^{1}H NMR ($CDCl_3$): 1.42 (t, 3H, *J* = 7.1); 2.57 (s, 3H); 3.74 (s, 2H); 4.34 (q, 2H, *J* = 7.1); 7.19 (m, 1H); 7.27 (m, 4H); 7.68 (dd, 1H, *J* = 2.5 and 8.8); 7.76 (d, 1H, *J* = 8.8); 8.30 (d, 1H, *J* = 2.5). ^{13}C NMR ($CDCl_3$): 13.4; 14.8; 27.7; 64.2; 107.5; 115.5; 125.8; 126.9; 128.2; 128.3; 137.7; 139.7; 140.7; 145.7; 152.2; 162.5. HRMS calcd for $C_{18}H_{18}ClN_3O$ + H: 328.1217. Found: 328.1186.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-bromopyridine (6j). Obtained in 44 % yield as a solid using 5-bromo-2-fluoropyridine in dimethylformamide at 130 °C for 12 h and a chromatography over silica gel (cyclohexane/dichloromethane 2/1) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 1.41 (t, 3H, *J* = 7.0); 2.57 (s, 3H); 3.74 (s, 2H); 4.34 (q, 2H, *J* = 7.0); 7.19 (m, 1H); 7.28 (m, 4H); 7.71 (m, 1H); 7.81 (m, 1H); 8.38 (m, 1H). ^{13}C ($CDCl_3$): 13.4; 14.8; 27.7; 64.3; 107.6; 115.0; 116.0; 125.8; 128.2; 128.3; 139.7; 140.5; 140.7; 147.9; 152.6; 162.5. HRMS calcd for $C_{18}H_{18}BrN_3O$ + H: 372.0711. Found: 372.0684.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-bromo-3-fluoropyridine (6k). Obtained in a 33 % yield as an oil using 5-bromo-2,3-difluoropyridine in acetonitrile at 180 °C for 2 h and a chromatography over silica gel (cyclohexane/ethyl acetate 97/3). ^{1}H ($CDCl_3$): 1.40 (t, 3H, *J* = 7.1); 2.22 (s, 3H); 3.76 (s, 2H); 4.34 (q, 2H, *J* = 7.1); 7.20 (m, 1H); 7.28 (m, 4H); 7.74 (m, 1H); 8.40 (d, 1H, *J* = 2.0). ^{13}C ($CDCl_3$): 10.9; 14.8; 27.9; 64.3; 106.3; 117.1; 125.9; 128.3; 128.31; 128.5 (21 Hz); 139.6; 140.0; 140.5; 144.8; 151.9 (270 Hz); 163.2. HRMS calcd for $C_{18}H_{17}{}^{79}BrN_3FO$ + H: 390.0617. Found: 390.0621.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-bromo-3-methylpyridine (6l). Obtained in a 62 % yield as solid using 5-bromo-2-fluoro-3-methylpyridine in acetonitrile at 180 °C for 3 h and a chromatography over silica gel (cyclohexane/ethyl acetate from 98/2 to 97/3). ^{1}H ($CDCl_3$): 1.39 (t, 3H, *J* = 7.3); 2.15 (s, 3H); 2.33 (s, 3H); 3.76 (s, 2H); 4.29 (q, 2H, *J* = 7.3); 7.20 (m, 1H); 7.27 (m, 4H); 7.80 (d, 1H, *J* = 2.4); 8.41 (d, 1H, *J* = 2.4). ^{13}C ($CDCl_3$):

10.8; 14.9; 18.1; 27.9; 64.2; 104.6; 119.0; 125.8; 128.2; 128.3; 132.3; 139.0; 140.9; 142.6; 146.8; 150.0; 162.1. HRMS calcd for $C_{20}H_{20}{}^{79}BrN_3O$ + H: 386.0868. Found: 386.0817.

6-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)nicotinonitrile (6m). Obtained in 47 % yield as a solid using 6-chloronicotinonitrile in dimethylformamide at 150 °C for 30 min and a chromatography over silica gel (cyclohexane/dichloromethane 1/2). ^{1}H ($CDCl_3$): 1.44 (t, 3H, *J* = 7.0); 2.64 (s, 3H); 3.74 (s, 2H); 4.35 (q, 2H, *J* = 7.0); 7.25 (m, 5H); 7.93 (m, 2H); 8.60 (m, 1H). ^{13}C ($CDCl_3$): 14.1; 14.7; 27.6; 64.4; 103.9; 109.7; 113.6; 117.3; 126.0; 128.2; 128.4; 140.2; 140.6; 140.8; 151.1; 155.7; 163.4. HRMS calcd for $C_{19}H_{18}N_4O$ + H: 319.1559. Found: 319.1532.

Methyl 6-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)nicotinate (6n). Obtained in 19 % yield as a solid using methyl 6-chloronicotinate in dimethylformamide at 150 °C for 30 min and a chromatography over silica gel (cyclohexane/ethyl acetate from 95/5 to 85/15). ^{1}H ($CDCl_3$): 1.43 (t, 3H, *J* = 7.0); 2.65 (s, 3H); 3.74 (s, 2H); 3.95 (s, 3H); 4.36 (q, 2H, *J* = 7.0); 7.18 (m, 1H); 7.27 (m, 4H); 7.88 (m, 1H); 8.30 (m, 1H); 8.97 (m, 1H). ^{13}C ($CDCl_3$): 14.0; 14.8; 27.6; 52.2; 64.3; 108.7; 113.2; 121.2; 125.9; 128.2; 128.3; 139.0; 140.5; 140.6; 149.5; 156.5; 163.0; 165.8. HRMS calcd for $C_{20}H_{21}N_3O_3$ + H: 352.1661. Found: 352.1663.

1-(6-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)pyridin-3-yl)ethanone (6o). obtained in 15 % yield as a solid using methyl 1-(6-bromopyridin-3-yl)ethanone at 150 °C for 30 min in dimethylformamide and a chromatography over silica gel (cyclohexane/ethyl acetate 9/1). ^{1}H ($CDCl_3$): 1.42 (t, 3H, *J* = 7.1); 2.63 (s, 3H); 2.66 (s, 3H); 3.75 (s, 2H); 4.37 (q, 2H, *J* = 7.1); 7.19 (m, 1H); 7.27 (m, 4H); 7.89 (m, 1H); 8.26 (m, 1H); 8.93 (m, 1H). ^{13}C ($CDCl_3$): 14.0; 14.8; 26.5; 27.7; 64.3; 109.0; 113.5; 125.9; 128.0; 128.2; 128.3; 137.5; 140.5; 140.6; 148.8; 156.5; 163.1; 195.7. HRMS calcd for $C_{20}H_{21}N_3O_2$ + H: 336.1712. Found: 336.1638.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-cyclopropyl-3-fluoropyridine (6r). Obtained in 17 % yield as an oil using 5-cyclopropyl-2,3-difluoropyridine at 140 °C for 4 h in

acetonitrile after a chromatography over silica gel (cyclohexane/ethyl acetate from 97/3 to 4/1) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.76 (m, 2H); 1.11 (m, 2H); 1.38 (t, 3H, *J* = 7.2); 1.98 (m, 1H); 2.14 (s, 3H); 3.76 (s, 2H); 4.33 (q, 2H, *J* = 7.2); 7.18 (m, 2H); 7.29 (m, 4H); 8.18 (d, 1H, *J* = 1.7). ^{13}C ($CDCl_3$): 9.6; 10.5 (2 Hz); 12.6; 14.9; 27.9; 64.9; 105.0; 121.8 (19 Hz); 125.7; 128.2; 128.3; 138.3 (11 Hz); 139.4; 140.8; 141.6 (6 Hz); 142.4 (5 Hz); 153.0 (260 Hz); 162.9. HRMS calcd for $C_{21}H_{22}FN_3O$ + H: 352.1825. Found: 352.1827.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-cyclopropylnicotinonitrile (6s). Obtained in 18 % yield as a solid using 2-chloro-5-cyclopropylnicotinonitrile at 160 °C for 4 h in acetonitrile after a chromatography over silica gel (cyclohexane/dichloromethane from 2/1 to 0/1). ^{1}H ($CDCl_3$): 0.76 (m, 2H); 1.11 (m, 2H); 1.43 (t, 3H, *J* = 7.2); 1.92 (m, 1H); 2.47 (s, 3H); 3.74 (s, 2H); 4.41 (q, 2H, *J* = 7.2); 7.18 (m, 1H); 7.27 (m, 4H); 7.67 (d, 1H, *J* = 2.5); 8.34 (d, 1H, *J* = 2.5). ^{13}C ($CDCl_3$): 9.1; 12.2; 12.6; 14.8; 27.7; 64.9; 101.3; 108.1; 116.8; 125.9; 128.2; 128.3; 135.7; 139.5; 140.4; 140.9; 149.3; 150.7; 162.4. HRMS calcd for $C_{22}H_{22}N_4O$ + H: 359.1872. Found: 359.1841.

2-(6-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)pyridin-3-yl)propan-2-ol (6t). Obtained in 67 % yield as an oil, using 2-(6-fluoropyridin-3-yl)propan-2-ol (**5t**) at 180 °C for 6 h in acetonitrile and a chromatography over silica gel (cyclohexane/ethyl acetate 4/1). ^{1}H ($CDCl_3$): 1.41 (t, 3H, *J* = 7.1); 1.60 (s, 6H); 2.12 (s, 1H); 2.57 (s, 3H); 3.76 (s, 2H); 4.36 (q, 2H, *J* = 7.1); 7.25 (m, 1H); 7.28 (m, 4H); 7.71 (dd, 1H, *J* = 0.8 and 8.7); 7.85 (dd, 1H, *J* = 2.5 and 8.7); 8.47 (dd, 1H, *J* = 0.8 and 2.5). ^{13}C ($CDCl_3$): 13.1; 14.9; 27.7; 31.6; 64.2; 71.2; 106.7; 114.6; 125.8; 128.2; 128.3; 134.8; 139.4; 140.2; 140.9; 143.7; 152.6; 163.2. HRMS calcd for $C_{21}H_{25}N_3O_2$ + H: 352.2520. Found: 352.2022.

5-Cyclopropyl-2-(3-ethoxy-5-methyl-4-phenoxy-1*H*-pyrazol-1-yl)pyridine (8a). Obtained in 17 % yield as an oil using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h

and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.73 (m, 2H); 1.04 (m, 2H); 1.38 (t, 3H, *J* = 7.2); 1.93 (m, 1H); 2.54 (s, 3H); 4.35 (q, 2H, *J* = 7.2); 7.04 (m, 3H); 7.30 (m, 2H); 7.42 (dd, 1H, *J* = 2.4 and 8.5); 7.69 (d, 1H, *J* = 8.5); 8.19 (d, 1H, *J* = 2.4). ^{13}C ($CDCl_3$): 8.6; 11.9; 12.5; 14.8; 64.8; 114.1; 115.1; 121.9; 124.8; 129.4; 133.3; 135.2; 135.6; 145.4; 151.8; 155.4; 158.6. HRMS calcd for $C_{20}H_{21}N_3O_2$ + H: 336.1712. Found: 336.1791.

5-Cyclopropyl-2-(3-ethoxy-4-(2-fluorophenoxy)-5-methyl-1*H*-pyrazol-1-yl)pyridine (8b). Obtained in 41 % yield as an oil using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.73 (m, 2H); 1.03 (m, 2H); 1.37 (t, 3H, *J* = 7.2); 1.92 (m, 1H); 2.55 (s, 3H); 4.35 (q, 2H, *J* = 7.2); 6.97 (m, 3H); 7.12 (m, 1H); 7.41 (dd, 1H, *J* = 2.5 and 8.6); 7.68 (d, 1H, *J* = 8.6); 8.19 (d, 1H, *J* = 2.5). ^{13}C ($CDCl_3$): 8.7; 11.8; 12.5; 14.8; 64.8; 114.1; 116.1; 116.4 (18 Hz); 123.3 (6 Hz); 124.0 (3 Hz); 124.4; 133.3; 135.2; 135.7; 145.5; 146.4 (11 Hz); 151.8; 152.1 (248 Hz); 155.1. HRMS calcd for $C_{20}H_{20}FN_3O_2$ + H: 354.1618. Found: 354.1563.

5-Cyclopropyl-2-(3-ethoxy-4-(2-chlorophenoxy)-5-methyl-1*H*-pyrazol-1-yl)pyridine (8c). Obtained in 70 % yield as an oil using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.72 (m, 2H); 1.03 (m, 2H); 1.37 (t, 3H, *J* = 7.2); 1.92 (m, 1H); 2.54 (s, 3H); 4.35 (q, 2H, *J* = 7.2); 6.89 (m, 1H); 6.96 (m, 2H); 7.15 (m, 1H); 7.42 (m, 2H); 7.69 (d, 1H, *J* = 8.5); 8.19 (d, 1H, *J* = 2.4). ^{13}C ($CDCl_3$): 8.7; 11.8; 12.6; 14.8; 64.8; 114.1; 115.0; 122.3; 122.7; 124.5; 127.5; 130.4; 133.3; 135.2; 135.8; 145.5; 151.8; 154.1; 155.1. HRMS calcd for $C_{20}H_{20}ClN_3O_2$ + H: 370.1322. Found: 370.1280.

5-Cyclopropyl-2-(3-ethoxy-4-(2-bromophenoxy)-5-methyl-1*H*-pyrazol-1-yl)pyridine (8d). Obtained in 50 % yield as an oil using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180

°C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.72 (m, 2H); 1.03 (m, 2H); 1.37 (t, 3H, *J* = 7.2); 1.92 (m, 1H); 2.53 (s, 3H); 4.35 (q, 2H, *J* = 7.2); 6.89 (m, 2H); 7.19 (m, 1H); 7.41 (dd, 1H, *J* = 2.5 and 8.5); 7.59 (dd, 1H, *J* = 1.6 and 7.8); 7.68 (d, 1H, *J* = 8.5); 8.19 (d, 1H, *J* = 2.5). ^{13}C ($CDCl_3$): 8.7; 11.9; 12.6; 14.8; 64.8; 111.2; 114.1; 114.9; 123.2; 124.6; 128.3; 133.3; 133.4; 135.2; 135.8; 145.5; 151.8; 155.1; 155.2. HRMS calcd for $C_{20}H_{20}BrN_3O_2$ + H: 414.0817. Found: 414.0807.

5-Cyclopropyl-2-(3-ethoxy-5-methyl-4-(2-(trifluoromethyl)phenoxy)-1*H*-pyrazol-1-yl)pyridine (8e). Obtained in 44 % yield as an oil using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.74 (m, 2H); 1.04 (m, 2H); 1.36 (t, 3H, *J* = 7.2); 1.91 (m, 1H); 2.51 (s, 3H); 4.35 (q, 2H, *J* = 7.2); 6.96 (m, 1H); 7.08 (m, 1H); 7.43 (m, 2H); 7.65 (m, 2H); 8.20 (d, 1H, *J* = 2.5). ^{13}C ($CDCl_3$): 8.7; 11.6; 12.5; 14.8; 64.9; 114.2; 114.6; 118.6 (31 Hz); 121.4; 123.6 (272 Hz); 123.9; 127.0 (5 Hz); 133.1; 133.4; 135.2; 135.9; 145.5; 151.7; 155.1; 153.3 (2 Hz). HRMS calcd for $C_{21}H_{20}F_3N_3O_2$ + H: 404.1586. Found: 404.1602.

5-Cyclopropyl-2-(3-ethoxy-5-methyl-4-(3-(trifluoromethyl)phenoxy)-1*H*-pyrazol-1-yl)pyridine (8f). Obtained in 55 % yield as an oil using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.73 (m, 2H); 1.03 (m, 2H); 1.36 (t, 3H, *J* = 7.2); 1.93 (m, 1H); 2.54 (s, 3H); 4.36 (q, 2H, *J* = 7.2); 7.18 (m, 1H); 7.20 (m, 2H); 7.40 (m, 2H); 7.70 (d, 1H; *J* = 8.5); 8.20 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 8.7; 11.8; 12.5; 14.7; 64.8; 112.2 (4 Hz); 114.1; 118.4; 118.7 (4 Hz); 123.9 (273 Hz); 124.0; 130.0; 131.9 (33 Hz); 133.3; 135.2; 135.8; 145.5; 151.8; 155.0; 158.6. HRMS calcd for $C_{21}H_{20}F_3N_3O_2$ + H: 404.1586. Found: 404.1596.

5-Cyclopropyl-2-(3-ethoxy-5-methyl-4-(4-(trifluoromethyl)phenoxy)-1*H*-pyrazol-1-yl)pyridine (8g). Obtained in 53 % yield as a solid using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.73 (m, 2H); 1.04 (m, 2H); 1.37 (t, 3H, *J* = 7.2); 1.94 (m, 1H); 2.52 (s, 3H); 4.35 (q, 2H, *J* = 7.2); 6.9 (d, 2H, *J* = 8.6); 7.42 (dd, 1H, *J* = 2.5 and 8.5); 7.57 (d, 2H, *J* = 8.6); 7.69 (d, 2H, *J* = 8.5); 8.20 (d, 1H, *J* = 2.5). ^{13}C ($CDCl_3$): 8.7; 11.8; 12.5; 14.7; 64.8; 114.1; 115.2; 123.9 124.3; (38 Hz); 124.4 (272 Hz); 126.9 (4 Hz); 131.3; 135.2; 135.9; 145.5; 151.7; 155.0; 161.0. HRMS calcd for $C_{21}H_{20}F_3N_3O_2$ + H: 404.1586. Found: 404.1638.

5-Cyclopropyl-2-(4-(2,3-dichlorophenoxy)-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (8h). Obtained in 50 % yield as a solid using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.72 (m, 2H); 1.03 (m, 2H); 1.37 (t, 3H, *J* = 7.2); 1.93 (m, 1H); 2.52 (s, 3H); 4.34 (q, 2H, *J* = 7.2); 6.82 (dd, 1H, *J* = 1.5 and 8.1); 7.08 (t, 1H, *J* = 8.1); 7.15 (dd, 1H, *J* = 1.5 and 8.1); 7.40 (dd, 1H, *J* = 2.5 and 8.5); 7.68 (d, 1H, *J* = 8.5); 8.20 (d, 1H, *J* = 2.5). ^{13}C ($CDCl_3$): 8.7; 11.8; 12.5; 14.8; 64.9; 112.9; 114.2; 121.5; 123.6; 124.3; 127.1; 133.3; 133.9; 135.2; 135.9; 145.5; 151.7; 154.9; 155.5. HRMS calcd for $C_{20}H_{19}Cl_2N_3O_2$ + H: 404.0933. Found: 404.0918.

5-Cyclopropyl-2-(4-(2,5-dichlorophenoxy)-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (8i). Obtained in 43 % yield as a solid using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.73 (m, 2H); 1.04 (m, 2H); 1.37 (t, 3H, *J* = 7.1); 1.93 (m, 1H); 2.54 (s, 3H); 4.34 (q, 2H, *J* = 7.1); 6.89 (d, 1H, *J* = 2.3); 6.96 (dd, 1H, *J* = 2.3 and 8.5); 7.33 (d, 1H, *J* = 8.5); 7.42 (dd, 1H, *J* = 2.5 and 8.5); 7.69 (d, 1H, *J* = 8.5); 8.20 (d, 1H, *J* = 2.5). ^{13}C ($CDCl_3$): 8.7; 11.8; 12.6; 14.8; 64.9; 114.1; 115.6; 120.8;

122.8; 124.0; 130.9; 133.1; 133.3; 135.2; 135.9; 145.5; 151.7; 154.5; 154.7. HRMS calcd for $C_{20}H_{19}Cl_2N_3O_2$ + H: 404.0933. Found: 404.0927.

5-Cyclopropyl-2-(4-(3,5-dichlorophenoxy)-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (8j). Obtained in 48 % yield as an oil using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.74 (m, 2H); 1.05 (m, 2H); 1.38 (t, 3H, *J* = 7.4); 1.93 (m, 1H); 2.52 (s, 3H); 4.34 (q, 2H, *J* = 7.4); 6.92 (d, 1H, *J* = 1.8); 7.03 (t, 1H, *J* = 1.8); 7.42 (dd, 1H, *J* = 2.3 and 8.5); 7.69 (d, 1H, *J* = 8.5); 8.20 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 8.7; 11.8; 12.6; 14.7; 64.8; 114.1; 114.3; 122.4; 123.7; 133.3; 135.2; 135.4; 135.9; 145.5; 151.7; 154.7; 159.5. HRMS calcd for $C_{20}H_{19}Cl_2N_3O_2$ + H: 404.0933. Found: 404.0961.

5-Cyclopropyl-2-(4-(2-fluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (8k). Obtained in 58 % yield as a solid using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane/ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.75 (m, 2H); 1.03 (m, 2H); 1.33 (d, 6H, *J* = 6.0); 1.92 (m, 1H); 2.54 (s, 3H); 4.98 (sept, 1H, *J* = 6.0); 6.98 (m, 3H); 7.12 (m, 1H); 7.40 (m, 1H); 7.68 (m, 1H); 8.18 (d, 1H, *J* = 2.4). ^{13}C ($CDCl_3$): 8.6; 11.8; 12.5; 22.1; 72.1; 114.2; 116.3; 116.4 (18 Hz); 122.3; 124.0; 125.1; 133.0; 135.1; 135.6; 145.4; 146.4 (10 Hz); 151.9; 152.3 (248 Hz); 154.5. HRMS calcd for $C_{21}H_{22}FN_3O_2$ + H: 368.1774. Found: 368.1742.

5-Cyclopropyl-2-(4-(3-fluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (8l). obtained in 57 % yield as an oil, using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane/ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.72 (m, 2H); 1.03 (m, 2H); 1.35 (d, 6H, *J* = 6.2); 1.92 (m, 1H); 2.52 (s, 3H); 5.00 (sept, 1H, *J* = 6.2); 6.73 (m, 2H); 6.82 (m, 1H); 7.22 (m, 1H); 7.41 (dd, 1H, *J* 2.4 and 8.5); 7.70 (d, 1H, *J* = 8.5); 8.19 (d, 1H, *J* = 2.4).

^{13}C ($CDCl_3$): 8.7; 11.9; 12.5; 21.1; 72.1; 103.1 (25 Hz); 108.8 (21 Hz); 111.0 (3 Hz); 114.1; 124.9; 130.1 (10 Hz); 133.1; 135.1; 135.7; 145.4; 151.9; 154.5; 160.0 (10 Hz); 163.6 (245 Hz). HRMS calcd for $C_{21}H_{22}FN_3O_2$ + H: 368.1774. Found: 368.1670.

5-Cyclopropyl-2-(4-(4-fluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (8m). obtained in 50 % yield as a solid, using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane/ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.72 (m, 2H); 1.03 (m, 2H); 1.34 (d, 6H, *J* = 6.2); 1.93 (m, 1H); 2.52 (s, 3H); 4.98 (sept, 1H, *J* = 6.2); 6.97 (m, 4H); 7.40 (dd, 1H, *J* = 2.3 and 8.5); 7.68 (d, 1H, *J* = 8.5); 8.19 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 8.6; 11.9; 12.5; 21.1; 72.0; 114.1; 115.6 (23 Hz); 116.2 (8 Hz); 125.6; 133.0; 135.1; 135.6; 145.4; 151.9; 154.7 (3 Hz); 158.0 (239 Hz). HRMS calcd for $C_{21}H_{22}FN_3O_2$ + H: 368.1774. Found: 368.1759.

5-Cyclopropyl-2-(4-(2,3-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (8n). obtained in 55 % yield as an oil, using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane/ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.72 (m, 2H); 1.03 (m, 2H); 1.34 (d, 6H, *J* = 6.2); 1.92 (m, 1H); 2.55 (s, 3H); 4.99 (sept, 1H, *J* = 6.2); 6.71 (m, 1H); 6.84 (m, 1H); 6.91 (m, 1H); 7.41 (dd, 1H, *J* 2.3 and 8.5); 7.68 (d, 1H, *J* = 8.5); 8.19 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 8.7; 11.8; 12.5; 21.1; 72.2; 110.2 (18 Hz); 111.2 (3 Hz); 114.2; 122.8 (5 and 9 Hz); 124.9; 133.0; 135.2; 135.8; 141.1 (15 and 249 Hz); 145.5; 148.0 (3 and 8 Hz); 151.5 (10 and 247 Hz); 151.8; 154.2. HRMS calcd for $C_{21}H_{21}F_2N_3O_2$ + H: 386.1680. Found: 386.1672.

5-Cyclopropyl-2-(4-(2,4-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (8o). obtained in 54 % yield as an oil, using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane/ethyl acetate

97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.72 (m, 2H); 1.03 (m, 2H); 1.33 (d, 6H, *J* = 6.2); 1.93 (m, 1H); 2.55 (s, 3H); 4.98 (sept, 1H, *J* = 6.2); 6.74 (m, 1H); 6.91 (m, 2H); 7.42 (dd, 1H, *J* 2.3 and 8.5); 7.67 (d, 1H, *J* = 8.5); 8.19 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 8.7; 11.7; 12.5; 22.1; 72.1; 104.8 (22 and 28 Hz); 110.3 (4 and 22 Hz); 114.2; 116.9 (2 and 10 Hz); 125.4; 132.9; 135.2; 135.7; 143.0 (4 and 11 Hz); 145.4; 151.8; 151.9 (12 and 242 Hz); 154.3; 157.2 (10 and 242 Hz). HRMS calcd for $C_{21}H_{21}F_2N_3O_2$ + H: 386.1680. Found: 386.1667.

5-Cyclopropyl-2-(4-(2,5-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (8p). obtained in 55 % yield as an oil, using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane/ethyl acetate 97/3) followed by concentration under high vacuum. ^{1}H ($CDCl_3$): 0.72 (m, 2H); 1.04 (m, 2H); 1.35 (d, 6H, *J* = 6.2); 1.93 (m, 1H); 2.55 (s, 3H); 5.00 (sept, 1H, *J* = 6.2); 6.67 (m, 2H); 7.08 (m, 1H); 7.42 (dd, 1H, *J* 2.3 and 8.5); 7.68 (d, 1H, *J* = 8.5); 8.19 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 8.7; 11.8; 12.5; 22.1; 72.2; 104.8 (28 Hz); 108.2 (6 and 24 Hz); 114.2; 116.9 (10 and 20 Hz); 124.5; 133.1; 135.2; 135.8; 145.4; 147.1 (22 Hz); 148.5 (4 and 243 Hz); 151.8; 154.2; 158.6 (3 and 242 Hz). HRMS calcd for $C_{21}H_{21}F_2N_3O_2$ + H: 386.1680. Found: 386.1648.

5-Cyclopropyl-2-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (8q). obtained in 53 % yield as an oil, using 5-cyclopropyl-2-fluoropyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate 98/2 to 97/3) followed by extensive drying under high vacuum. ^{1}H ($CDCl_3$): 0.72 (m, 2H); 1.01 (m, 2H); 1.25 (d, 6H, *J* = 6.2); 1.91 (m, 1H); 2.63 (s, 3H); 4.89 (sept, 1H, *J* = 6.2); 6.88 (m, 2H); 7.01 (m, 1H); 7.37 (m, 1H); 7.62 (d, 1H, *J* = 8.5); 8.18 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 8.6; 11.6; 12.5; 21.9; 71.9; 111.9 (6 and 16 Hz); 114.2; 123.4 (9 Hz); 129.1; 131.0; 134.7 (13 Hz); 135.0; 135.4; 145.4; 152.0; 153.4; 155.7 (4 and 250 Hz). HRMS calcd for $C_{21}H_{21}F_2N_3O_2$ + H: 386.1680. Found: 386.1664.

3-Cyclopropyl-6-(3-ethoxy-4-(2-fluorophenoxy)-5-methyl-1*H*-pyrazol-1-yl)pyridazine (10b). Obtained in 57 % yield as a solid using 3-chloro-6-cyclopropylpyridazine (**9**) in acetonitrile at 180 °C for 2 h after a chromatography over silica gel (cyclohexane-ethyl acetate 6/1). ^{1}H ($CDCl_3$): 1.15 (m, 2H); 1.22 (m, 2H); 1.36 (t, 3H, *J* = 7.0); 2.17 (m, 1H); 2.66 (s, 3H); 4.34 (q, 2H, *J* = 7.0); 6.93 (m, 1H); 7.00 (m, 2H); 7.16 (m, 1H); 7.34 (d, 1H, *J* = 9.2); 7.95 (d, 1H, *J* = 9.2). ^{13}C ($CDCl_3$): 10.3; 12.4; 14.7; 15.4; 64.9; 116.1; 116.6 (17 Hz); 118.9; 122.6 (7 Hz); 124.1 (4 Hz); 125.5; 127.1; 134.1; 146.1 (11 Hz); 152.2 (246 Hz); 155.5; 156.1; 161.6. HRMS calcd for $C_{19}H_{19}FN_4O_2$ + H: 355.1570. Found: 355.1533.

3-(4-(2-Chlorophenoxy)-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-6-cyclopropylpyridazine (10c). Obtained in 62 % yield as a solid using the procedure described for the preparation of compound **10b**. ^{1}H ($CDCl_3$): 1.14 (m, 2H); 1.22 (m, 2H); 1.36 (t, 3H, *J* = 7.2); 2.15 (m, 1H); 2.65 (s, 3H); 4.34 (q, 2H, *J* = 7.2); 6.87 (m, 1H); 6.97 (m, 1H); 7.15 (ddd, 1H, *J* = 1.8, 7.4 and 8.6); 7.32 (d, 1H, *J* = 9.2); 7.41 (dd, 1H, *J* = 1.6 and 7.9); 7.94 (d, 1H, *J* = 9.2). ^{13}C ($CDCl_3$): 10.3; 12.4; 14.7; 15.4; 64.9; 114.9; 118.8; 122.4; 122.9; 125.5; 127.1; 127.6; 130.5; 134.2; 153.9; 155.5; 156.1; 161.6. HRMS calcd for $C_{19}H_{19}ClN_4O_2$ + H: 371.1275. Found: 371.1380.

3-(4-(2-Bromophenoxy)-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-6-cyclopropylpyridazine (10d). Obtained in 62 % yield as a solid using the procedure described for the preparation of compound **10b**. ^{1}H ($CDCl_3$): 1.15 (m, 2H); 1.22 (m, 2H); 1.36 (t, 3H, *J* = 7.2); 2.17 (m, 1H); 2.64 (s, 3H); 4.34 (q, 2H, *J* = 7.2); 6.81 (dd, 2H, *J* = 1.4 and 8.3); 6.91 (m, 1H); 7.20 (m, 1H); 7.34 (d, 1H, *J* = 9.2); 7.59 (dd, 1H, *J* = 1.5 and 7.9); 7.94 (d, 1H, *J* = 9.2). ^{13}C ($CDCl_3$): 10.3; 12.4; 14.7; 15.4; 65.0; 111.2; 114.8; 118.8; 123.4; 125.6; 127.1; 128.3; 133.5; 134.2; 154.8; 155.5; 156.1; 161.6. HRMS calcd for $C_{19}H_{19}BrN_4O_2$ + H: 415.0770. Found: 415.0713.

3-Cyclopropyl-6-(3-ethoxy-5-methyl-4-(2-(trifluoromethyl)phenoxy)-1*H*-pyrazol-1-yl)pyridazine (10e). Obtained in 65 % yield as a solid using the procedure described for the preparation of compound **10b**. ^{1}H ($CDCl_3$): 1.15 (m, 2H); 1.22 (m, 2H); 1.35 (t, 3H, *J* = 7.2);

2.16 (m, 1H); 2.63 (s, 3H); 4.33 (q, 2H, *J* = 7.2); 6.94 (d, 1H, *J* = 8.3); 7.10 (m, 1H); 7.34 (d, 1H, *J* = 9.2); 7.43 (m, H); 7.64 (m, 1H); 7.94 (d, 1H, *J* = 9.2). ^{13}C ($CDCl_3$): 10.3; 12.2; 14.6; 15.4; 65.0; 114.5; 118.7 (31 Hz); 118.8; 121.6; 127.9; 126.1 (274 Hz); 127.0 (3 Hz); 127.1; 133.1; 134.3; 155.5; 156.0 (20 Hz); 156.1; 161.7. HRMS calcd for $C_{20}H_{19}F_3N_4O_2$ + H: 405.1538. Found: 405.1521.

3-Cyclopropyl-6-(3-ethoxy-5-methyl-4-(3-(trifluoromethyl)phenoxy)-1*H*-pyrazol-1-yl)pyridazine (10f). Obtained in 64 % yield as a solid using the procedure described for the preparation of compound **10b**. ^{1}H ($CDCl_3$): 1.15 (m, 2H); 1.22 (m, 2H); 1.36 (t, 3H, *J* = 7.0); 2.17 (m, 1H); 2.62 (s, 3H); 4.35 (q, 2H, *J* = 7.0); 7.19 (m, 1H); 7.25 (m, 1H); 7.30 (m, 1H); 7.35 (d, 1H; *J* = 9.2); 7.41 (m, 1H); 7.96 (d, 1H; *J* = 9.2). ^{13}C ($CDCl_3$): 10.3; 12.4; 14.6; 15.4; 64.9; 112.2 (4 Hz); 118.5; 118.8 (4 Hz); 123.8 (272 Hz); 125.0; 127.1; 130.1; 132.0 (33 Hz); 134.2; 155.5; 155.9; 158.4; 161.7. HRMS calcd for $C_{20}H_{19}F_3N_4O_2$ + H: 405.1538. Found: 405.1534.

3-Cyclopropyl-6-(3-ethoxy-5-methyl-4-(4-(trifluoromethyl)phenoxy)-1*H*-pyrazol-1-yl)pyridazine (10g). Obtained in 57 % yield as a solid using the procedure described for the preparation of compound **10b**. ^{1}H ($CDCl_3$): 1.15 (m, 2H); 1.22 (m, 2H); 1.37 (t, 3H, *J* = 7.0); 2.17 (m, 1H); 2.64 (s, 3H); 4.35 (q, 2H, *J* = 7.0); 7.8 (m, 2H); 7.35 (d, 1H, *J* = 9.2); 7.57 (m, 2H); 7.96 (d, 2H, *J* = 9.2). ^{13}C ($CDCl_3$): 10.4; 12.4; 14.6; 15.4; 64.9; 115.2; 118.8; 124.3; (270 Hz); 124.5 (33 Hz); 124.9; 127.0 (4 Hz); 127.1; 134.2; 155.5; 155.9; 160.7; 161.7. HRMS calcd for $C_{20}H_{19}F_3N_4O_2$ + H: 405.1538. Found: 405.1541.

3-Cyclopropyl-6-(4-(2,3-dichlorophenoxy)-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)pyridazine (10h). Obtained in 65 % yield as a solid using the procedure described for the preparation of compound **10b**. ^{1}H ($CDCl_3$): 1.15 (m, 2H); 1.22 (m, 2H); 1.35 (t, 3H, *J* = 7.2); 2.16 (m, 1H); 2.64 (s, 3H); 4.33 (q, 2H, *J* = 7.2); 6.78 (dd, 1H, *J* = 1.5 and 8.2); 7.08 (t, 1H, *J* = 8.2); 7.14 (dd, 1H, *J* = 1.6 and 8.2); 7.34 (d, 1H, *J* = 9.2); 7.93 (d, 1H, *J* = 9.2). ^{13}C

($CDCl_3$): 10.4; 12.4; 14.7; 15.4; 65.0; 112.8; 118.8; 121.6; 123.8; 125.3; 127.1; 127.2; 134.0; 134.2; 155.2; 155.5; 155.8; 161.8. HRMS calcd for $C_{19}H_{18}Cl_2N_4O_2$ + H: 405.0885. Found: 405.0800.

3-Cyclopropyl-6-(4-(2,5-dichlorophenoxy)-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)pyridazine (10i). Obtained in 50 % yield as a solid using the procedure described for the preparation of compound **10b**. ^1H ($CDCl_3$): 1.15 (m, 2H); 1.22 (m, 2H); 1.37 (t, 3H, *J* = 7.2); 2.16 (m, 1H); 2.66 (s, 3H); 4.35 (q, 2H, *J* = 7.2); 6.85 (d, 1H, *J* = 2.2); 6.96 (dd, 1H, *J* = 2.2 and 8.4); 7.33 (d, 1H, *J* = 8.4); 7.35 (d, 1H, *J* = 9.2); 7.95 (d, 1H, *J* = 9.2). ^{13}C ($CDCl_3$): 10.4; 12.4; 14.7; 15.4; 65.0; 115.4; 118.8; 120.9; 123.1; 124.9; 127.2; 131.0; 133.1; 134.2; 154.3; 155.6; 155.65; 161.8. HRMS calcd for $C_{19}H_{18}Cl_2N_4O_2$ + H: 405.0885. Found: 405.0833.

3-Cyclopropyl-6-(4-(3,5-dichlorophenoxy)-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)pyridazine (10j). Obtained in 55 % yield as a solid the procedure described for the preparation of compound **10b**. ^1H ($CDCl_3$): 1.15 (m, 2H); 1.23 (m, 2H); 1.38 (t, 3H, *J* = 7.2); 2.17 (m, 1H); 2.63 (s, 3H); 4.35 (q, 2H, *J* = 7.2); 6.90 (d, 1H, *J* = 1.8); 7.04 (t, 1H, *J* = 1.8); 7.35 (d, 1H, *J* = 9.2); 7.94 (d, 1H, *J* = 9.2). ^{13}C ($CDCl_3$): 10.4; 12.4; 14.7; 15.4; 65.0; 114.3; 118.8; 122.6; 124.7; 127.1; 134.2; 135.5; 155.5; 155.7; 159.2; 161.8. HRMS calcd for $C_{19}H_{18}Cl_2N_4O_2$ + H: 405.0885. Found: 405.0847.

3-Cyclopropyl-6-(4-(2-fluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridazine (10k). Obtained in 67 % yield as a solid the procedure described for the preparation of compound **10b**. ^1H ($CDCl_3$): 1.15 (m, 2H); 1.22 (m, 2H); 1.33 (d, 6H, *J* = 6.2); 2.16 (m, 1H); 2.66 (s, 3H); 4.97 (sept, 1H, *J* = 6.2); 6.92 (m, 1H); 6.99 (m, 2H); 7.14 (m, 1H); 7.68 (d, 1H, *J* = 9.2); 7.94 (d, 1H, *J* = 9.2). ^{13}C ($CDCl_3$): 10.3; 12.3; 15.4; 22.0; 72.3; 116.3; 116.5 (18 Hz); 118.8; 119.1; 122.6 (7 Hz); 124.1 (4 Hz); 126.1; 127.1; 133.9; 146.2 (11 Hz); 152.2 (247 Hz); 155.5; 155.6; 161.5. HRMS calcd for $C_{20}H_{21}FN_4O_2$ + H: 369.1727. Found: 369.1725.

3-Cyclopropyl-6-(4-(3-fluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridazine (10l). Obtained in 67 % yield as a solid using the procedure described for the preparation of compound **10b**. ^{1}H ($CDCl_3$): 1.15 (m, 2H); 1.22 (m, 2H); 1.35 (d, 6H, *J* = 6.2); 2.19 (m, 1H); 2.63 (s, 3H); 4.99 (sept, 1H, *J* = 6.2); 6.73 (m, 2H); 6.80 (m, 1H); 7.23 (m, 2H); 7.34 (d, 1H, *J* = 9.2); 7.95 (d, 1H, *J* = 9.2). ^{13}C ($CDCl_3$): 10.3; 12.4; 15.4; 22.0; 72.3; 103.1 (26 Hz); 109.0 (21 Hz); 111.0 (3 Hz); 118.9; 125.8; 130.2 (9 Hz); 134.0; 155.5; 155.6; 159.6 (10 Hz); 161.6; 163.6 (246 Hz) (one signal missing). HRMS calcd for $C_{20}H_{21}FN_3O_2$ + H: 369.1727. Found: 369.1769.

3-Cyclopropyl-6-(4-(4-fluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridazine (10m). Obtained in 67 % yield as an oil using the procedure described for the preparation of compound **10b**. ^{1}H ($CDCl_3$): 1.15 (m, 2H); 1.22 (m, 2H); 1.33 (d, 6H, *J* = 6.2); 2.17 (m, 1H); 2.63 (s, 3H); 4.97 (sept, 1H, *J* = 6.2); 6.96 (m, 4H); 7.33 (d, 1H, *J* = 9.2); 7.94 (d, 1H, *J* = 9.2). ^{13}C ($CDCl_3$): 10.3; 12.4; 15.4; 22.0; 72.3; 115.8 (23 Hz); 116.3 (8 Hz); 118.8; 126.5; 127.1; 133.9; 154.4 (2 Hz); 155.5; 155.6; 158.1 (240 Hz); 161.5. HRMS calcd for $C_{20}H_{21}FN_4O_2$ + H: 369.1727. Found: 369.1712.

3-Cyclopropyl-6-(4-(2,3-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridazine (10n). Obtained in 52 % yield as a solid using the procedure described for the preparation of compound **10b**. ^{1}H ($CDCl_3$): 1.15 (m, 2H); 1.22 (m, 2H); 1.33 (d, 6H, *J* = 6.2); 2.18 (m, 1H); 2.63 (s, 3H); 4.89 (sept, 1H, *J* = 6.2); 6.70 (m, 1H); 6.85 (m, 1H); 6.92 (m, 1H); 7.33 (d, 1H, *J* = 9.2); 7.93 (d, 1H, *J* = 9.2). ^{13}C ($CDCl_3$): 10.3; 12.3; 15.4; 22.0; 72.4; 110.5 (17 Hz); 111.2 (3 Hz); 118.8; 122.9 (5 and 8 Hz); 125.9; 127.1; 133.9; 141.1 (14 and 249 Hz); 147.7 (2 and 7 Hz); 151.5 (10 and 247 Hz); 155.2; 155.5; 161.7. HRMS calcd for $C_{20}H_{20}F_2N_4O_2$ + H: 387.1633. Found: 387.1552.

3-Cyclopropyl-6-(4-(2,4-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridazine (10o). Obtained in 69 % yield as an oil using the procedure described for the

preparation of compound **10b**. ^{1}H ($CDCl_3$): 1.13 (m, 2H); 1.18 (m, 2H); 1.33 (d, 6H, *J* = 6.2); 2.16 (m, 1H); 2.66 (s, 3H); 4.96 (sept, 1H, *J* = 6.2); 6.72 (m, 1H); 6.80 (m, 3H); 7.33 (d, 1H, *J* = 9.2); 7.92 (d, 1H, *J* = 9.2). ^{13}C ($CDCl_3$): 10.3; 12.3; 15.4; 22.0; 72.3; 104.9 (22 and 27 Hz); 110.3 (4 and 23 Hz); 117.0 (2 and 9 Hz); 118.8; 126.5; 133.7; 142.6 (3 and 10 Hz); 151.9 (12 and 250 Hz); 155.3; 155.5; 157.4 (9 and 244 Hz); 161.6 (one signal missing). HRMS calcd for $C_{20}H_{20}F_2N_4O_2$ + H: 387.1633. Found: 387.1627.

3-Cyclopropyl-6-(4-(2,5-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridazine (10p). Obtained in 77 % yield as a solid using the procedure described for the preparation of compound **10b**. ^{1}H ($CDCl_3$): 1.16 (m, 2H); 1.23 (m, 2H); 1.36 (d, 6H, *J* = 6.2); 2.16 (m, 1H); 2.67 (s, 3H); 5.00 (sept, 1H, *J* = 6.2); 6.68 (m, 2H); 7.07 (m, 2H); 7.34 (d, 1H, *J* = 9.3); 7.95 (d, 1H, *J* = 9.3). ^{13}C ($CDCl_3$): 10.4; 12.3; 15.4; 22.0; 72.4; 104.1 (28 Hz); 108.5 (7 and 24 Hz); 116.7 (10 and 20 Hz); 118.9; 125.6; 127.1; 134.0; 146.7 (10 and 12 Hz); 148.5 (3 and 242 Hz); 155.1; 155.5; 158.5 (2 and 243 Hz); 161.7. HRMS calcd for $C_{20}H_{20}F_2N_4O_2$ + H: 387.1633. Found: 387.1618.

3-Cyclopropyl-6-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridazine (10q). Obtained in 22 % yield as an oil, using the procedure described for the preparation of compound **10b**. ^{1}H ($CDCl_3$): 1.11 (m, 2H); 1.21 (m, 2H); 1.26 (d, 6H, *J* = 6.2); 2.15 (m 1H); 2.75 (s, 3H); 4.88 (sept, 1H, *J* = 6.2); 6.91 (m, 2H); 7.02 (m, 1H); 7.29 (d, 1H, *J* = 9.1); 7.88 (d, 1H, *J* = 9.1). ^{13}C ($CDCl_3$): 10.2; 12.1; 15.4; 21.9; 72.1; 111.9 (6 and 17 Hz); 118.8; 123.6 (9 Hz); 126.9; 129.8; 131.8; 134.5 (14 Hz); 154.4; 155.5 (4 and 250 Hz); 155.7; 161.3. HRMS calcd for $C_{18}H_{18}F_2N_4O_2$ + H: 387.1633. Found: 387.1628.

2-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (18a). Obtained in 66 % yield as an oil, using 2-fluoropyridine in acetonitrile at 180 °C for 6 h, and a chromatography over silica gel (cyclohexane-ethyl acetate 95/5). ^{1}H ($CDCl_3$): 1.26 (d, 6H, *J* = 6.2); 2.68 (s, 3H); 4.91 (sept, 1H, *J* = 6.2); 7.01 (m, 2H); 7.06 (m, 2H); 7.72 (m, 2H); 8.36 (m,

1H). ^{13}C ($CDCl_3$): 11.9; 21.9; 72.0; 111.9 (6 and 17 Hz); 114.3; 119.6; 123.4 (9 Hz); 129.4; 131.3; 134.7 (14 Hz); 137.9; 147.2; 153.7; 154.1; 155.6 (5 and 250 Hz). HRMS calcd for $C_{18}H_{17}F_2N_3O_2$ + H: 346.1367. Found: 346.1409.

2-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-5-methylpyridine (18b). Obtained in 34 % yield as an oil, using 2-fluoro-5-methylpyridine in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane/ethyl acetate 97/3). ^1H ($CDCl_3$): 1.26 (d, 6H, *J* = 6.2); 2.33 (s, 3H); 2.64 (s, 3H); 4.90 (sept, 1H, *J* = 6.2); 6.92 (m, 2H); 7.01 (m, 1H); 7.54 (m, 1H); 7.64 (d, 1H, *J* = 8.4); 8.18 (m, 1H). ^{13}C ($CDCl_3$): 11.6; 17.7; 21.9; 71.9; 111.9 (6 and 17 Hz); 114.2; 123.4 (9 Hz); 129.1; 129.2; 131.0; 134.7 (14 Hz); 138.7; 147.1; 152.0; 153.4; 155.7 (5 and 250 Hz). HRMS calcd for $C_{19}H_{19}F_2N_3O_2$ + H: 360.1524. Found: 360.1450.

2-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-5-(trifluoromethyl)pyridine (18c). Obtained in 64 % yield as a solid , using 2-chloro-5-(trifluoromethyl)pyridine in acetonitrile at 180 °C for 4 h after a chromatography over silica gel (cyclohexane-dichloromethane 8/1). ^1H ($CDCl_3$): 1.27 (d, 6H, *J* = 6.1); 2.72 (s, 3H); 4.93 (sept, 1H, *J* = 6.1); 6.92 (m, 2H); 7.05 (m, 1H); 7.91 (m, 2H); 8.61 (m, 1H). ^{13}C ($CDCl_3$): 12.3; 21.8; 72.0; 111.9 (6 and 17 Hz); 113.0; 121.9 (33 Hz); 121.6 (9 Hz); 123.9 (272 Hz); 130.3; 132.0; 134.4 (13 Hz); 134.9 (3 Hz); 144.7 (4 Hz); 154.6; 155.6 (5 and 250 Hz); 156.4. HRMS calcd for $C_{19}H_{16}F_5N_3O_2$ + H: 414.1241. Found: 414.1207.

5-Cyclopropyl-2-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-3-fluoropyridine (18d). obtained in 46 % yield as an oil, using 5-cyclopropyl-2,3-difluoropyridine (**5r**) in acetonitrile at 180 °C for 3 h and a first chromatography over silica gel (cyclohexane/ethyl acetate 7/1) and a second one over silica gel (dichloromethane). ^1H ($CDCl_3$): 0.76 (m, 2H); 1.11 (m, 2H); 1.22 (d, 6H, *J* = 6.1); 1.97 (m, 1H); 2.27 (s, 3H); 4.87 (sept, 1H, *J* = 6.1); 6.82 (m, 3H); 7.16 (m, 1H); 8.16 (d, 1H, *J* = 2.0). ^{13}C ($CDCl_3$): 9.2; 9.6;

12.6; 21.9; 71.9; 111.9 (6 and 16 Hz); 121.9 (18 Hz); 123.5 (9 Hz); 128.3; 131.0; 134.7 (14 Hz); 138.1 (10 Hz); 141.6; 142.3; 152.9 (263 Hz); 154.1; 155.8 (5 and 250 Hz). HRMS calcd for $C_{21}H_{20}F_3N_3O_2$ + H: 404.1586. Found: 404.1527.

5-Cyclopropyl-2-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)nicotinonitrile (18e). obtained in 96 % yield as a solid, using 2-chloro-5-cyclopropylnicotinonitrile in acetonitrile (**5s**) at 150 °C for 40 min and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3). ^{1}H ($CDCl_3$): 0.76 (m, 2H); 1.12 (m, 2H); 1.28 (d, 6H, *J* = 6.2); 1.94 (m, 1H); 2.58 (s, 3H); 4.94 (sept, 1H, *J* = 6.2); 6.94 (m, 2H); 7.05 (m, 1H); 7.67 (d, 1H, *J* = 2.4); 8.34 (d, 1H, *J* = 2.4). ^{13}C ($CDCl_3$): 9.0; 11.4; 12.2; 21.8; 72.8; 100.6; 111.9 (6 and 16 Hz); 116.7; 123.7 (9 Hz); 130.0; 131.1; 134.3 (14 Hz); 135.7; 141.1; 149.3; 152.7; 153.9; 155.7 (4 and 249 Hz). HRMS calcd for $C_{22}H_{20}F_2N_4O_2$ + H: 411.1633. Found: 411.1630.

5-Bromo-2-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (18f). Obtained in 79 % yield as a solid, using 2-fluoro-5-bromopyridine in acetonitrile at 160 °C for 3 h and a chromatography over silica gel (cyclohexane-ethyl acetate 98/2 to 9/1). ^{1}H ($CDCl_3$): 1.25 (d, 6H, *J* = 6.2); 2.65 (s, 3H); 4.89 (sept, 1H, *J* = 6.2); 6.94 (m, 2H); 7.02 (m, 1H); 7.69 (d, 1H, *J* = 8.8); 7.80 (dd, 1H, *J* = 2.6 and 8.8); 8.39 (d, 1H, *J* = 2.6). ^{13}C ($CDCl_3$): 12.0; 21.9; 72.1; 111.9 (6 and 16 Hz); 115.1; 115.4; 123.5 (9 Hz); 129.7; 131.5; 134.5 (13 Hz); 140.4; 147.9; 152.8; 154.0; 155.6 (5 and 250 Hz). HRMS calcd for $C_{18}H_{16}BrF_2N_3O_2$ + H: 424.0472. Found: 424.0443.

5-Bromo-2-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-3-fluoropyridine (18g). Obtained in 73 % yield as a solid, using 5-bromo-2,3-difluoropyridine in acetonitrile at 180 °C for 3 h and a chromatography over silica gel (cyclohexane-ethyl acetate 98/2). ^{1}H ($CDCl_3$): 1.23 (d, 6H, *J* = 6.2); 2.35 (s, 3H); 4.86 (sept, 1H, *J* = 6.2); 6.91 (m, 2H); 7.02 (m, 1H); 7.75 (d, 1H, *J* = 2.1 and 9.1); 8.38 (d, 1H, *J* = 2.1). ^{13}C ($CDCl_3$): 9.6;

21.8; 72.1; 111.9 (6 and 17 Hz); 117.6 (2 Hz); 123.7 (9 Hz); 128.6 (21 Hz); 129.0; 131.2; 134.5 (14 Hz); 139.9 (9 Hz); 144.7 (5 Hz); 151.7 (270 Hz); 154.5; 155.7 (4 and 250 Hz). HRMS calcd for $C_{18}H_{15}BrF_3N_3O_2$ + H: 442.0378. Found: 442.0346.

5-Bromo-2-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-3-methylpyridine (18h). Obtained in 84 % yield as an oil, using 5-bromo-2-fluoro-3-methylpyridine in acetonitrile at 180 °C for 3 h and a chromatography over silica gel (cyclohexane-ethyl acetate 98/2). ^{1}H ($CDCl_3$): 1.23 (d, 6H, *J* = 6.2); 2.25 (s, 3H); 2.32 (s, 3H); 4.79 (sept, 1H, *J* = 6.2); 6.90 (m, 2H); 7.01 (m, 1H); 7.78 (d, 1H, *J* = 2.3); 8.39 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 9.5; 18.2; 21.9; 72.0; 111.9 (6 and 17 Hz); 119.0; 123.5 (9 Hz); 128.0; 130.7; 132.1; 134.7 (14 Hz); 142.7; 146.7; 149.7; 153.3; 155.7 (4 and 250 Hz). HRMS calcd for $C_{19}H_{18}BrF_2N_3O_2$ + H: 438.0629. Found: 438.0589.

1-(6-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridin-3-yl)ethanone (18j). Obtained in 52 % yield as a solid, using 1-(6-bromopyridin-3-yl)ethanone in acetonitrile at 130 °C for 3 h and a chromatography over silica gel (cyclohexane-ethyl acetate 95/5 to 9/1). ^{1}H ($CDCl_3$): 1.27 (d, 6H, *J* = 6.1); 2.63 (s, 3H); 2.74 (s, 3H); 4.93 (sept, 1H, *J* = 6.1); 6.92 (m, 2H); 7.03 (m, 1H); 7.87 (d, 1H, *J* = 8.7); 8.25 (dd, 1H, *J* = 2.5 and 8.7); 8.92 (m, 1H). ^{13}C ($CDCl_3$): 12.5; 21.8; 26.5; 72.2; 112.0 (6 and 16 Hz); 113.0; 123.7 (10 Hz); 128.2; 130.4; 132.1; 134.3 (13 Hz); 137.4; 148.8; 154.7; 155.6 (4 and 250 Hz); 156.7; 195.7. HRMS calcd for $C_{20}H_{19}F_2N_3O_3$ + H: 388.1473. Found: 388.1447.

2-(6-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridin-3-yl)propan-2-ol (18k). Obtained in 68 % yield as an oil using 2-(6-fluoropyridin-3-yl)propan-2-ol (**5t**) in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate 4/1). ^{1}H ($CDCl_3$): 1.25 (d, 6H, *J* = 6.2); 1.63 (s, 6H); 1.86 (s, 1H); 2.65 (s, 3H); 4.90 (sept, 1H, *J* = 6.2); 6.90 (m, 2H); 6.99 (m, 1H); 7.70 (dd, 1H, *J* = 0.7 and 8.6); 8.25 (dd, 1H, *J* = 2.5 and 8.6); 8.48 (dd, 1H, *J* = 0.7 and 2.5). ^{13}C ($CDCl_3$): 11.8; 21.9; 31.7; 71.3; 72.0;

111.9 (6 and 17 Hz); 113.8; 123.4 (9 Hz); 129.3; 131.2; 134.7 (14 Hz); 134.8; 140.2; 143.7; 152.9; 153.6; 155.6 (4 and 250 Hz). HRMS calcd for $C_{21}H_{23}F_2N_3O_3$ + H: 404.1786. Found: 404.1767.

2-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-5-ethylpyridine (18l). obtained in 49 % yield as an oil, using 5-ethyl-2-fluoropyridine (**17l**) in acetonitrile at 180 °C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by drying under high vacuum. ^{1}H ($CDCl_3$): 1.26 (d, 6H, *J* = 6.2); 1.27 (t, 3H, *J* = 7.6); 2.64 (s, 3H); 2.65 (q, 2H, *J* = 7.6); 4.90 (sept, 1H, *J* = 6.2); 6.92 (m, 2H); 7.00 (m, 1H); 7.56 (dd, 1H, *J* = 1.9 and 8.5); 7.66 (d, 1H, *J* = 8.5); 8.20 (d, 1H, *J* = 1.9). ^{13}C ($CDCl_3$): 11.6; 15.4; 21.9; 25.5; 71.9; 111.9 (6 and 17 Hz); 114.3; 123.4 (9 Hz); 129.1; 131.0; 134.7 (14 Hz); 135.4; 137.6; 146.4; 152.2; 153.5; 155.6 (4 and 250 Hz). HRMS calcd for $C_{20}H_{21}F_2N_3O_2$ + H: 374.1680. Found: 374.1680.

2-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-5-ethyl-3-fluoropyridine (18m). obtained in 34 % yield as an oil, using 2,3-difluoro-5-ethylpyridine (**17m**) in acetonitrile at 140 °C for 4 h and a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by drying under high vacuum. ^{1}H ($CDCl_3$): 1.23 (d, 6H, *J* = 6.2); 1.31 (t, 3H, *J* = 7.6); 2.28 (s, 3H); 2.74 (q, 2H, *J* = 7.6); 4.88 (sept, 1H, *J* = 6.2); 6.91 (m, 2H); 7.01 (m, 1H); 7.41 (m, 1H); 8.20 (m, 1H). ^{13}C ($CDCl_3$): 9.3; 15.0; 21.9; 25.3; 71.9; 111.9 (6 and 17 Hz); 123.5 (9 Hz); 124.8 (17 Hz); 128.3; 131.1; 134.7 (14 Hz); 138.5 (11 Hz); 141.0 (3 Hz); 143.5 (5 Hz); 152.8 (260 Hz); 154.1; 155.8 (4 and 250 Hz). HRMS calcd for $C_{20}H_{20}F_3N_3O_2$ + H: 392.1586. Found: 392.1572.

5-(1,1-Difluoroethyl)-2-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (18n). obtained in 12 % yield as an oil using 2-bromo-5-(1,1-difluoroethyl)pyridine (**17n**) in acetonitrile at 140 °C for 6 h and a chromatography over silica gel (cyclohexane-ethyl acetate from 98.5/1.5 to 9/1). ^{1}H ($CDCl_3$): 1.26 (d, 6H, *J* = 6.2); 1.98

(t, 3H, *J* = 18); 2.70 (s, 3H); 4.92 (sept, 1H, *J* = 6.2); 6.93 (m, 2H); 7.02 (m, 1H); 7.84 (m, 2H); 8.50 (s, 1H). ^{13}C ($CDCl_3$): 12.1; 21.9; 25.7 (30 Hz); 72.1; 111.9 (6 and 16 Hz); 113.3; 121.0 (239 Hz); 123.5 (9 Hz); 129.3 (27 Hz); 129.8; 131.6; 134.5 (14 Hz); 134.6 (5 Hz); 144.0 (6 Hz); 154.2; 155.1; 155.6 (4 and 250 Hz). HRMS calcd for $C_{20}H_{19}F_4N_3O_2$ + H: 410.1492. Found: 410.1469.

2-Bromo-5-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyrazine (21a). Obtained in 59 % yield as a white powder using 2,5-dibromopyrazine in acetonitrile at 120 °C for 5 h and a chromatography over silica gel (cyclohexane-dichloromethane from 2/1 to 1/1). ^{1}H ($CDCl_3$): 1.26 (d, 6H, *J* = 6.2); 2.64 (s, 3H); 4.91 (sept, 1H, *J* = 6.2); 6.91 (m, 2H); 7.05 (m, 1H); 8.35 (d, 1H, *J* = 1.3); 8.87 (d, 1H, *J* = 1.3). ^{13}C ($CDCl_3$): 11.8; 21.8; 72.4; 111.9 (6 and 17 Hz); 123.8 (9 Hz); 130.4; 131.8; 133.4; 134.2 (13 Hz); 134.6; 143.1; 149.1; 154.9; 155.6 (4 and 250 Hz). HRMS calcd for $C_{17}H_{15}BrF_2N_4O_2$ + H: 425.0425. Found: 425.0418.

2-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-5-(trifluoromethyl)pyrazine (21b). Obtained in 32 % yield as a solid using from 2-chloro-5-(trifluoromethyl)pyrazine in acetonitrile at 180 °C for 4 h after a chromatography over silica gel (cyclohexane-dichloromethane 2/1). ^{1}H ($CDCl_3$): 1.27 (d, 6H, *J* = 6.2); 2.70 (s, 3H); 4.97 (sept, 1H, *J* = 6.2); 6.92 (m, 2H); 7.07 (m, 2H); 8.60 (s, 1H); 9.21 (s, 1H). ^{13}C ($CDCl_3$): 12.1; 21.7; 72.6; 112.0 (6 and 16 Hz); 121.5 (273 Hz); 123.9 (9 Hz); 131.0; 132.3; 134.0 (13 Hz); 136.1; 137.7 (36 Hz); 138.3 (3 Hz); 151.5; 155.5 (4 and 250 Hz); 155.6. HRMS calcd for $C_{18}H_{15}F_5N_4O_2$ + H: 415.1193. Found: 415.1183.

2-Cyclopropyl-5-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyrazine (21d). Obtained in 45 % yield as an oil using 2-bromo-5-cyclopropylpyrazine in acetonitrile at 160 °C for 2 h and a chromatography over silica gel (cyclohexane-dichloromethane from 3/2 to 1/2). ^{1}H ($CDCl_3$): 1.04 (m, 4H); 1.25 (d, 6H, *J* = 6.2); 2.07 (m, 1H); 2.61 (s, 3H); 4.88 (sept, 1H, *J* = 6.2); 6.91 (m, 2H); 7.02 (m, 1H); 8.17 (d, 1H, *J* = 1.4);

8.90 (d, 1H, *J* = 1.4). ^{13}C ($CDCl_3$): 9.6; 11.4; 14.1; 28.1; 72.1; 111.9 (6 and 17 Hz); 123.5 (9 Hz); 129.5; 131.2; 134.5 (14 Hz); 136.4; 138.7; 147.8; 153.2; 154.1; 155.6 (4 and 250 Hz). HRMS calcd for $C_{20}H_{20}F_2N_4O_2$ + H: 387.1633. Found: 387.1718.

3-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-6-methylpyridazine (22a). obtained in 29 % yield as a solid, using 3-chloro-6-methylpyridazine in acetonitrile at 140 °C for 2 h and two consecutive chromatography processes, the first one over silica gel (cyclohexane-ethyl acetate 3/1), the second one over alumina containing 1.5 % of water (cyclohexane-dichloromethane from 1/1 to 1/2). ^{1}H ($CDCl_3$): 1.25 (d, 6H, *J* = 6.2); 2.69 (s, 3H); 2.75 (s, 3H); 4.88 (sept, 1H, *J* = 6.2); 6.89 (m, 2H); 7.00 (m, 1H); 7.35 (d, 1H, *J* = 9.1); 7.90 (d, 1H, *J* = 9.1). ^{13}C ($CDCl_3$): 12.1; 21.6; 21.8; 72.1; 112.0 (6 and 17 Hz); 118.9; 123.6 (9 Hz); 128.8; 129.9; 131.9; 134.4 (13 Hz); 154.5; 155.6 (4 and 250 Hz); 155.8; 156.7. HRMS calcd for $C_{18}H_{18}F_2N_4O_2$ + H: 361.1476. Found: 361.1491.

3-Chloro-6-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridazine (22b). Obtained in 58 % yield as a solid, using 3,6-dichloropyridazine in acetonitrile at 140 °C for 1 h and a chromatography over silica gel (cyclohexane-ethyl acetate from 97/3 to 95/5). ^{1}H ($CDCl_3$): 1.25 (d, 6H, *J* = 6.2); 2.75 (s, 3H); 4.88 (sept, 1H, *J* = 6.2); 6.89 (m, 2H); 7.01 (m, 1H); 7.50 (d, 1H, *J* = 9.3); 8.01 (d, 1H, *J* = 9.3). ^{13}C ($CDCl_3$): 12.3; 21.8; 72.3; 112.0 (6 and 17 Hz); 121.2; 123.8 (9 Hz); 129.8; 130.5; 132.2; 134.2 (14 Hz); 152.6; 155.1; 155.6 (4 and 250 Hz); 156.4. HRMS calcd for $C_{17}H_{15}ClF_2N_4O_2$ + H: 381.0930. Found: 381.0927.

5-Cyclopropyl-2-(3-ethoxy-4-iodo-5-methyl-1*H*-pyrazol-1-yl)pyridine (12a). In a 20 mL Biotage tube, 3-ethoxy-4-iodo-5-methyl-1*H*-pyrazole (1.53 g, 6.07 mmol), cesium carbonate (2.2 g, 6.98 mmol and 5-cyclopropyl-2-fluoropyridine (0.87 g, 6.37 mmol) were dispersed in acetonitrile (14 mL, dried over 4 Å molecular sieves). This was heated at 180 °C for 12 h in the microwave oven. The resulting suspension was adsorbed over silica gel and purified by a chromatography over silica gel (cyclohexane-dichloromethane from 97.5/2.5 to 96.5/3.5) to

yield in this order, compound **12a** (0.3 g, 13 %) as a solid, unreacted (and volatile) 5-cyclopropyl-2-fluoropyridine (0.3 g, 34 %) and compound **12b** which was further purified under a high vacuum as an oil (0.14 g, 9 %). Washing the column with ethyl acetate led then to the isolation of the reduced and UV/TLC-invisible 3-ethoxy-5-methyl-1*H*-pyrazole. 5-cyclopropyl-2-(3-ethoxy-4-iodo-5-methyl-1*H*-pyrazol-1-yl)pyridine (**12a**): ^{1}H ($CDCl_3$): 0.73 (m, 2H); 1.03 (m, 2H); 1.45 (t, 3H, *J* = 7.2); 1.92 (m, 1H); 2.66 (s, 3H); 4.36 (q, 2H, *J* = 7.2); 7.39 (dd, 1H, *J* = 2.4 and 8.5); 7.62 (d, 1H, *J* = 8.5); 8.20 (d, 1H, *J* = 2.4). ^{13}C ($CDCl_3$): 8.8; 12.6; 14.7; 15.2; 52.8; 65.0; 114.7; 135.1; 136.3; 143.0; 145.5; 151.3; 162.4. HRMS calcd for $C_{14}H_{16}IN_3O$ + H: 370.0416. Found: 370.0441. 5-cyclopropyl-2-(3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (**12b**): ^{1}H ($CDCl_3$): 0.71 (m, 2H); 1.02 (m, 2H); 1.42 (t, 3H, *J* = 7.2); 1.92 (m, 1H); 2.62 (s, 3H); 4.26 (q, 2H, *J* = 7.2); 5.66 (s, 1H); 7.38 (dd, 1H, *J* = 2.4 and 8.5); 7.66 (d, 1H, *J* = 8.5); 8.19 (d, 1H, *J* = 2.4). ^{13}C ($CDCl_3$): 8.6; 12.5; 14.8 (two signals); 64.4; 94.9; 114.8; 135.0; 135.6; 142.2; 140.4; 151.6; 162.3.

2-(4-Bromo-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-cyclopropylpyridine (12c). From 3-ethoxy-4-bromo-5-methyl-1*H*-pyrazole (preparation provided below), using the protocol described for the preparation of compound **12a**, compound **12c** was obtained in a 48 % yield as an oil. ^{1}H ($CDCl_3$): 0.72 (m, 2H); 1.04 (m, 2H); 1.46 (t, 3H, *J* = 7.2); 1.93 (m, 1H); 2.63 (s, 3H); 4.38 (q, 2H, *J* = 7.2); 7.40 (dd, 1H, *J* = 2.3 and 8.5); 7.62 (d, 1H, *J* = 8.5); 8.21 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 8.7; 12.6; 13.5; 14.7; 65.0; 84.4; 114.6; 135.2; 136.2; 140.0; 145.5; 151.4; 159.7. HRMS calcd for $C_{14}H_{16}BrN_3O$ + H: 322.0555. Found: 322.0517. 3-ethoxy-4-bromo-5-methyl-1*H*-pyrazole: 3-ethoxy-5-methyl-1*H*-pyrazole (6.64 g, 52.63 mmol) was dissolved in dry acetonitrile (200 mL), N-bromosuccinimide (9.83 g, 55.26 mmol) was added and the solution was stirred at room temperature overnight. The acetonitrile was then removed under vacuum, this was dissolved in water and ethyl acetate and the organic layer was washed six times with water once with brine and dried over magnesium sulfate. Removal of the

solvent under vacuum allowed the isolation of pure 4-bromopyrazole as a white powder (9.83 g, 91 %). ^{1}H ($CDCl_3$): 1.42 (t, 3H, *J* = 7.0); 2.21 (s, 3H); 4.28 (q, 2H, *J* = 7.0); 9.40 (s(l), 1H). ^{13}C ($CDCl_3$): 10.6; 14.8; 65.1; 79.7; 139.2; 160.2.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-methoxypyridine (6p). In a 10 mL Biotage tube, compound **4** (0.14 g, 0.633 mmol), 5-methoxy-2-bromopyrimidine (0.12 g, 0.665 mmol), cesium carbonate (0.22 g, 0.696 mmol), 4 Å molecular sieves (0.1 g, 3.2 mm pellets) [*N,N'*-bis-((2'-pyridine)-methylene)]-1,2-diaminocyclohexane[68] (0.018 g, 0.063 mmol) were dispersed in acetonitrile (4.5 mL, dried over 4 Å molecular sieves). This was degassed using a slow stream of argon bubbling in the suspension. Copper oxide (0.004 g, 0.031 mmol) was then added and the tube was sealed. This was shaken thoroughly, heated for 30 seconds in the microwave oven at 100 °C and shaken again. At this stage the pink copper oxide is well dissolved in the reaction mixture; if not, another 30 seconds heating at 100 °C is required. The heating was then resumed at 180 °C for 6 h. The resulting suspension was directly adsorbed over a small amount of silica gel and this was subjected to a chromatography over silica gel (cyclohexane/ethyl acetate 9/1) to give the 5-methoxypyridine derivative (0.11 g, 53 %) as a white solid. ^{1}H ($CDCl_3$): 1.42 (t, 3H, *J* = 7.2); 2.51 (s, 3H); 3.76 (s, 2H); 3.88 (s, 3H); 4.36 (q, 2H, *J* = 7.2); 7.19 (m, 1H); 7.30 (m, 5H); 7.67 (d, 1H, *J* = 8.5); 8.09 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 12.6; 14.9; 27.8; 55.9; 64.4; 105.9; 116.4; 123.9; 125.7; 128.2 (two signals); 133.4; 138.8; 141.1; 147.6; 153.2; 162.0. HRMS calcd for $C_{19}H_{21}N_3O_2$ + H: 324.1712. Found: 324.1678.

2-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-5-methoxypyridine (18i). By using the same procedure described above for the preparation of 2-(4-benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-methoxypyridine (**6p**), this compound was obtained as a solid in 64 % yield after a chromatography over silica gel (cyclohexane/ethyl acetate from 97/3 to 95/5). ^{1}H ($CDCl_3$): 1.25 (d, 6H, *J* = 6.2); 2.60 (s, 3H); 3.87 (s, 3H); 4.88 (sept, 1H, *J* =

6.2); 6.90 (m, 2H); 6.98 (m, 1H); 7.30 (dd, 1H, *J* = 2.4 and 8.5); 7.65 (d, 1H, *J* = 8.5); 8.06 (d, 1H, *J* = 2.4). ^{13}C ($CDCl_3$): 11.3; 21.9; 55.9; 71.9; 112.0 (6 and 17 Hz); 115.7; 123.4 (9 Hz); 124.0; 128.8; 133.2; 134.8 (13 Hz); 147.7; 153.3; 155.7 (4 and 250 Hz). HRMS calcd for $C_{19}H_{19}F_2N_3O_3$ + H: 376.1473. Found: 376.1510.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-isopropylpyridine (6u). Compound **6t** (0.17 g, 0.48 mmol) was dissolved in dichloromethane (10 mL) and trifluoroacetic acid (2 mL). Triethylsilane (0.28 mL, 1.75 mmol) was added and the reaction was stirred at room temperature for 4 h. An LC/MS pointed out a very slow reaction. Trifluoromethane sulfonic acid (0.2 mL, 2.26 mmol) was added followed by some more triethylsilane (0.2 mL, 1.25 mmol). A hydrogen evolution was observed and LC/MS monitoring pointed out the occurrence of compound **6u**. More triethylsilane (0.2 mL, 1.25 mmol) was added and this was stirred 24 h. The resulting solution was diluted in ethyl acetate, washed until neutrality with saturated sodium hydrogenocarbonate, brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by two consecutive chromatography processes, the first one over silica gel (cyclohexane-ethyl acetate from 97/3), the second one over silica gel (toluene), to yield compound **6u** (0.04 g, 24 %) as an oil. ^{1}H ($CDCl_3$): 1.30 (t, 6H, *J* = 6.8); 1.41 (t, 3H, *J* = 7.1); 2.55 (s, 3H); 2.96 (sept, 1H, *J* = 6.8); 3.75 (s, 2H); 4.35 (q, 2H, *J* = 7.1); 7.18 (m, 1H); 7.28 (m, 4H); 7.61 (dd, 1H, *J* = 2.4 and 8.6); 7.67 (d, 1H, *J* = 8.6); 8.25 (d, 1H, *J* = 2.4). ^{13}C ($CDCl_3$): 11.9; 13.9; 22.7; 26.7; 30.2; 63.1; 105.2; 114.1; 124.7; 127.2 (two signals); 135.0; 138.1; 138.8; 140.0; 144.5; 151.1; 161.1. HRMS calcd for $C_{21}H_{25}N_3O$ + H: 336.2076. Found: 336.2051.

2-(4-Benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-cyclopropylpyridine (6q). In a tube adapted for microwave oven, 2-(4-benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-bromopyridine (0.16 g, 0.43 mmol), cesium carbonate (0.7 g, 2.14 mmol), cyclopropyl boronic acid (0.11 g, 1.28 mmol) in dimethylformamide (4 ml, dried over 4 Å molecular

sieves) were mixed. This suspension was degassed by a gentle stream of argon, [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium complexed with dichloromethane (0.017 g, 0.021 mmol) was added, the tube was sealed and heated in a microwave oven at 110 °C for 1 h. The resulting suspension was diluted in water, extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to dryness. The residue was purified first by a chromatography over silica gel (cyclohexane-ethyl acetate from 2/1 to 3/2) to yield the 5-cyclopropyl derivative as a white powder (0.07 g, 48 %). ^{1}H ($CDCl_3$): 0.78 (m, 2H); 1.03 (m, 2H); 1.41 (t, 3H, *J* = 7.0); 1.91 (m, 1H); 2.54 (s, 3H); 3.76 (s, 2H); 4.35 (q, 2H, *J* = 7.0); 7.18 (m, 1H); 7.28 (m, 4H); 7.38 (m, 1H); 7.65 (m, 1H); 8.20 (m, 1H). ^{13}C ($CDCl_3$): 8.7; 12.5; 12.9; 14.9; 27.8; 64.2; 106.3; 115.0; 125.7; 128.2; 128.3; 135.1; 135.3; 139.1; 141.0; 145.4; 151.8; 162.2. HRMS calcd for $C_{21}H_{23}N_3O$ + H: 334.1919. Found: 334.1931.

(1-(5-Cyclopropylpyridin-2-yl)-3-ethoxy-5-methyl-1*H*-pyrazol-4-yl)(phenyl)methanone (13). Under an atmosphere of argon, compound **12a** (0.31 g, 0.83 mmol) was dissolved in dry THF (10 mL). This was cooled to -78°C and 2M butyl lithium in cyclohexane (0.63 mL, 1.25 mmol) was added. This was stirred at -78 °C for 5 min before adding benzoyl chloride (0.14 mL, 1.25 mmol). The resulting solution was allowed to warm to room temperature, water was added and this was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (cyclohexane-ethyl acetate from 97/3 to 95/5) to yield the benzoyl derivative **13** as a glass (0.13 g, 44 %). ^{1}H ($CDCl_3$): 0.78 (m, 2H); 1.09 (m, 2H); 1.23 (t, 3H, *J* = 7.2); 1.92 (m, 1H); 2.75 (s, 3H); 4.28 (q, 2H, *J* = 7.2); 7.47 (m, 4H); 7.53 (m, 1H); 7.64 (d, 1H, *J* = 8.5); 7.84 (dd, 1H, *J* = 8.5 and 2.3); 8.29 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 9.1; 12.7; 13.8; 14.4; 64.6; 108.8; 116.9; 127.7; 129.4; 132.0; 135.1; 137.7; 139.4; 145.9; 146.2; 150.5; 161.3; 190.7. HRMS calcd for $C_{21}H_{21}N_3O_2$ + H: 348.1712. Found: 348.1738.

(1-(5-Cyclopropylpyridin-2-yl)-3-ethoxy-5-methyl-1*H*-pyrazol-4-yl)(phenyl)methanol (14a). Compound **13** (0.07 g, 0.2 mmol) and sodium borohydride (0.074 g, 2.01 mmol) were stirred overnight in methanol (15 mL) at room temperature. This was neutralized with acetic acid, concentrated to dryness and diluted in ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (dichloromethane – ethanol from 99.5/0.5 to 98/2) to yield the alcohol as a glass (0.05 g, 71 %). ^{1}H ($CDCl_3$): 0.72 (m, 2H); 1.03 (m, 2H); 1.38 (t, 3H, J = 7.2); 1.92 (m, 1H); 2.51 (s, 3H); 4.35 (q, 2H, J = 7.2); 5.82 (s, 1H); 7.25 (m, 1H); 7.37 (m, 3H); 7.47 (m, 2H); 7.60 (d, 1H, J = 8.5); 8.20 (d, 1H, J = 2.3). ^{13}C ($CDCl_3$): 8.7; 12.6; 12.9; 14.8; 64.5; 67.8; 109.2; 115.6; 126.0; 127.0; 128.2; 129.8; 135.1; 138.9; 143.6; 145.6; 151.4; 160.9. HRMS calcd for $C_{21}H_{23}N_3O_2$ + H: 350.1869. Found: 350.1829.

1-(1-(5-Cyclopropylpyridin-2-yl)-3-ethoxy-5-methyl-1*H*-pyrazol-4-yl)-1-phenylethanol (14b). Under an argon atmosphere, compound **13** (0.05 g, 0.14 mmol) was dissolved in dry tetrahydrofuran (5 mL) at room temperature. A 1.6 M solution of methyllithium in ether (0.5 mL, 0.84 mmol) was added and the solution stirred for 5 minutes. This was diluted in water, extracted with ethyl acetate, the organic layer was washed with water, brine, dried over magnesium sulfate and concentrated to dryness. The residue was further purified by a chromatography over silica gel (dichloromethane – ethanol from 98/2) to yield the tertiary alcohol as a glass (0.04 g, 76 %). ^{1}H ($CDCl_3$): 0.72 (m, 2H); 1.04 (m, 2H); 1.38 (t, 3H, J = 7.2); 1.91 (m, 1H); 1.95 (s, 3H); 2.31 (s, 3H); 3.52 (s, 1H); 4.32 (m, 2H); 7.25-7.55 (m, 7H); 8.21 (d, 1H, J = 2.3). ^{13}C ($CDCl_3$): 8.8; 12.6; 13.3; 14.8; 31.2; 64.6; 73.3; 112.6; 116.9; 125.5; 126.7; 126.9; 127.9; 135.0; 136.6; 138.5; 145.7; 151.2; 161.6. HRMS calcd for $C_{22}H_{25}N_3O_2$ + H: 364.2025. Found: 364.1948.

5-Cyclopropyl-2-(3-ethoxy-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)pyridine (15). In a vial adapted for microwave heating, compound **12c** (0.21 g, 0.65 mmol), phenylboronic acid

(0.087 g, 0.71 mmol) and cesium carbonate (0.53 g, 1.69 mmol) were dissolved in a 2/3 mixture of propanol and water (5 mL). This was degassed by a gentle steam of argon, [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium complexed with dichloromethane (0.026 g, 0.032 mmol) was added and the sealed tube heated at 120 °C for 30 minutes. The resulting solution was diluted in water, extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to dryness. The residue was purified first by a chromatography over alumina containing 1.5 % water (cyclohexane-dichloromethane from 1/0 to 1/1) to yield the 4-phenyl derivative as a solid (0.07 g, 33 %). ^{1}H ($CDCl_3$): 0.74 (m, 2H); 1.05 (m, 2H); 1.44 (t, 3H, *J* = 7.2); 1.93 (m, 1H); 2.68 (s, 3H); 4.40 (q, 2H, *J* = 7.2); 7.27 (m, 1H); 7.43 (m, 3H); 7.51 (m, 2H); 7.68 (d, 1H, *J* = 8.4); 8.24 (d, 1H, *J* = 2.3). ^{13}C ($CDCl_3$): 8.7; 12.6; 13.7; 14.9; 64.4; 109.3; 115.6; 126.2; 128.3; 129.2; 131.9; 135.1; 135.9; 138.9; 145.6; 151.6; 160.9. HRMS calcd for $C_{20}H_{21}N_3O$ + H: 320.1763. Found: 320.1747.

Alternative preparation of 2-(4-benzyl-3-ethoxy-5-methyl-1*H*-pyrazol-1-yl)-5-cyclopropylpyridine (6q) from compound 12c. First step, preparation of benzylzinc bromide: A 100 mL round-bottom flask was charged with lithium chloride (3.9 g, 92.6 mmol.). This was thoroughly dried with an open flame for two min under vacuum and then allowed to cool under an argon atmosphere. Still under an inert atmosphere, zinc dust (5.5 g, 84.2 mmol.; VWR Technical 6% oxide) was added. Anhydrous tetrahydrofuran (50 mL) was injected, and the flask cooled using an ice bath. Benzyl bromide (5 mL, 42.1 mmol.) was added via the septum; the mixture was sonicated for 45 seconds and allowed to stir at 4 °C overnight (17 h). This solution was stocked for 3 month at 4 °C, leading to a 0.68 molar (80 %) transparent solution of benzylzinc bromide as measured by the titration method previously reported.[69] Second step: compound **12c** (0.23 g, 0.71 mmol.), palladium acetate (0.008 g, 0.036 mmol.) and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) (0.084 g, 0.071 mmol.) were added in a flask flushed with argon. Anhydrous tetrahydrofuran (5 mL)

was injected and the resulting solution was allowed to stir a few minutes. A fraction of the solution of benzylzinc bromide described above (3.2 mL, 2.14 mmol.) was injected and the mixture heated for 16 h at 50 °C. The resulting suspension was diluted in ethyl acetate and water. The aqueous layer was extracted once with ethyl acetate, the organic layer was washed with brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (dichloromethane - ethanol 99.5:0.5) followed by drying under high vacuum to yield compound **6q** as a yellowish oil (0.17 g, 71%) with analytical data identical with the one described above.

5-Cyclopropyl-2-(3-ethoxy-5-methyl-4-(1-phenylethyl)-1*H*-pyrazol-1-yl)pyridine (16). First step, preparation of (1-phenylethyl)zinc chloride: A 20 mL tube adapted for microwave heating was charged with lithium chloride (0.48 g, 11.3 mmol.). This was thoroughly dried with an open flame for two min and then allowed to cool under an argon atmosphere. Still under an inert atmosphere, zinc dust (0.74 g, 11.3 mmol.; size < 10 μm) was added and the tube was sealed. Anhydrous tetrahydrofuran (10 mL) was injected, followed by 0.2 M dibromoethane solution in tetrahydrofuran (1.9 mL, 0.38 mmol.). The tube was heated using microwave irradiation for 5 min at 85 °C. This was allowed to cool, a 0.06 M trimethylsilychloride solution in tetrahydrofuran (1.25 mL, 0.075 mmol.) was added and the tube was heated again with microwave irradiation for 5 min at 85 °C. After cooling, (1-chloroethyl)benzene (1 mL, 7.5 mmol.) was added via the septum, and the mixture was heated using microwave irradiation for 1 h at 80 C. This led to a 0.47 molar (88 %) yellow solution of (1-phenylethyl)zinc chloride as measured by the titration method previously reported.[69] Second step: Compound **12c** (0.31 g, 0.96 mmol.), palladium acetate (0.011 g, 0.048 mmol.) and 2-dicyclohexylphosphino-2′,6′-bis(N,N-dimethylamino)biphenyl (CPhos) (0.042 g, 0.096 mmol.) were added in a flask flushed with argon. The decanted solution of (1-phenylethyl)zinc chloride described above (6.1 mL, 2.89 mmol.) was injected and the mixture

heated for 16 h at 50 °C. The resulting suspension was diluted in ethyl acetate and water. The aqueous layer was extracted once with ethyl acetate, the organic layer was washed with brine, dried over magnesium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (dichloromethane) followed by drying under high vacuum to yield compound **16** as a colorless oil (0.14 g, 42%). ^{1}H NMR ($CDCl_3$): 0.72 (m, 2H); 1.04 (m, 2H); 1.42 (t, 3H, *J* = 7.1); 1.71 (d, 3H, *J* = 7.4); 1.92 (m, 1H); 2.51 (s, 3H); 4.08 (q, 1H, *J* = 7.3); 4.30 (m, 2H); 7.20 (m, 1H); 7.30 (m, 2H); 7.40 (m, 3H); 7.61 (d, 1H, *J* = 8.5); 8.20 (d, 1H, *J* = 2.4). ^{13}C NMR ($CDCl_3$): 8.6; 12.6; 12.8; 14.9; 20.0; 34.2; 64.1; 111.0; 115.4; 125.7; 127.3; 128.1; 135.0; 135.4; 138.0; 145.5; 146.1; 151.8; 161.9. HRMS calcd for $C_{22}H_{25}N_3O$ + H: 348.2076. Found: 348.2016.

2-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-3-fluoro-5-propylpyridine (18o). Compound **18d** (0.17 g, 0.42 mmol) and 10 % palladium over charcoal (0.066 g, 0.062 mmol) were dispersed in ethanol (20 mL). This was charge with hydrogen at 1 atmosphere and stirred at room temperature for 5 days. The suspension was filtered, the filtrate concentrated to dryness and the residue purified by a chromatography over silica gel (cyclohexane-ethyl acetate 97/3) followed by drying under high vacuum to give compound **18o** as an oil (0.05 g, 30 %). ^{1}H ($CDCl_3$): 1.00 (t, 3H, *J* = 7.3); 1.23 (d, 6H, *J* = 6.2); 1.69 (m, 2H); 2.28 (s, 3H); 2.66 (t, 2H, *J* = 7.4); 4.88 (sept, 1H, *J* = 6.2); 6.89 (m, 2H); 7.01 (m, 1H); 7.39 (m, 1H); 8.18 (m, 1H). ^{13}C ($CDCl_3$): 9.3; 13.5; 21.9; 24.0; 34.2; 71.9; 111.9 (6 and 17 Hz); 123.5 (9 Hz); 125.2 (17 Hz); 128.3; 131.1; 134.7 (14 Hz); 138.5 (11 Hz); 139.5 (3 Hz); 144.0 (5 Hz); 152.7 (260 Hz); 154.1; 155.7 (4 and 250 Hz). HRMS calcd for $C_{21}H_{22}F_3N_3O_2$ + H: 406.1742. Found: 406.1713.

5-Cyclopropyl-2-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-3-methoxypyridine (18p). Compound **18d** (0.11 g, 0.272 mmol), cesium carbonate (0.13 g, 0.409 mmol) dissolved in methanol (2 mL) are heated in a microwave oven at 150 °C for 90

minutes. This is concentrated to dryness and the residue purified by a chromatography over silica gel (cyclohexane – ethyl acetate 4/1) to yield the methoxy ether **18p** (0.08 g, 70 %) as an oil. ^{1}H ($CDCl_3$): 0.77 (m, 2H); 1.08 (m, 2H); 1.21 (d, 6H, *J* = 6.2); 1.96 (m, 1H); 2.11 (s, 3H); 3.79 (s, 3H); 4.87 (sept, 1H, *J* = 6.2); 6.87 (m, 2H); 7.00 (m, 2H); 7.97 (d, 1H, *J* = 2.0). ^{13}C ($CDCl_3$): 9.0; 9.3; 13.0; 22.0; 56.0; 71.7; 111.9 (6 and 16 Hz); 118.2; 123.4 (9 Hz); 127.4; 131.2; 134.9 (14 Hz); 138.7; 139.2; 141.4; 150.7; 153.5; 155.8 (4 and 249 Hz). HRMS calcd for $C_{22}H_{23}F_2N_3O_3$ + H: 416.1786. Found: 416.1779.

5-Cyclopropyl-2-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-N,N-dimethylpyridin-3-amine (18q). Compound **18d** (0.06 g, 0.148 mmol), cesium and a 2N solution of dimethylamine in tetrahydrofuran (0.5 mL) in tetrahydrofuran (2 mL) are heated in a microwave oven at 180 °C for 9 h. This is concentrated to dryness and the residue purified by a chromatography over silica gel (cyclohexane – ethyl acetate 9/1) to yield the N-dimethylamine **18q** (0.04 g, 62 %) as an oil. ^{1}H ($CDCl_3$): 0.75 (m, 2H); 1.03 (m, 2H); 1.20 (d, 6H, *J* = 6.2); 1.91 (m, 1H); 2.09 (s, 3H); 2.56 (s, 6H); 4.89 (sept, 1H, *J* = 6.2); 6.91 (m, 3H); 5.98 (m, 1H); 7.86 (d, 1H, *J* = 2). ^{13}C ($CDCl_3$): (one signal missing) 8.8; 9.0; 13.0; 21.9; 41.3; 71.8; 111.9 (6 and 16 Hz); 122.8; 123.3 (9 Hz); 127.5; 130.9; 135.0 (13 Hz); 139.7; 140.4; 144.3; 153.4; 155.7 (4 and 249 Hz). HRMS calcd for $C_{23}H_{26}F_2N_4O_3$ + H: 429.2102. Found: 429.2023.

3-(Benzyloxy)-5-cyclopropyl-2-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridine (18r). Compound **18d** (0.38 g, 0.94 mmol), cesium carbonate (0.34 g, 1.03 mmol) dissolved in benzylalcohol (2 mL) are heated in a microwave oven at 150 °C for 90 minutes. This is concentrated to dryness and the residue purified by two consecutive chromatography processes, the first one over silica gel (cyclohexane-ethyl acetate 4/1), the second one over alumina containing 1.5 % of water (cyclohexane-dichloromethane 1/1) to yield the benzyl ether **18r** (0.14 g, 29 %) as an oil. ^{1}H ($CDCl_3$): 0.74 (m, 2H); 1.08 (m, 2H);

1.22 (d, 6H, *J* = 6.1); 1.92 (m, 1H); 2.13 (s, 3H); 4.89 (sept, 1H, *J* = 6.1); 5.02 (s, 2H); 6.97 (m, 2H); 7.02 (m, 2H); 7.31 (m, 5H); 8.01 (d, 1H, *J* = 2.0). ^{13}C ($CDCl_3$): 9.1; 9.4; 12.9; 22.0; 71.1; 71.8; 111.9 (6 and 17 Hz); 123.4 (9 Hz); 127.1; 127.5; 128.0; 128.5; 131.2; 134.9 (14 Hz); 135.9; 139.3; 139.9; 141.4; 149.8; 153.6; 155.8 (4 and 249 Hz). HRMS calcd for $C_{29}H_{27}F_2N_3O_3$ + H: 492.2099. Found: 492.2076.

5-Cyclopropyl-2-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyridin-3-ol (18s). Compound **18r** (0.22 g, 0.44 mmol), ammonium formate (0.11 g, 1.79 mmol) and 10 % palladium over charcoal (0.023 g, 0.021 mmol) were heated to reflux in ethanol (50 mL) for 45 minutes. This was adsorbed over silica gel and purified by a chromatography over silica gel (cyclohexane-ethyl acetate 95/5) to yield the hydroxyl derivative **18s** (0.13 g, 72 %) as an oil. ^{1}H ($CDCl_3$): 0.71 (m, 2H); 1.01 (m, 2H); 1.25 (d, 6H, *J* = 6.1); 1.89 (m, 1H); 2.69 (s, 3H); 4.75 (sept, 1H, *J* = 6.1); 6.92 (m, 3H); 7.04 (m, 1H); 7.75 (d, 1H, *J* = 2.0); 10.98 (s, 1H). ^{13}C ($CDCl_3$): 8.9; 11.8; 12.4; 21.9; 72.9; 112.0 (6 and 17 Hz); 121.9; 123.7 (9 Hz); 128.0; 132.6; 134.5 (14 Hz); 135.8; 137.5; 138.1; 144.9; 151.2; 155.6 (5 and 250 Hz). HRMS calcd for $C_{21}H_{21}F_2N_3O_3$ + H: 402.1629. Found: 402.1642.

5-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-2-methylpyridine (19a). By using the procedure described above for the preparation of compound **6p**, this compound was obtained from 5-bromo-2-methylpyridine as a solid in 34 % yield after two consecutive chromatography processes, the first one over silica gel (cyclohexane – ethyl acetate 3/1), the second one over alumina containing 1.5 % of water (cyclohexane – dichloromethane from 2/3 to 1/1). ^{1}H ($CDCl_3$): 1.23 (d, 6H, *J* = 6.2); 2.32 (s, 3H); 2.59 (s, 3H); 4.83 (sept, 1H, *J* = 6.2); 6.92 (m, 2H); 7.02 (m, 1H); 7.22 (d, 1H, *J* = 8.4); 7.66 (dd, 1H, *J* = 2.5 and 8.4); 8.58 (d, 1H, *J* = 2.5). ^{13}C ($CDCl_3$): 10.0; 21.9; 23.9; 72.1; 112.0 (6 and 17 Hz); 123.2; 123.6 (9 Hz); 128.4; 129.6; 131.5; 134.4; 134.6 (14 Hz); 144.0; 153.8; 155.7 (4 and 250 Hz); 156.4. HRMS calcd for $C_{19}H_{19}F_2N_3O_2$ + H: 360.1524. Found: 360.1515.

5-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-2-ethylpyridine (19b). By using the procedure described above for the preparation of compound **6p**, this compound was obtained from 5-bromo-2-ethylpyridine as an oil in 42 % yield after two consecutive chromatography processes, the first one over silica gel (cyclohexane – ethyl acetate 5/1), the second one over alumina containing 1.5 % of water (cyclohexane – dichloromethane 3/2). ^{1}H ($CDCl_3$): 1.23 (d, 6H, J = 6.2); 1.33 (t, 3H, J = 7.6); 2.33 (s, 3H); 2.87 (q, 2H, J = 7.6); 4.83 (sept, 1H, J = 6.2); 6.91 (m, 2H); 7.02 (m, 1H); 7.23 (d, 1H, J = 8.5); 7.68 (dd, 1H, J = 2.4 and 8.5); 8.58 (d, 1H, J = 2.4). ^{13}C ($CDCl_3$): 10.0; 13.8; 21.9; 30.9; 72.1; 112.0 (6 and 17 Hz); 122.0; 123.6 (10 Hz); 128.4; 129.6; 131.6; 134.5; 134.6 (14 Hz); 144.1; 153.8; 155.7 (4 and 250 Hz); 161.5. HRMS calcd for $C_{20}H_{21}F_2N_3O_2$ + H: 374.1680. Found: 374.1667.

5-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-2-methoxypyridine (19c). By using the procedure described above for the preparation of compound **6p**, this compound was obtained from 5-bromo-2-methoxypyridine as a solid in 16 % yield after a chromatography over silica gel (cyclohexane – ethyl acetate 9/1). ^{1}H ($CDCl_3$): 1.23 (d, 6H, J = 6.2); 2.27 (s, 3H); 3.97 (s, 3H); 4.81 (sept, 1H, J = 6.2); 6.82 (d, 1H, J = 8.7); 6.91 (m, 2H); 7.02 (m, 1H); 7.65 (dd, 1H, J = 2.7 and 8.7); 8.20 (d, 1H, J = 2.7). ^{13}C ($CDCl_3$): 9.7; 21.9; 53.8; 72.0; 111.9; 112.9 (6 and 17 Hz); 123.6 (9 Hz); 127.9; 129.8; 130.9; 134.7 (14 Hz); 135.4; 142.3; 153.5; 155.8 (4 and 250 Hz); 162.6. HRMS calcd for $C_{19}H_{19}F_2N_3O_3$ + H: 376.1473. Found: 376.1446.

2-*tert*-Butyl-5-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyrimidine (20a). By using the procedure described above for the preparation of compound **6p**, this compound was obtained from 5-bromo-2-tert-butylpyrimidine as a solid in 24 % yield after two consecutive chromatography processes, the first one over silica gel (cyclohexane – ethyl acetate 95/5), the second one over alumina containing 1.5 % of water

(cyclohexane – dichloromethane 4/1). ^{1}H ($CDCl_3$): 1.24 (d, 6H, *J* = 6.2); 1.46 (s, 9H); 2.36 (s, 3H); 4.82 (sept, 1H, *J* = 6.2); 6.92 (m, 2H); 7.03 (m, 1H); 8.82 (s, 2H). ^{13}C ($CDCl_3$): 10.0; 21.9; 29.6; 39.3; 72.2; 112.0 (6 and 16 Hz); 123.8; (10 Hz); 128.9; 129.6; 132.5; 134.4 (14 Hz); 150.4; 155.6 (4 and 250 Hz); 174.6. HRMS calcd for $C_{21}H_{24}F_2N_4O_2$ + H: 403.1946. Found: 403.1900.

2-Cyclopropyl-5-(4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)pyrimidine (20b). In an open flask, compound **7q** (0.37 g, 1.38 mmol), a very aged sample of commercially available 2-cyclopropylpyrimidin-5-ylboronic acid (0.25 g, 1.51 mmol), pyridine (0.23 mL, 2.75 mmol, dried over 4 Å molecular sieves), 4 Å molecular sieves (0.5 g) and copper (II) acetate hydrate (0.41 g, 2.06 mmol) were dispersed in dichloromethane (50 mL). The reaction was stirred in open air for 48 h. The suspension was absorbed on a small amount of silica gel and purified by two consecutive chromatography processes, the first one over silica gel (cyclohexane - ethyl acetate 4/1) the second one over alumina containing 1.5 % of water (cyclohexane-dichloromethane 1/1) to give the N-arylated compound **20b** (0.01 g, 1.8 %) as an oil. ^{1}H ($CDCl_3$): 1.11 (m, 2H); 1.15 (m, 2H); 1.24 (d, 6H, *J* = 6.1); 2.30 (m, 1H); 2.35 (s, 3H); 4.82 (sept, 1H, *J* = 6.1); 6.93 (m, 2H); 7.05 (m, 1H); 8.68 (s, 2H). ^{13}C ($CDCl_3$): 9.9; 11.0; 17.9; 21.9; 72.2; 112.0 (6 and 16 Hz); 123.8; (9 Hz); 128.8; 129.6; 132.5; 134.4 (14 Hz); 151.1; 155.4; 155.7 (4 and 250 Hz). HRMS calcd for $C_{20}H_{20}F_2N_4O_2$ + H: 387.1633. Found: 387.1643.

2-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-5-methoxypyrazine (21c). Compound **21a** (0.076 g, 0.17 mmol), cesium carbonate (0.087 g, 0.26 mmol) dissolved in methanol (4 mL) are heated in a microwave oven at 140 °C for 60 minutes. This was concentrated to dryness and the residue purified by a chromatography over silica gel (cyclohexane – dichloromethane from 3/2 to 2/1) to yield the methoxy ether **21c** (0.04 g, 59 %) as a white powder. ^{1}H ($CDCl_3$): 1.25 (d, 6H, *J* = 6.2); 2.55 (s, 3H); 3.99 (s, 3H); 4.88

(sept, 1H, *J* = 6.2); 6.89 (m, 2H); 7.00 (m, 1H); 7.98 (d, 1H, *J* = 1.3); 8.54 (d, 1H, *J* = 1.3). ^{13}C ($CDCl_3$): 11.0; 21.9; 53.9; 72.1; 112.0 (6 and 17 Hz); 123.5 (9 Hz); 129.0; 130.8; 130.9; 133.1; 134.5 (14 Hz); 144.4; 153.8; 155.6 (4 and 249 Hz); 157.8. HRMS calcd for $C_{18}H_{18}F_2N_4O_3$ + H: 377.1425. Found: 377.1372.

3-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-6-methoxypyridazine (22c). By using the procedure described for the preparation of compound **21a**, compound **22c** was obtained from compound **22b** as a white powder in 80 % after a chromatography over silica gel (cyclohexane – dichloromethane from 9/1). ^{1}H ($CDCl_3$): 1.24 (d, 6H, *J* = 6.2); 2.72 (s, 3H); 4.14 (s, 3H); 4.86 (sept, 1H, *J* = 6.2); 6.91 (m, 2H); 7.03 (m, 2H); 7.96 (d, 1H, *J* = 9.4). ^{13}C ($CDCl_3$): 12.0; 21.9; 54.9; 72.1; 111.9 (6 and 17 Hz); 119.8; 123.2; 123.6 (9 Hz); 129.6; 131.5; 134.5 (14 Hz); 153.8; 154.2; 155.6 (4 and 249 Hz); 163.0. HRMS calcd for $C_{18}H_{18}F_2N_4O_3$ + H: 377.1425. Found: 377.1364.

3-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-6-ethoxypyridazine (22d). By using the procedure described for the preparation of compound **21a**, compound **22d** was obtained from **22b** and ethanol as a solid in 71 % after a chromatography over silica gel (cyclohexane – dichloromethane from 9/1). ^{1}H ($CDCl_3$): 1.24 (d, 6H, *J* = 6.2); 1.47 (d, 6H, *J* = 7.1); 2.72 (s, 3H); 4.58 (q, 2H, *J* = 7.1); 4.86 (sept, 1H, *J* = 6.2); 6.92 (m, 2H); 7.03 (m, 2H); 7.96 (d, 1H, *J* = 9.5). ^{13}C ($CDCl_3$): 11.9; 14.5; 21.9; 63.4; 72.1; 120.0 (6 and 17 Hz); 119.8; 123.2; 123.5 (9 Hz); 129.6; 131.5; 134.5 (14 Hz); 153.6; 154.1; 155.6 (4 and 249 Hz); 162.8. HRMS calcd for $C_{19}H_{20}F_2N_4O_3$ + H: 391.1582. Found: 391.1577.

3-(4-(2,6-Difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazol-1-yl)-6-ethyl-1,2,4-triazin-5-ol (23). From 6-ethyl-3-(methylthio)-1,2,4-triazin-5-ol (0.17 g, 1.01 mmol) and 4-(2,6-difluorophenoxy)-3-isopropoxy-5-methyl-1*H*-pyrazole (0.272 g, 1.01 mmol) were heated in a sealed tube at 200 °C four 12 h. The resulting tarry solid was dispersed in ethanol, adsorbed over silica and purified by two consecutive chromatography processes over silica

gel (dichloromethane - ethanol 98/2) and (cyclohexane - ethyl acetate from 2/1 to 1/1) to give the N-arylated derivative as a glass (0.04 g, 10 %). ^{1}H ($CDCl_3$): 1.23 (t, 3H, *J* = 7.5); 1.25 (d, 6H, *J* = 6.2); 2.71 (s, 3H); 2.76 (q, 2H, *J* = 7.5); 4.86 (sept, 1H, *J* = 6.2); 6.90 (m, 2H); 7.04 (m, 1H); 10.89 (s(l), 1H). ^{13}C ($CDCl_3$): 10.0; 12.1; 21.6; 24.0; 73.2; 111.9 (6 and 17 Hz); 124.2 (9 Hz); 131.4; 133.7 (14 Hz); 133.8; 150.4; 154.4; 155.4 (4 and 250 Hz); 156.1; 162.7. HRMS calcd for $C_{18}H_{19}F_2N_5O_3$ + H: 392.1534. Found: 392.1538.

4-(2,6-Difluorophenoxy)-1-(1-ethyl-1*H*-imidazol-4-yl)-3-isopropoxy-5-methyl-1*H*-pyrazole (24). In a 10 mL Biotage tube compound **7q** (0.2 g, 0.74 mmol), 1-ethyl-4-iodo-1*H*-imidazole (0.17 g, 0.78 mmol), cesium carbonate (0.27 g, 0.83 mmol), 4 Å molecular sieves (0.1 g, 3.2 mm pellets) [*N,N'*-bis-((2'-pyridine)-methylene)]-1,2-diaminocyclohexane[68] were dispersed in acetonitrile (4.5 mL, dried over 4 Å molecular sieves). This was degassed using a slow stream of argon bubbling in the suspension. Copper oxide (0.005 g, 0.034 mmol) was then added and the tube was sealed. This was shaken thoroughly, heated for 30 seconds in the microwave oven at 100 °C and shaken again. At this stage the pink copper oxide is well dissolved in the reaction mixture; if not, another 30 seconds heating at 100 °C is required. The heating was then resumed at 180 °C for 90 minutes. The resulting suspension was directly adsorbed over a small amount of silica gel and this was subjected to a chromatography over silica gel (dichloromethane - ethanol 99/1 -> 98/2) to give compound **24** as an oil (0.13 g, 48 %). ^{1}H ($CDCl_3$): 1.22 (d, 6H, *J* = 5.2); 1.51 (t, 3H, *J* = 7.3); 2.39 (s, 3H); 4.00 (q, 2H, *J* = 7.3); 4.85 (m, 1H); 6.90 (m, 2H); 6.98 (m, 1H); 7.06 (s(br)); 7.44 (s(br), 1H). ^{13}C ($CDCl_3$): 9.8; 16.0; 22.0; 42.6 (br); 71.8; 111.9 (6 and 17 Hz); 123.4 (9 Hz); 130.5 (br); 134.8 (14 Hz); 140.2 (br); 153.7 (4 and 250 Hz). HRMS calcd for $C_{18}H_{20}N_4O_2F_2$ + H: 363.1633. Found: 363.1605.

Supporting information

A pdf file containing the ^{1}H and ^{13}C spectra of all the compounds assayed as well as a csv file providing the SMILES string description of all the compounds assayed in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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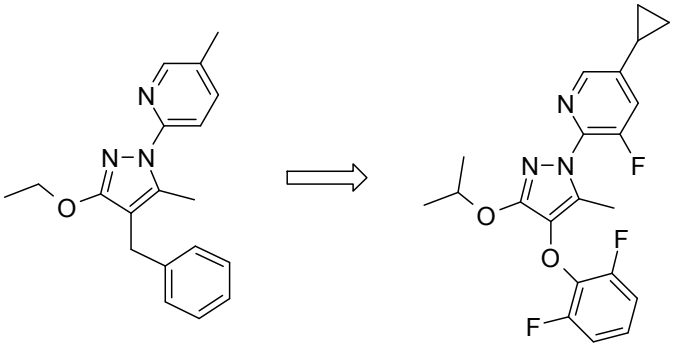
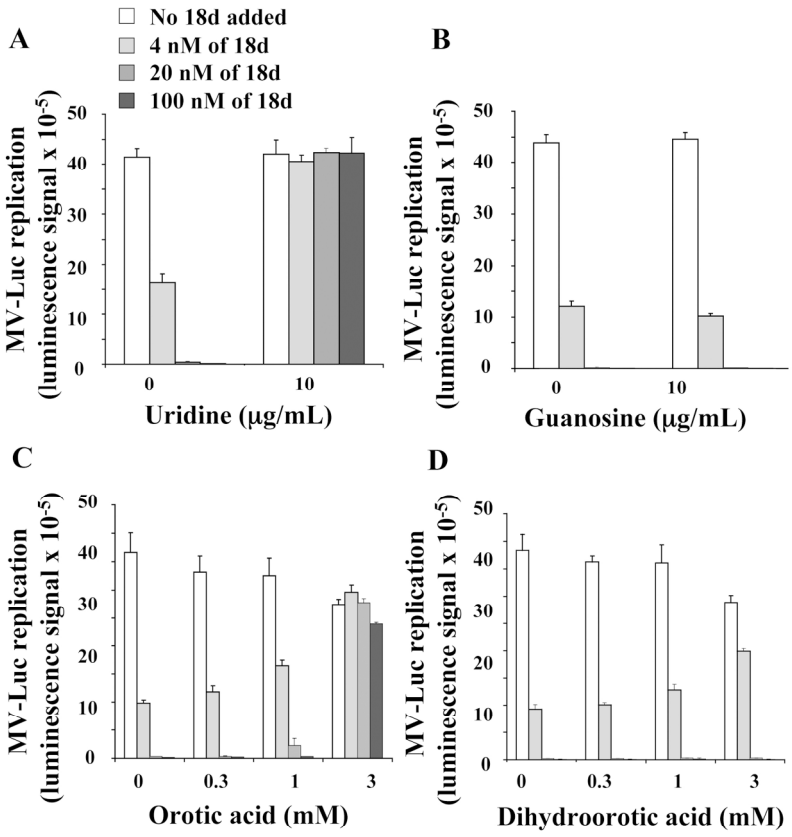


MIC_{50} = 650 nM

MIC_{50} = 2.7 nM (measles virus replication)
IC_{50} = 25 ± 5 nM (human DHODH inhibition)

Table of content graphic



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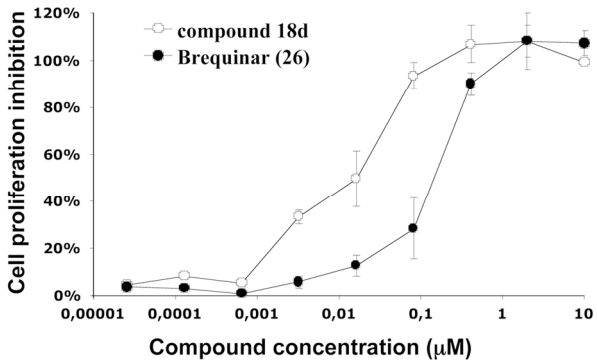

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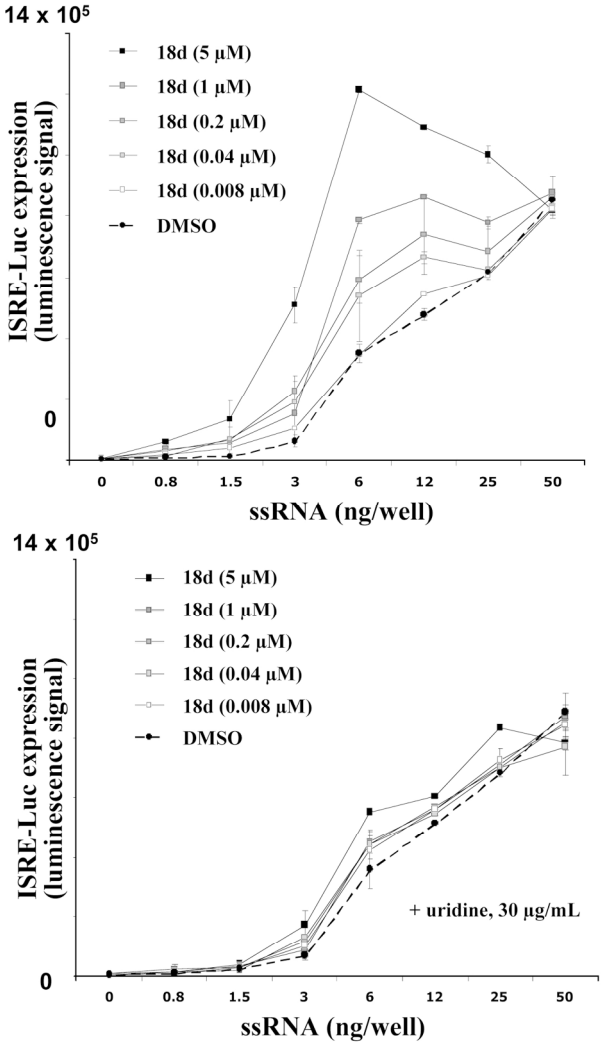

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