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Original article

New aminopyrimidine derivatives as inhibitors of the TAM family

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ABSTRACT

In this study, we describe the synthesis of new pyrimidine analogs of BMS-777607, a potent and selective inhibitor of Met kinase. Inhibition of Met and Axl remained high whereas inhibition of Tyro3 and Mer decreased to some extend. The preferential moderate inhibition of the non-phosphorylated form of Abl1 of some derivatives suggests that they behave as type II inhibitors. This hypothesis was confirmed by docking studies into the structure of Met (3F82) and in a Tyro3 model where key interactions with the hinge region, the DFG-out motif and the allosteric pocket explain this inhibition.

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1. Introduction

Transmembrane receptor tyrosine kinases (RTKs) play fundamental roles in cellular processes, including proliferation, migration, metabolism, differentiation, and survival. The approval of imatinib (Gleevec) for chronic myeloid leukemia (CML) [1] and erlotinib (Tarceva) [2,3] for non-small cell lung cancer (NSCLC) has provided proof-of-principle that small molecule kinase inhibitors can be effective drugs. Currently, 20 kinase inhibitors are on the market as drugs, mainly for the treatment of different types of human tumors including pancreas, lung, kidney, breast, thyroid and bone marrow, as well as CML, GIST (Gastro-intestinal stromal tumors), and NSCLC [4–6]. These treatments have been designed to selectively target oncogenic pathways in specific cancers, as opposed to traditional highly cytotoxic chemotherapeutics which non-specifically kill any actively dividing cells [7]. It has, however to be noted that the 20 kinase inhibitor drugs known to date, target a small number of kinases, although many other kinases are involved in the processes leading to tumor cell proliferation and survival and are presently under investigation. Among these new therapeutic targets, Met and the three close proteins Tyro3, Axl and Mer, defining the TAM subfamily of receptor protein kinases (the four proteins forming the HGFR/TAM family) have appeared as promising targets for different types of cancers [7–10]. In order to target kinases, two main categories of kinase inhibitors have been identified. Thus, type I inhibitors, form the largest of the two classes, binding to the active site (the ATP-binding site) in the so-called DFG-in active form of the enzyme, and type II inhibitors which bind to a DFG-out conformation of the enzyme, where a large hydrophobic allosteric pocket, adjacent to the active site, becomes accessible [11,12]. The Met inhibitor BMS-777607 (compound **1**, Fig. 1), currently evaluated against solid tumors in a phase II clinical trial [13,14], is a type II inhibitor that is also a potent inhibitor of the TAM family [15]. Conversely, various inhibitors of Tyro3, Axl and Mer receptor protein kinases have been described [7–9,16,17], but most of them also target Met, and, to date, no inhibitor of these kinases has been approved as an anticancer drug. In

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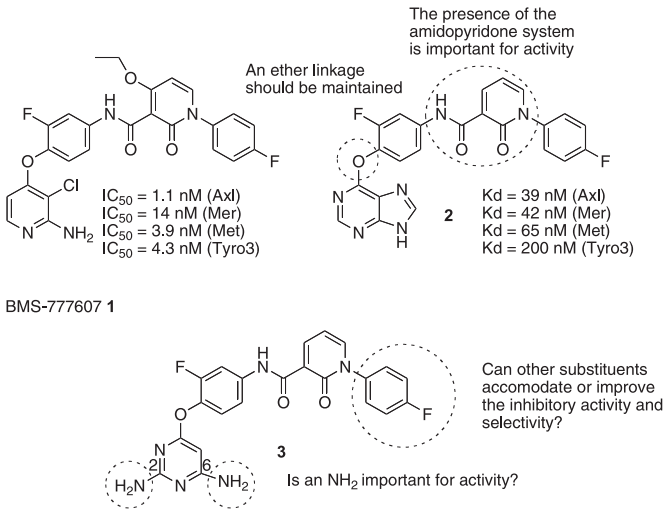


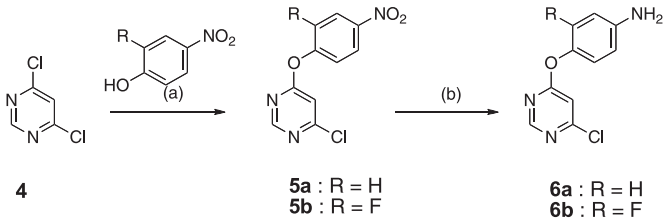
Fig. 1. Probing the anti-TAM SAR around the pyrimidine scaffold (**3**); Met and TAM family inhibitors BMS-777607 **1** [15] and **2** [19].

this context of drug design, the selectivity profile is an important issue, and it would be of high interest to design inhibitors selective for any protein of the HGFR/TAM family. However, in view of the high level of sequence similarity between Met and the enzymes of the TAM family (44% identity and 60% similarity between Met and Tyro3, and 46% identity and 64% similarity between Met and Mer), the design of selective inhibitors within the HGFR/TAM family remains a challenge. Because type II inhibitors are usually expected to display better selectivity profiles, compound **1** appeared to us as a possible starting molecule to search for more selective inhibitors within the TAM family. Among them, we paid special attention to Tyro3, a well validated drug target for bladder cancer [18], for which no specific drug is available.

Based on biochemical and docking studies, we have previously shown that the purine scaffold was also compatible with type II inhibition against Met, Tyro3, Axl and Mer, as observed in compound **2** (Fig. 1) [19]. We highlighted the necessity of the presence of an ether linkage between the purine scaffold and the amidopyridone chain, since changing this linkage led to complete loss of inhibitory activity against all considered kinases in the case of a carbon–carbon bonding and to a reduction of inhibitory activity in the case of an amino bonding, which was complete for Tyro3. The presence of the amidopyridone group in this lateral chain was found to be important (Fig. 1) [19].

In the present work, we explored the possibility to change the purine scaffold to a pyrimidine in order to modulate the selectivity profile of the inhibitor.

In addition, the effect of the presence and the position of the NH_2 was examined, since H-bond donor groups involved in protein–ligand interactions are present in similar positions in **1** and **2**.



Scheme 1. Synthesis of intermediates **6**. Reagents and conditions: (a) K_2CO_3, DMF, 80 °C, 3 h, 87% (**5a**); 93% (**5b**); (b) Raney Ni, H_2, MeOH, rt, 5 h, 47% (**6a**); 75% (**6b**).

We also tested whether other substituents on the terminal phenyl ring could modulate activity or selectivity (Fig. 1).

2. Results and discussion

2.1. Chemistry

Our initial SAR efforts began by investigating the importance of the substituent on the terminal phenyl (*p*-fluorophenyl in **1**, **2** and **3**). For this purpose, aminophenoxypyrimidines **6** were prepared by coupling 4,6-dichloropyrimidine **4** with 4-nitrophenol, followed by reduction of the nitro group of intermediates **5** by Raney nickel (Scheme 1).

Michael addition of the anilines **7a**–**e** to 3-carbomethoxy-2-pyrone followed by intramolecular cyclization of the Michael adduct provided the phenyl-2-pyridone ester **8a**–**e** [20], which were hydrolyzed to pyridone carboxylic acids **9a**–**e** with LiOH (Scheme 2).

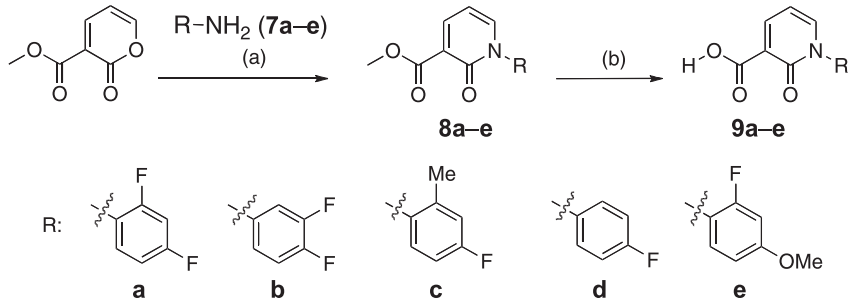
Coupling of 3-fluoroaniline **6b** with pyridone acid **9d** in the presence of TBTU/DIPEA in DMF at 0 °C led to the 6-chloropyrimidine derivative **10d** (Scheme 3). However, the chlorine atom at 6 could not be substituted by *para*-methoxybenzylamine under various conditions including in refluxing DME for 6 h. Interestingly, when the coupling of carbocylic acids **9a**–**e**, with anilines **6** was carried out at 60 °C, the O^6-(benzotriazol-1-yl)pyrimidine derivatives **11a**–**e** were isolated, resulting from the substitution of the chlorine atom by HOBT which is formed during the amide coupling. As displacement of O^6-(benzotriazol-1-yl) from a purine (inosine) with a variety of nucleophiles has been illustrated by Lakshman [21], we thought this reaction would also be efficient in pyrimidines to introduce an amino group. Indeed the O^6-benzotriazol intermediates **11a**–**e** were easily substituted with various amines to provide compounds **12a**–**e** and **14**–**15** in high yield. To the best of our knowledge, this is an unprecedented example of the use of a O^6-(benzotriazol-1-yl) as a leaving group in pyrimidine series which can lead to 6-aminopyrimidine derivatives by S_NAr displacement. A similar reaction was however reported previously [22], in the synthesis of O^2-pyrimidine ethers. Final hydrolysis of benzylamino derivatives **12a**–**e** in TFA led to amino derivatives **13a**–**e**.

In order to study the best position of the amino group (2 or 6) in the pyrimidine series, isomers of compounds **12d**, **13d**, and **15** were synthesized. For this purpose, aminophenoxypyrimidines **19a** and **19b** were prepared by coupling 2,4-dichloropyrimidine **16** with 2-fluoro-4-nitrophenol, followed by smooth substitution of the 2-chlorine atom by 4-methoxybenzylamine or methylamine, respectively. Reduction of the nitro group of intermediates **18a** and **18b** was achieved by Zn/NH_4Cl and led to **19a** and **19b** (Scheme 4). Coupling of **19a** and **19b** with **9d** was performed as for the synthesis of **11a**–**e** (Scheme 3) and led to **20a** and **20b**, respectively while treatment of **20a** with TFA led to 2-aminopyrimidine derivative **21** (Scheme 5). Thus **20a**, **21** and **20b** (Scheme 5) are isomers of **12d**, **13d** and **15**, respectively (Scheme 3).

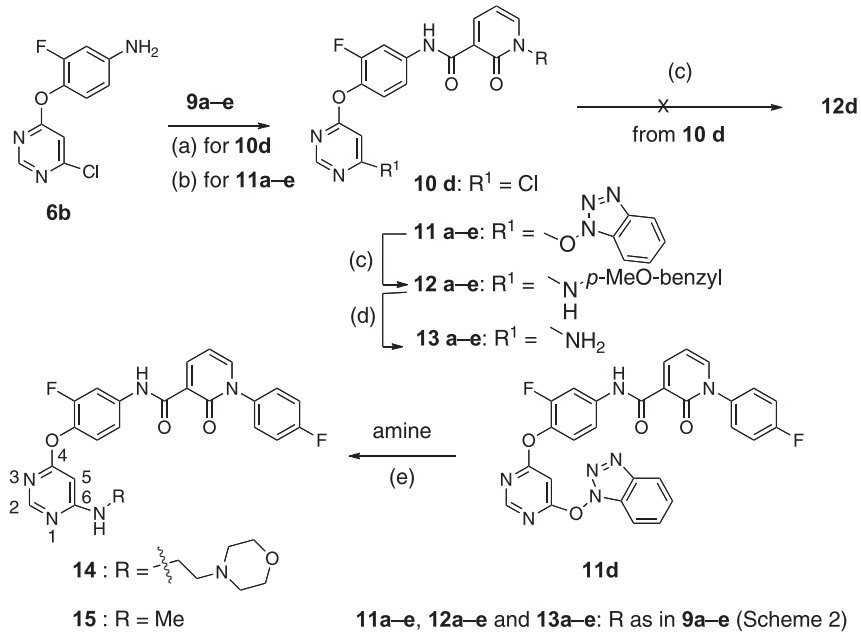
Compound **23** was then synthesized to be compared to **13d**, in order to evaluate the influence of the *ortho* fluoro atom on the phenyl ether on the inhibitory activity. The same sequence used for the synthesis of **13a**–**e** (Scheme 3) was used from 6-chloropyrimidine **6a**. As for **13a**–**e**, the amino derivative **23** was obtained after treatment of the *p*-methoxybenzylamino precursor with trifluoro acetic acid (Scheme 6).

2.2. Biological results

With the goal of targeting Tyro3, a first screening performed against Tyro3 kinase domain using an enzyme-linked-immunosorbent ELISA assay, showed that **10d**, **11a**–**e**, **12d**, **13b**,



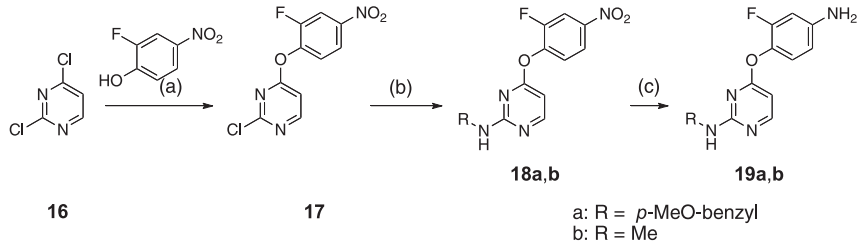
Scheme 2. Synthesis of the pyridone carboxylic acids **9a**–**e**. Reagents and conditions: (a) 1) DMF, 7 h, 0 °C 2) EDCI, DMAP, 12 h, rt; yields: **8a**–**e**, 30, 34, 27, 52 and 21%, respectively (b) LiOH, THF, 3 h, rt; yields: **9a**–**e**, 98, 96, 90, 96 and 92%, respectively.



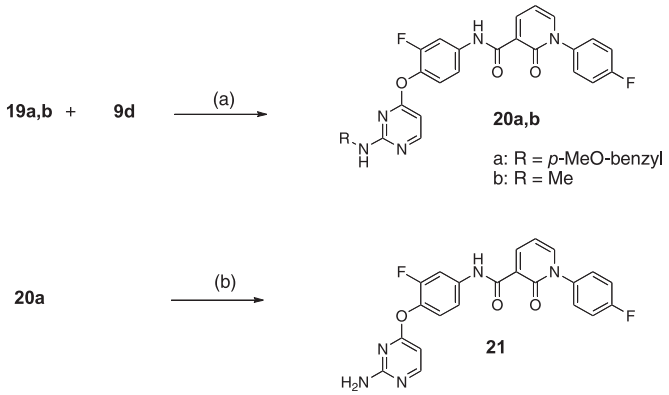
Scheme 3. Coupling of carboxylic acids **9a**–**e** with aniline **6b** and synthesis of **10d**, **11**, **12**, **13**, **14** and **15**. Reagents and conditions: (a) TBTU, DIPEA, DMF, 0 °C, 4 h; (b) TBTU, DIPEA, DMF, 60 °C, 4 h, yields: **11a**–**e**, 82, 82, 84, 88 and 84% respectively (c) *p*-MeO-benzylamine, Cs_2CO_3, DME, reflux, 6 h; yields: **12a**–**e**, 85, 90, 77, 94, 83% respectively (d) TFA, DCM, reflux, 6 h, yields: **13a**–**e**, 74, 55, 83, 68 and 91% respectively; (e) Cs_2CO_3, DME, reflux, 2 h, amine: 4-(2-aminoethyl)morpholine, or methylamine, 76% (**14**), 55% (**15**). TBTU, *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate; DIPEA, diisopropylethylamine; DMF, dimethylformamide; DME, 1,2-dimethoxyethane; TFA, trifluoro acetic acid; DCM, dichloromethane.

13e, **15**, **20a** and **20b** were inactive when assayed up to 50 μM (data not shown). The six active compounds against Tyro3 kinase were then assayed against the two other proteins of the HGFR/TAM family (Axl and Mer), Met, and a small panel of more distant tyrosine kinases to characterize their selectivity profile (Table 1).

The pyridine ring in BMS-777607 (**1**) was replaced in **21** and **13d** by a pyrimidine ring substituted in position 2 and 6 respectively (see Scheme 3 for atom numbering). As already shown for **1**, the presence of an OEt substituent on the pyridone ring is not necessary for the inhibition of Met [15]. In addition, the presence of an NH_2 in positions 2 or 6 are both compatible with activity, and **21** and **13d** have very similar selectivity profiles against the kinases included in the study. It should however be noted that BMS-777607 (**1**) was found to inhibit the non-phosphorylated form of Abl1 (i.e. the DFG-out form),



Scheme 4. Synthesis of 4-amino-2-fluorophenoxy-pyrimidine intermediates **19a** and **19b**. Reagents and conditions: (a) K_2CO_3, DMF, 80 °C, 3 h, yield: 58% (**17**); (b) K_2CO_3, DMF, 60 °C, 30 min, *p*-MeO–benzyl-NH_2, yield: 26% (**18a**) or $MeNH_2$, yield: 16% (**20**); (c) Zn, NH_4Cl, MeOH/THF 1:1, rt, 1 h, yields: 96% (**19a**), 99% (**19b**).



Scheme 5. Synthesis of the 2-amino derivatives **20** and **21**. Reagents and conditions: (a) TBTU, DIPEA, DMF, 0 °C, 4 h, yields: 85% (**20a**), 40% (**20b**); (b) TFA, DCM, reflux, 12 h, yield: 85% (**21**).

whereas **13d** and **21** were less active against Abl1. Interestingly, they exhibited more activity against the unphosphorylated form of Abl1 than the phosphorylated Abl1, which shows that they behave as type II inhibitors, at least against Abl1. Similarly, at high concentration of inhibitors, **13d** and **21** were less active than BMS-777607 against Braf and EGFR. These two observations indicate that substitution of the pyridine ring by a pyrimidine ring seems to increase the specificity towards the four proteins of the HGFR/TAM family. Such improvement in selectivity is also shared by compound **2**, in which the pyridine ring of BMS-777607 was replaced by a purine ring [19].

23 only differs from **13d** by the absence of a fluorine atom on the phenyl group born by the pyrimidine scaffold. These two molecules present very similar activities against Met and the TAM family, which shows that the presence of this fluorine atom is not crucial for the inhibitory activity. Substitution of the fluorine atom of the terminal phenyl by a larger O-Met group moiety, as in **13e**, leads to a loss of activity. Similar results have already been observed in the case of compound **2**, where replacement of F atom by a CF_3 group suppressed inhibition against Tyro3 [19].

Adding a second substituent of moderate size in *ortho* of the terminal phenyl (**13a**, substitution with F or **13c**, substitution with CH_3) is compatible with inhibition activity, although with a loss in the case of Tyro3 and Mer. These substitutions, however did not affect potency against Axl and Met, whereas substitution in *meta* of the terminal phenyl (**13b**), led to complete loss of inhibitory activity against Tyro3.

All compounds bearing no H-bond donor group on the pyrimidine ring were found to be inactive against Tyro3, namely compounds **11a** and **10d**. Most of the compounds bearing a substituted −NH group on the pyrimidine ring as H-bond donors (instead of NH_2) were also found to be inactive, namely compounds **12d**, **15**, **20a**, and **20b**, molecule **14** being the only exception to this observation.

At this point, further analysis of Table 1 urged us to add that, in the context of searching for Met inhibitors (which was not the main goal here), some of the molecules synthesized in the present study could be of interest. When compared to BMS-777607, all the molecules in Table 1 display similar inhibition activities against Met. However, they are all less potent against Braf and Abl1. In addition, they tend to be less active against Tyro3 and Mer, at least in the case of **13a** and **23**. Overall, they present a better selectivity than the reference molecule BMS-777607 currently under development as an anticancer agent.

2.3. Molecular modeling

In order to provide structural interpretation for the biological tests, we undertook molecular modeling studies. The synthesized molecules derive from inhibitor **1**, a type II inhibitor of Met, as observed in the 3F82 PDB structure. As shown in Fig. 2 in the case of **1**, type II inhibitors bind to the protein via several key interactions including (i) at least one H-bond, but often two H-bonds, one as donor and one as acceptor (with the backbone atoms of M1160 in the case of 3F82), (ii) a hydrophobic interaction in the hinge region (with the side chain of M1211 in the case of 3F82), (iii) interactions with the DFG motif (a H-bond with the side chain of the D and a hydrophobic interaction with the F residue, corresponding to D1222 and F1223 in 3F82), and hydrophobic interactions in the allosteric site. Molecules that are unable to bind to the protein via these conserved interactions are not expected to be type II inhibitors.

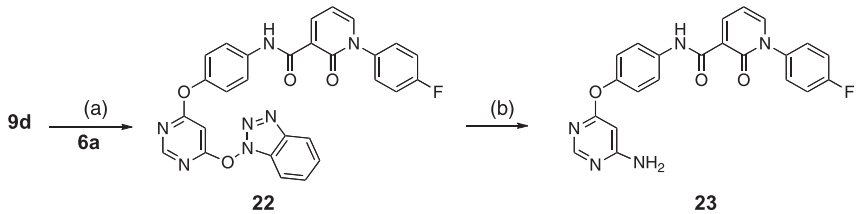
We docked the 14 synthesized molecules into the 3F82 structure of Met, the only kinase from the HGFR/TAM family for which DFG-out crystal structure is available, and into a DFG-out model of structure for Tyro3 [19], and we analyzed their predicted binding modes.

When docked in Tyro3, all active molecules with an NH_2 group on the pyrimidine ring can form a double H-bond with M606, as shown in Fig. 2 in the case of **13d**. They also present all the other interactions expected for type II inhibitors, as shown in Fig. 2 (poseview figure of **13d** docked in 3F82 and in Tyro3). The same result holds when these molecules are docked in 3F82 (as shown in Table 1, all molecules active against Tyro3 are also active against Met).

On the contrary, inactive molecules against Tyro3 bearing no H-bond donor group substituted on the pyrimidine ring, namely compounds **11a** and **10d**, were unable to form an H-bond with M606 when docked in the model of Tyro3 (as shown in Fig. 2 in the case of **10d**), or with M1160 when docked in 3F82.

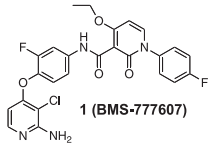
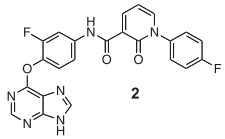
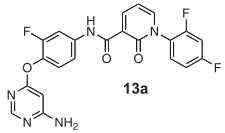
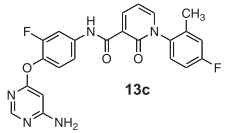
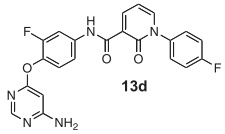
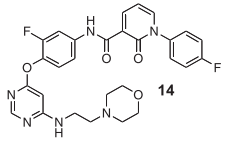
The same result was observed for the inactive molecules bearing a substituted −NH group as H-bond donors on the pyrimidine ring, namely compounds **12d**, **15**, **20a**, and **20b**. Indeed, a substituent on the −NH group leads to displacements of the pyrimidine group within the ATP-binding site in order to avoid steric hindrance, preventing the formation of the two conserved H-bonds.

Substitution of the *para*-F atom on the terminal phenyl by a larger group such as O-Met, as in the **13e** molecule, leads to a displacement of the docking pose with respect to the reference



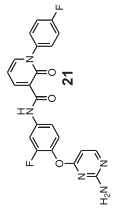
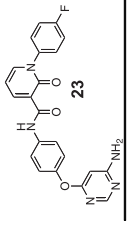
Scheme 6. Synthesis of 6-aminopyrimidine derivative **23**. Reagents and conditions: (a) TBTU, DIPEA, DMF, 0 °C, 4 h, then 60 °C, 12 h, yield: 72% (**22**); (b) 1) *p*-MeO−benzyl-NH_2, DME, reflux, 6 h 2) TFA, DCM, reflux, 12 h, yield for two steps: 69% (**23**).

Table 1
The percent inhibition refers to the percentage of kinase captured from the solid support that has been displaced by the inhibitor [23]; Concentrations tested: 0.5, 1 and 75 μM; nd, not determined.

% Inhibition at various concentrations in μM																											
	0.5	1	75	0.5	1	75	0.5	1	75	0.5	1	75	0.5	1	75	0.5	1	75	0.5	1	75	0.5	1	75	0.5	1	75
Protein	Tyro3			Axl			Mer			Met			Abl1-non phosphor.			Abl1-phosphor.			Braf			EGFR			FGFR3		
 1 (BMS-777607)	96	99	92	99	99	99	98	98	95	96	95	96	96	98	100	37	35	99	0	0	95	0	1	78	0	0	0
 2	73	94	100	98	100	98	77	93	nd	93	98	95	17	32	66	0	0	20	0	0	43	0	9	0	0	0	16
 13a	27	63	100	74	93	100	50	71	87	91	97	99	25	37	85	8	4	21	0	0	11	7	8	17	0	0	9
 13c	48	65	100	93	98	100	53	65	99	99	100	99	10	27	98	0	0	47	0	0	29	4	0	19	0	0	6
 13d	77	94	100	97	100	100	89	93	83	98	98	98	23	41	94	0	0	39	4	0	21	5	10	14	0	0	16
 14	50	63	75	95	99	100	90	93	49	98	99	99	12	12	71	1	0	13	6	0	11	9	8	8	0	0	0

(*continued on next page*)

Table 1 (*continued*)

Protein	% Inhibition at various concentrations in μM																							
	Tyro3			Axl			Mer			Met			Abl1-non phosphor.			Abl1-phosphor.			Braf			EGFR			FGFR3		
	0.5	1	75	0.5	1	75	0.5	1	75	0.5	1	75	0.5	1	75	0.5	1	75	0.5	1	75	0.5	1	75	0.5	1	75
 **21**	61	75	nd	96	100	100	94	95	nd	99	100	99	27	50	32	0	0	30	0	0	17	5	7	0	0	0	12
 **23**	41	75	81	85	95	100	73	82	100	95	98	97	14	31	94	0	0	26	0	0	0	0	0	9	0	0	3

molecule **1**, which might explain reduced hydrophobic interactions in the allosteric pocket, and loss of inhibition activity.

Docking studies were however unable to explain why the difluoro derivative (in *meta* and *para*) was not compatible with inhibition of Tyro3 as in **13b**, whereas the *ortho-para*-difluoro-substituted derivative **13a** exhibited only reduced potency.

3. Conclusion

The aim of this work was to modify the selectivity profile of the Met inhibitor **1**, and to increase the inhibitory potency in favor of Tyro3. For this purpose, pyrimidine analogs of **1** have been synthesized and tested against Tyro3 and a panel of other kinases. The synthesis of derivatives bearing an NH_2 group at position 6 of the pyrimidine ring was obtained thanks to the unanticipated substitution of the chlorine atom at position 6 of various pyrimidines by an oxybenzotriazol during the peptide coupling at 60 °C, which was beneficial as this chlorine atom could not be substituted with *p*-methoxybenzylamine under reflux of DME (Scheme 3). On the contrary, S_NAr displacement of the O^6-benzotriazol could be achieved under mild conditions, with several amines, and in particular, with methoxybenzylamine which gave an easy access to various free 6-aminopyrimidine derivatives **13a**–**e** after acid hydrolysis.

All derivatives were assayed against Tyro3 tyrosine kinase and the most active inhibitors were evaluated against the HGFR/TAM family and a panel of more distant kinases. We identified 6 pyrimidine inhibitors, namely **13a**, **13c**, **13d**, **14**, **21**, and **23**, with a slight decrease in potency against Tyro3 and Mer. Compounds **13c**, **13d**, **14** and **21** were the most potent inhibitors of Axl and Met, and remained not active against more distant kinases such as Braf, EGFR and FGFR3. They are therefore selective. Furthermore, the weak inhibition of Abl1 in phosphorylated and unphosphorylated forms by the pyrimidine inhibitors **13a**–**d**, **14**, **21** and **23** deserves to be noted, as compared to **1** which is a strong inhibitor of Abl1, at least in its unphosphorylated form.

The presence of an exocyclic NH_2 on either side of the pyrimidine N-1 is crucial for maintaining the inhibitory activity, since replacement of such an NH_2 by a chlorine atom (in **10d**) canceled the inhibition of Tyro3. Docking studies suggested that this NH_2 group is required to form two H-bonds in the ATP-binding pocket, as observed with known type II inhibitors.

To improve the selectivity for Tyro3 within this family, comparison of its ligand-binding pocket with those of Axl, Mer and Met reveals the presence of a unique subpocket near the ATP binding site due to the presence of Ala 581 in human Tyro3, a residue replaced by amino acids with larger side-chains at this position in Axl, Mer and Met. Our current efforts are aimed at synthesizing new type II inhibitors that would occupy this Ala 581 pocket, to improved selectivity for Tyro3, as shown by Powell in murine Sky for type I inhibitors [25].

4. Experimental section

4.1. Chemistry

NMR spectra were recorded at 300 MHz (^{1}H NMR) or 75.3 MHz (^{13}C NMR) with $CDCl_3$, CD_2Cl_2 or DMSO-d_6 as solvents and tetramethylsilane as internal standard on a Bruker AC300 spectrometer. Chemical shifts are expressed in ppm (δ) downfield from TMS. *J* values are expressed in Hertz (Hz). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. MS spectra were recorded on a Waters ZQ2000 mass spectrometer with direct injection. HRMS spectra were performed by the mass spectrometry service Imagif at the ICSN (Gif-sur-Yvette). Anilines are commercially available. Abbreviations used for reagents are given in the legend of Scheme 3.

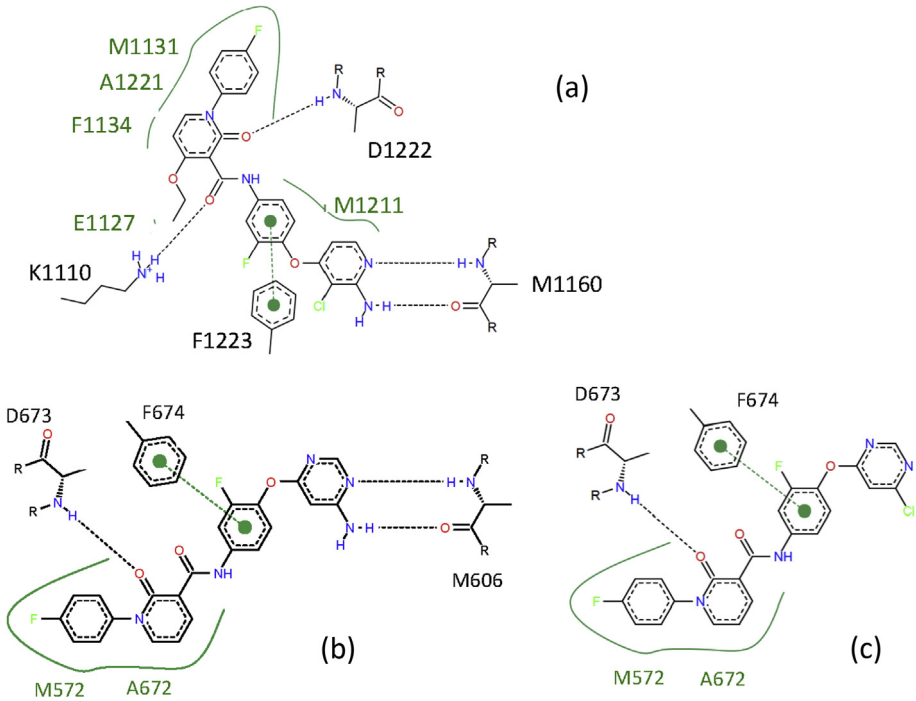


Fig. 2. Protein–ligand interactions between (a) **1** in Met (PDB code 3F82), (b) **13d** docked in Tyro3, (c) **10d** docked in Tyro3. Figures were generated using Poseview [24].

*4.1.1. General procedure for the synthesis of 4-chloro-6-(4-nitrophenoxy)pyrimidine (**5a**) and 4-chloro-6-(2-fluoro-4-nitrophenoxy)pyrimidine (**5b**)*

In a dry sealed tube under argon were placed, 4,6-dichloropyrimidine (1 g, 6.7 mmol), 4-nitrophenol (1.1 g, 7.9 mmol), or 2-fluoro-4-nitrophenol (1.24 g, 7.9 mmol), (potassium carbonate (1.3 g, 9.3 mmol) in DMF (13 mL) and the mixture was heated at 80 °C for 3 h. The mixture was then cooled at room temperature and the solvent evaporated under high vacuum. The residue was extracted with EtOAc, washed with a saturated solution of $NaHCO_3$, water and brine. The organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated to give the crude product as a yellow solid. The residue was purified by flash chromatography using Cyclohexane/DCM 35: 65 as eluent to afford the desired product which was used in the next step without any further purification.

*4.1.1.1. 4-Chloro-6-(4-nitrophenoxy)pyrimidine (**5a**).* Light yellow solid in 87% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.70 (s, 1H), 8.36 (d, J = 12 Hz, 2H), 7.6 (s, 1H), 7.57 (d, J = 12 Hz, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 169, 161.2, 158.4, 156.8, 144.9, 125.6, 122.8, 108.9. MS (EI) ES$^+$: 252 ([M$^+$ + H], 100).

*4.1.1.2. 4-Chloro-6-(2-fluoro-4-nitrophenoxy)pyrimidine (**5b**).* This compound was obtained with 93% yield according to the general method. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.70 (d, J = 3 Hz, 1H), 8.43–8.39 (dd, J = 6 Hz, J = 3 Hz, 1H), 8.24–8.20 (m, 1H), 7.82–7.77 (m, 1H), 7.75 (d, J = 3 Hz, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 169.5, 168.2, 161.5, 158.4, 154.7, 151.4, 145.7, 145.6, 144.2, 144.1, 124.9, 121.1, 121, 113.3, 113, 108.3. MS (EI) ES$^+$: 270 ([M$^+$ + H], 100).

*4.1.2. General procedure for the synthesis of 4-((6-chloropyrimidin-4-yl)oxy) aniline (**6a**), and 4-((6-chloropyrimidin-4-yl)oxy)-3-fluoroaniline (**6b**)*

A solution of 4-chloro-6-(4-nitrophenoxy)pyrimidine **5a** (0.5 g, 1.98 mmol) or 4-chloro-6-(2-fluoro-4-nitrophenoxy)pyrimidine **5b** (0.5 g, 1.85 mmol) in methanol (48 mL) was treated with Ni Raney (1.2 g aqueous slurry) and the mixture was stirred under hydrogen at room temperature for 3 h. The catalyst was then filtered over a pad of celite, washed with EtOAc and DCM and the filtrate was evaporated. The brown residue was extracted with EtOAc. The organic layer was washed with water and brine; dried over $MgSO_4$ and filtered. The solvent was evaporated to give the crude product as a brown solid. This residue was purified by flash chromatography using Cyclohexane/Ethyl acetate 65:35 as eluent to afford the desired product as a solid.

*4.1.2.1. 4-((6-Chloropyrimidin-4-yl)oxy) aniline (**6a**).* A white solid was obtained in 47% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.62 (s, 1H), 7.13 (s, 1H), 6.99–6.78 (m, 2H), 6.70–6.49 (m, 2H), 5.13 (s, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 170.8, 160.6, 158.6, 146.8, 141.7, 121.6, 114.3, 107.2. MS (EI) ES$^+$: 222 ([M$^+$ + H], 100).

*4.1.2.2. 4-((6-Chloropyrimidin-4-yl)oxy)-3-fluoroaniline (**6b**).* This compound was obtained with 75% yield according to the general procedure. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.64 (s, 1H), 7.40 (s, 1H), 6.97 (t, J = 9 Hz, 1H), 6.49–6.44 (dd, J = 9 Hz, J = 6 Hz, 1H), 6.40–6.36 (m, 1H), 5.44 (s, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 169.9, 160.8, 158.8, 155.5, 152.3, 148.7, 148.5, 128, 127.8, 123.7, 123.6, 109.6, 109.5, 107.3, 101.1, 100.8 MS (EI) ES$^+$: 240 ([M$^+$ + H], 100).

*4.1.3. General procedure A for the synthesis of substituted pyridones (**8a–e**)*

In a dry flask under argon, a solution of methyl-2-oxo-2*H*-pyran-3-carboxylate (1.5 g, 9.7 mmol) in DMF (10 mL) was placed at 0 °C and the corresponding substituted aniline (10 mmol) was added dropwise to the mixture and stirred 7 h at this temperature. Then EDCI (N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide) (2.4 g, 12 mmol) and DMAP (4-Dimethylaminopyridine) (0.3 g, 2.4 mmol) were added to the mixture and stirred at room temperature for 12 h. The solvent was removed under high vacuum and the brown oil was extracted with EtOAc, washed with water, brine, dried over $MgSO_4$ and filtered. The solvent was evaporated to give the crude product as a brown oil which was purified by flash chromatography to afford the desired product.

*4.1.3.1. Methyl-1-(2,4-difluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (**8a**).* From 2,4-difluoroaniline (**7a**). Flash chromatography using DCM/Ethyl acetate 95:5 as eluent affords the desired product with 30% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.18 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 7.98 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 7.64–7.54 (m, 2H), 7.31–7.25 (m, 1H), 6.47 (t, $J = 6$ Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): δ 164.7, 163.8, 163.7, 160.5, 158.7, 158.5, 157.4, 155.3, 155.1, 145.4, 144.4, 130.6, 130.5, 124.6, 124.5, 124.4, 124.3, 120.4, 112.4, 112.3, 112.1, 112.0, 105.2, 104.9, 104.8, 104.5, 51.8. MS (EI) ES$^+$: 266 ([M$^+$ + H], 100), 288 ([M$^+$ + Na], 70).

*4.1.3.2. Methyl-1-(3,4-difluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (**8b**).* From 3,4-difluoroaniline (**7b**) Flash chromatography using DCM/Ethyl acetate 95:5 as eluent affords the desired product with 34% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.14 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 7.97 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 7.76–7.57 (m, 2H), 7.35–7.21 (m, 1H), 6.44 (t, $J = 6$ Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 164.8, 157.9, 150.9, 150.4, 147.7, 145, 143.9, 136.9, 136.8, 136.7, 124.5, 124.4, 124.3, 120.6, 117.8, 117.6, 117.3, 117.1, 104.6, 51.8. MS (EI) ES$^+$: 266 ([M$^+$ + H], 10); 288 ([M$^+$ + Na], 100).

*4.1.3.3. Methyl-1-(4-fluoro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (**8c**).* From 4-fluoro-2-methylaniline (**7c**). Flash chromatography using 2%–5% Ethanol/DCM as eluent affords the desired product with 27% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.17 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 7.86 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 7.36–7.27 (m, 2H), 7.21–7.16 (m, 1H), 6.44 (t, $J = 6$ Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 164.9, 163.3, 160, 157.7, 145, 144.3, 137.5, 137.4, 136, 129.5, 129.3, 120, 117.2, 117, 113.8, 113.5, 104.6, 51.8, 17.1. MS (EI) ES$^+$: 284 ([M$^+$ + Na], 100).

*4.1.3.4. Methyl-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (**8d**).* From 4-fluoroaniline (**7d**). Flash chromatography using 0.5% Ethanol/DCM as eluent affords the desired product with 52% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.25 (dd, $J = 9$ Hz, 1H), 7.57 (dd, $J = 6$ Hz, 1H), 7.33–7.38 (m, 2H), 7.17 (t, $J = 9$ Hz, 2H), 6.34 (t, $J = 6$ Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 164.1, 160.8, 145.0, 143.3, 136.1, 128.6, 128.5, 122.0, 116.5, 116.2, 105.5, 51.8. MS (EI) ES$^+$: 270 ([M$^+$ + Na], 100).

*4.1.3.5. Methyl-2-oxo-1-(2-fluoro-4-methoxyphenyl)-1,2-dihydropyridine-3-carboxylate (**8e**).* From 2-fluoro-4-methoxyaniline (**7e**). Flash chromatography using DCM/Ethyl acetate 95:5 as eluent affords the desired product with 21% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.16 (dd, $J_1 = 3$ Hz, $J_2 = 6$ Hz, 1H), 7.95 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 7.46 (t, $J = 9$ Hz, 1H), 7.10 (dd, $J_1 = 3$ Hz, $J_2 = 9$ Hz, 1H), 6.94 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 6.44 (t, $J = 6$ Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm): 164.8, 160.8, 160.7, 158.8, 157.6, 155.5, 145.1, 144.7, 129.6, 129.5, 120.6, 120.5, 120.4, 110.6, 110.5, 104.6, 102.3, 102, 55.9, 51.8. MS (EI) ES$^+$: 278 ([M$^+$ + H], 80); 300 ([M$^+$ + Na], 30).

*4.1.4. General procedure B for the synthesis of substituted pyridone carboxylic acids (**9a**–**e**)*

A solution of the corresponding substituted pyridone ester (1.4 g, mmol) in THF (45 mL) at room temperature was treated with an aqueous solution of LiOH 1 M (10 mL) during 3 h. The solvent was evaporated; the residue was extracted with EtOAc and the pH was adjusted to 2. The organic layer was dried over $MgSO_4$, filtered and the solvent was removed to give the crude product as a yellow powder, which will be used without any further purification.

*4.1.4.1. 1-(2,4-Difluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**9a**).* The desired product was obtained with 98% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 13.8 (s, 1H), 8.51 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 8.24 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 7.79–7.71 (m, 1H), 7.65–7.58 (m, 1H), 7.36–7.30 (m, 1H), 6.83 (t, $J = 6$ Hz, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 164.3, 164.1, 162.7, 160.9, 160.8, 158.4, 154.2, 155, 154.9, 146.8, 145.2, 130.6, 130.4, 123.3, 123.1, 117.6, 112.6, 112.2, 108.3, 105.4, 105.1, 104.8. MS (EI) ES$^+$: 274 ([M$^+$ + Na], 100). MS (EI) ES$^-$: 250 ([M$^-$ − H], 90).

*4.1.4.2. 1-(3,4-Difluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**9b**).* The desired product was obtained with 96% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 14.07 (s, 1H), 8.50 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 8.22 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 7.88–7.81 (m, 1H), 7.70–7.63 (m, 1H), 7.49 (t, $J = 3$ Hz, 1H), 6.81 (t, $J = 6$ Hz, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 164.4, 163.4, 151.4, 151.3, 150.2, 148.1, 148, 147.4, 146.4, 144.9, 135.5, 135.4, 124.4, 118.1, 117.8, 117.5, 117, 108.2. MS (EI) ES$^+$: 274 ([M$^+$ + Na], 100). MS (EI) ES$^-$: 250 ([M$^-$ − H], 90).

*4.1.4.3. 1-(4-Fluoro2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**9c**).* The desired product was obtained with 90% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 14.16 (s, 1H), 8.53 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 8.15 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 7.50–7.46 (m, 1H), 7.37–7.33 (dd, $J = 3$ Hz, $J = 9$ Hz, 1H), 7.25–7.21 (td, 1H), 6.83 (t, $J = 6$ Hz, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 164.5, 163.6, 163.3, 160.4, 146.4, 145.1, 137.4, 137.2, 134.8, 134.7, 129.4, 129.3, 117.5, 117.2, 114, 113.7, 108.5, 16.9. MS (EI) ES$^-$: 246 ([M$^-$ − H], 90), 202 ([M$^-$ − CO_2H], 70).

*4.1.4.4. 1-(4-Fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**9d**).* The desired product was obtained with 96% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 14.23 (s, 1H), 8.49 (d, $J = 6$ Hz, 1H), 8.21 (d, $J = 6$ Hz, 1H), 7.62–7.59 (m, 2H), 7.44–7.39 (td, 2H), 6.81 (t, $J = 9$ Hz, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 164.6, 163.7, 160.4, 146.3, 145.2, 135.4, 129.2, 129.0, 117.4, 116.3, 116.0, 108.3. MS (EI) ES$^+$: 256 ([M$^+$ + Na], 100). MS (EI) ES$^-$: 232 ([M − H], 100).

*4.1.4.5. 1-(2-Fluoro-4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (**9e**).* The desired product was obtained with 92% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 13.97 (s, 1H), 8.51 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 8.21 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 7.58 (t, $J = 9$ Hz, 1H), 7.16 (dd, $J = 3$ Hz, $J = 9$ Hz, 1H), 6.98 (dd, $J = 3$ Hz, $J = 9$ Hz, 1H), 6.81 (t, $J = 6$ Hz, 1H), 3.84 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) d (ppm): 164.4, 163.1, 161.4, 161.3, 158.5, 155.2, 146.6, 145.7, 129.4, 119.2, 119, 117.3, 110.9, 108.3, 102.4, 102.1, 56.1. MS (EI) ES$^+$: 286 ([M$^+$ + Na], 100).

*4.1.5. General procedure C for the synthesis of N-(4-(6-chloropyrimidin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**10d**) and N-(4-((6-((1H-benzo[d][1,2,3]triazol-1-yl)oxy)pyrimidin-4-yl)oxy)-3-fluorophenyl)-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide (**11a**–**e**)*

In a dry flask under argon, were placed the corresponding carboxylic acid (0.68 mmol), TBTU (0.81 mmol) in DMF (1 mL) and the solution was cool down at 0 °C. Then DIPEA (1.8 mmol) was added and the mixture was stirred during 15 min. The amino-pyrimidine **6b** (0.62 mmol) was added and the mixture stirred 4 h at 0 °C for compound **10d**, then 12 h at 60 °C for compounds **11a**–**e**. The solvent was removed under high vacuum and the brown oil was extracted with EtOAc, washed with water, brine, dried over $MgSO_4$ and filtered. The solvent was evaporated to give the crude product as a brown solid which was purified by flash chromatography to afford the desired product.

*4.1.5.1. N-(4-(6-Chloropyrimidin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**10d**).* ^{1}H NMR (CD_2Cl_2, 300 MHz) δ (ppm): 12.09 (s, 1H), 8.74 (dd, $J = 6$ Hz, $J = 2$ Hz, 1H), 8.56 (s, 1H), 8.0 (dd, $J = 12$ Hz, $J = 2$ Hz, 1H), 7.69 (dd, $J = 6$ Hz, $J = 2$ Hz, 1H), 7.46–7.41 (m, 2H), 7.32–7.26 (m, 3H), 7.18 (t, $J = 8$ Hz, 1H), 7.06 (s, 1H), 6.66–6.61 (t, $J = 6$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 169.6, 164.4, 162.4, 161.9, 161.4, 161.1, 158.4, 155.6, 152.3, 145.2, 141.7, 137.6, 137.5, 135.8, 135.7, 135.1, 134.9, 128.4, 128.3, 123.3, 121.9, 117, 116.7, 116.2, 116.1, 109.5, 109.2, 107.6, 107.3. MS (EI) ES$^+$: 477 ([M$^+$ + Na], 100). HRMS-ESI (*m/z*) calcd for $C_{22}H_{14}ClF_2N_4O_3$ (M + H$^+$) 455.0720, found: 455.0716.

*4.1.5.2. N-(4-((6-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)pyrimidin-4-yl)oxy)-3-fluorophenyl)-1-(2,4-difluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**11a**).* Flash chromatography using 1%–5% Ethyl acetate/DCM as eluent affords the desired product with 82% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 11.86 (s, 1H), 8.78 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 8.35 (s, 1H), 8.14 (d, $J = 6$ Hz, 1H), 7.98 (dd, $J = 3$ Hz, $J = 12$ Hz, 1H), 7.61–7.36 (m, 7H), 7.20–7.08 (m, 3H), 6.67–6.63 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 171.3, 171.2, 161.9, 161.2, 158.3, 155.6, 152.3, 145.6, 143.4, 141.9, 137.6, 137.4, 135.3, 129, 128.5, 125, 123.3, 122, 120.6, 116.3, 116.2, 109.5, 109.2, 108.6, 107.5, 90.3, 60.4, 21, 14.2. MS (EI) ES$^+$: 594 ([M$^+$ + Na], 10). MS (EI) ES$^-$: 570 ([M$^-$ − H], 100); 616 ([M$^+$ + CO_2H], 30).

*4.1.5.3. N-(4-((6-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)pyrimidin-4-yl)oxy)-3-fluorophenyl)-1-(3,4-difluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**11b**).* Flash chromatography using 1%–5% Ethyl acetate/DCM as eluent affords the desired product with 82% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 11.91 (s, 1H), 8.77 (dd, $J = 3$ Hz, $J = 9$ Hz, 1H), 8.35 (s, 1H), 8.14 (d, $J = 9$ Hz, 1H), 7.97 (dd, $J = 3$ Hz, $J = 9$ Hz, 1H), 7.63–7.57 (m, 2H), 7.54–7.43 (m, 2H), 7.41–7.30 (m, 2H), 7.24–7.15 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 171.3, 171.2, 162.2, 161.2, 158.3, 155.6, 152.3, 152.1, 149.2, 148.7, 145.4, 143.4, 141.3, 137.6, 137.4, 135.7, 135.3, 135.1, 129, 128.5, 125, 123.4, 122.1, 120.6, 118.5, 116.2, 109.5, 109.2, 108.6, 107.5, 90.3. MS (EI) ES$^-$: 570 ([M$^-$ − H], 100); 616 ([M$^+$ + CO_2H], 30).

*4.1.5.4. N-(4-((6-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)pyrimidin-4-yl)oxy)-3-fluorophenyl)-1-(2-methyl-4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**11c**).* Flash chromatography using 3%–5% Ethyl acetate/DCM as eluent affords the desired product with 84% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 12.04 (s, 1H), 8.79 (dd, $J_1 = 3$ Hz, $J_2 = 9$ Hz, 1H), 8.34 (s, 1H), 8.14 (d, $J = 9$ Hz, 1H), 7.99 (dd, $J = 3$ Hz, $J = 12$ Hz, 1H), 7.59–7.45 (m, 4H), 7.39 (m, 1H), 7.24–7.10 (m, 4H), 6.66 (m, 2H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 170.7, 170.6, 163.5, 161.5, 161.4, 160.3, 158.1, 154.9, 151.6, 145.1, 144.2, 142.7, 137.5, 137.4, 135.5, 129.5, 129.4, 128.2, 125.3, 124.1, 120.1, 119.9, 117.4, 117.1, 116.2, 113.9, 113.6, 109.3, 108.3, 108, 107.2, 90.8, 17. MS (EI) ES$^+$: 590 ([M$^+$ + Na], 100).

*4.1.5.5. N-(4-((6-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)pyrimidin-4-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**11d**).* Flash chromatography using Cyclohexane/Ethyl acetate 65:35 as eluent affords the desired product with 88% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 12.01 (s, 1H), 8.76 (dd, $J = 3$ Hz, $J = 6$ Hz, 1H), 8.35 (s, 1H), 8.14 (d, $J = 6$ Hz, 1H), 7.99 (dd, $J = 3$ Hz, $J = 12$ Hz, 1H), 7.65–7.25 (m, 9H), 7.19 (t, $J = 6$ Hz, 1H), 6.67 (s, 1H), 6.65 (t, $J = 6$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 171.2, 164.4, 162.4, 161.4, 161.1, 158.3, 155.6, 152.3, 145.2, 143.4, 141.8, 137.7, 137.5, 135.8, 135.7, 135.1, 129, 128.5, 128.4, 128.3, 125, 123.3, 121.9, 120.6, 117, 116.7, 116.1, 109.4, 109.1, 108.6, 107.3, 90.3. MS (EI) ES$^+$: 576 ([M$^+$ + Na], 100). MS (EI) ES$^-$: 552 ([M$^-$ − H], 100). HRMS-ESI (*m/z*) calcd for $C_{28}H_{18}F_2N_7O_4$ (M + H$^+$): 554.1385, found: 554.1378.

*4.1.5.6. N-(4-((6-((1H-Benzo[d][1,2,3]triazol-1-yl)oxy)pyrimidin-4-yl)oxy)-3-fluorophenyl)-1-(2-fluoro-4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**11e**).* Flash chromatography using DCM/Ethyl acetate 98:2 as eluent affords the desired product with 84% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 11.98 (s, 1H), 8.76 (dd, $J_1 = 3$ Hz, $J_2 = 9$ Hz, 1H), 8.34 (s, 1H), 8.14 (d, $J = 9$ Hz, 1H), 7.98 (dd, $J = 3$ Hz, $J = 12$ Hz, 1H), 7.61–7.30 (m, 6H), 7.19 (t, $J = 9$ Hz, 1H), 6.88 (m, 2H), 6.66 (s, 1H), 6.64 (t, $J = 9$ Hz, 1H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 171.2, 162.2, 161.9, 161.7, 161.5, 158.3, 155.8, 152.3, 145.3, 143.3, 142.5, 137.7, 135.2, 135, 129, 128.7, 128.5, 125, 123.3, 121.8, 120.5, 120, 119.8, 110.8, 110.7, 108.6, 107.2, 102.7, 90.3, 60.4, 60.3, 56.2, 14.2. MS (EI) ES$^+$: 585 ([M$^+$ + H], 100).

*4.1.6. General procedure D for the synthesis of 1-(substituted phenyl)-N-(3-fluoro-4-(6-(4-methoxybenzylamino)pyrimidin-4-yloxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**12a–e**)*

In a dry flask under argon, a solution of the corresponding benzotriazol **11** (0.36 mmol), 4-methoxy-benzylamine (0.43 mmol) and cesium carbonate (0.72 mmol) in DME (6 mL) was heated at reflux during 6 h. The solvent was removed, the residue was extracted with EtOAc, washed with water, brine, dried over $MgSO_4$ and filtered. The solvent was evaporated to give the crude product which was purified by flash chromatography to afford the desired product.

*4.1.6.1. 1-(2,4-Difluorophenyl)-N-(3-fluoro-4-(6-(4-methoxybenzylamino)pyrimidin-4-yloxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**12a**).* Flash chromatography using DCM/Ethyl acetate 70:30 as eluent affords the desired product with 85% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 11.85 (s, 1H), 8.63 (dd, $J = 6$ Hz, $J = 2$ Hz, 1H), 8.17–8.11 (m, 2H), 7.93–7.72 (m, 3H), 7.65–7.58 (m, 1H), 7.42–7.17 (m, 5H), 6.90 (d, $J = 9$ Hz, 2H), 6.79 (t, $J = 6$ Hz, 1H), 5.95 (s, 1H), 4.43 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 168.1, 164.5, 164, 162.8, 161.2, 160.8, 158.6, 158.2, 155.2, 155, 152, 145.5, 144.2, 136.4, 136.3, 135.4, 135.3, 130.7, 130.6, 128.5, 124.3, 124, 123.8, 123.1, 120.1, 116.1, 113.7, 112.5, 112.2, 108.4, 108, 107.3, 105, 104.7, 54.9, 43.2. MS (EI) ES$^+$: 574 ([M$^+$ + H], 100).

*4.1.6.2. 1-(3,4-Difluorophenyl)-N-(3-fluoro-4-(6-(4-methoxybenzylamino)pyrimidin-4-yloxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**12b**).* Flash chromatography using DCM/Ethyl acetate 70:30 as eluent affords the desired product with 90% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 11.97 (s, 1H), 8.60 (dd, $J = 6$ Hz, $J = 2$ Hz, 1H), 8.14–8.11 (m, 2H), 7.93–7.85 (m, 3H), 7.70–7.66 (m, 1H), 7.46–7.17 (m, 5H), 6.90 (d, $J = 9$ Hz, 2H), 6.75 (t, $J = 6$ Hz, 1H), 5.95 (s, 1H), 4.43 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 168.2, 164.5, 161.6, 161.3, 160.8, 158.2, 155.3, 152, 151.3, 150.7, 150.5, 147.8, 147.4, 145, 143.8, 136.5, 136.4, 135.4, 135.2, 130.8, 128.5, 124.3, 120.2, 118, 117.7, 117.5, 117.2, 115.9, 113.7, 108.3, 108, 107, 54.9, 43.2. MS (EI) ES$^+$: 574 ([M$^+$ + H], 100).

*4.1.6.3. 1-(4-Fluoro-2-methylphenyl)-N-(3-fluoro-4-(6-(4-methoxybenzylamino) pyrimidin-4-yloxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**12c**).* Flash chromatography using DCM/Ethyl acetate 90:10 as eluent affords the desired product with 77% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.97 (s, 1H), 8.58 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 8.13 (m, 2H), 7.93–7.83 (m, 3H), 7.73–7.63 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 7.48–7.38 (m, 2H), 7.25 (m, 3H), 6.90 (d, $J = 8$ Hz, 2H), 6.73 (t, $J = 7$ Hz, 1H), 5.95 (s, 1H), 4.43 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 164.5, 163.5, 161.5, 161.4, 160.2, 158.2, 157.8, 155.2, 152, 145, 144.1, 137.5, 137.4, 136.5, 135.5, 128.5, 124.3, 120.1, 117.4, 117.1, 116, 113.9, 113.7, 108.3, 108, 107.2, 54.9, 42.1, 17. MS (EI) ES$^+$: 570 ([M$^+$ + H], 10); 592 ([M$^+$ + Na], 15).

*4.1.6.4. 1-(4-Fluorophenyl)-N-(3-fluoro-4-(6-(4-methoxybenzylamino)pyrimidin-4-yloxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**12d**).* Flash chromatography using Cyclohexane/Ethyl acetate 60:40 as eluent affords the desired product with 94% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 11.93 (s, 1H), 8.76 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 8.25 (s, 1H), 7.93 (dd, $J = 12$ Hz, $J = 2$ Hz, 1H), 7.62 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 7.44–7.39 (m, 2H), 7.24–7.12 (m, 5H), 7.15 (t, $J = 7$ Hz, 1H), 6.91–6.37 (m, 2H), 6.64 (t, $J = 7$ Hz, 1H), 5.84 (s, 1H), 5.31 (s, 1H), 4.43 (s, $J = 6$ Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 169, 164.4, 164.0, 163.4, 161.7, 161.1, 160.2, 158.2, 148.5, 144.6, 143.8, 136.3, 136.2, 135.3, 129.3, 128.5, 122, 120.9, 120.4, 116.1, 115.8, 113.7, 106.9, 54.9, MS (EI) ES$^+$: 556 ([M$^+$ + H], 60); 578 ([M$^+$ + Na], 100). HRMS-ESI (m/z) calcd for $C_{30}H_{24}F_2N_5O_4$ (M + H$^+$): 556.1791, found: 556.1774.

*4.1.6.5. 1-(2-Fluoro-4-methoxyphenyl)-N-(3-fluoro-4-(6-(4-methoxybenzylamino) pyrimidin-4-yloxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**12e**).* Flash chromatography using 1%–2% Ethanol/DCM as eluent affords the desired product with 83% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 11.94 (s, 1H), 8.60 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 8.13 (dd, $J = 7$ Hz, $J = 2$ Hz, 2H), 7.91 (d, $J = 12$ Hz, 2H), 7.54 (t, $J = 8$ Hz, 1H), 7.40 (d, $J = 8.0$ Hz, 1H), 7.24 (d, $J = 8$ Hz, 3H), 7.13 (dd, $J = 12$ Hz, $J = 2$ Hz, 1H), 6.97 (dd, $J = 8$ Hz, $J = 2$ Hz, 1H), 6.89 (d, $J = 8$ Hz, 2H), 6.74 (t, $J = 7$ Hz, 1H), 5.94 (s, 1H), 4.43 (s, 2H), 3.85 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 164.5, 161.4, 161.2, 161.1, 158.7, 158.2, 155.4, 155.2, 152, 145.2, 144.6, 136.5, 136.3, 135.2, 129.5, 128.5, 124.3, 120, 119.8, 116, 113.7, 110.7, 108.3, 108, 107.1, 102.4, 102.1, 56, 54.9, 43.2 MS (EI) ES$^+$: 586 ([M$^+$ + H], 50).

*4.1.7. General procedure E for the synthesis of N-(4-(6-aminopyrimidin-4-yloxy)-3-fluorophenyl)-1-(substituted-phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**13a–e**)*

In a dry flask under argon, to a solution of the corresponding compound **12** (0.22 mmol) in DCM (1 mL) was added dropwise TFA (3 mL) and the mixture was heated at reflux during 6 h. The solvent was removed, the residue was extracted with EtOAc, washed with basic water until neutral pH, then with brine, dried over $MgSO_4$ and filtered. The solvent was evaporated to give the crude product which was purified by flash chromatography to afford the desired product.

*4.1.7.1. N-(4-(6-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-1-(2,4-difluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**13a**).* Flash chromatography using 2%–5% Ethanol/DCM as eluent affords the desired product with 74% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 11.85 (s, 1H), 8.62 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 8.16 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 8.05 (s, 1H), 7.92 (dd, $J = 12$ Hz, $J = 2$ Hz, 1H), 7.84–7.68 (m, 1H), 7.61 (td, $J = 12$ Hz, $J = 2$ Hz, 1H), 7.34 (m, 3H), 6.93 (s, 2H), 6.77 (t, $J = 7$ Hz, 1H), 5.86 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 168.4, 166, 164.1, 164, 161.2, 161.1, 160.8, 160.7, 158.6, 158.4, 158, 155.3, 155, 152, 145.5, 144.2, 136.4, 136.3, 135.4, 135.3, 130.7, 124.4, 124, 123.9, 123.8, 120.1, 116.1, 112.5, 112.2, 108.4, 108.1, 107.3, 105.4, 105.1, 104.7. MS (EI) ES$^+$: 454 ([M$^+$ + H], 100). HRMS-ESI (m/z) calcd for $C_{22}H_{15}F_3N_5O_3$ (M + H$^+$): 454.1124, found: 454.1144.

*4.1.7.2. N-(4-(6-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-1-(3,4-difluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**13b**).* Flash chromatography using 2%–5% Ethanol/DCM as eluent affords the desired product with 55% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 11.97 (s, 1H), 8.58 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 8.13 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 8.04 (s, 1H), 7.98–7.78 (m, 2H), 7.68 (dd, $J = 20$ Hz, $J = 9$ Hz, 1H), 7.54–7.34 (m, 2H), 7.27 (t, $J = 9$ Hz, 1H), 6.92 (s, 2H), 6.73 (t, $J = 7$ Hz, 1H), 5.85 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 170.3, 168.4, 165.9, 161.6, 161.3, 158, 155.3, 152, 151.1, 150, 147.8, 147.2, 145, 143.8, 136.5, 136.4, 135.2, 124.4, 120.2, 118, 117.4, 117.2, 116, 108.3, 108, 107, 85.7, 59.7, 20.7, 14. MS (EI) ES$^+$: 454 ([M$^+$ + H], 100). HRMS-ESI (m/z) calcd for $C_{22}H_{15}F_3N_5O_3$ (M + H$^+$): 454.1124, found: 454.1116.

*4.1.7.3. N-(4-(6-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-1-(2-methyl-4-fluoro-phenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**13c**).* Flash chromatography using 1%–3% Ethanol/DCM as eluent affords the desired product with 83% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.03 (s, 1H), 8.62 (d, $J = 6$ Hz, 1H), 8.06 (d, $J = 3$ Hz, 1H), 8.03 (s, 1H), 7.93 (d, $J = 15$ Hz, 1H), 7.39–7.23 (m, 5H), 6.91 (s, 2H), 6.76 (t, $J = 6$ Hz, 1H), 5.83 (s, 1H), 2.08 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 170.3, 168.4, 165.9, 163.5, 161.5, 161.4, 160.2, 158, 155.3, 152, 145, 144.1, 137.5, 136.5, 135.5, 129.5, 129.4, 124.5, 120.1, 117.4, 117.1, 116, 113.9, 113.6, 108.3, 108, 107.2, 85.7, 59.7, 20.7, 17, 14. MS (EI) ES$^+$: 472 ([M$^+$ + H], 50). MS (EI) ES$^-$: 448 ([M$^-$ + H], 100). HRMS-ESI (m/z) calcd for $C_{23}H_{18}F_2N_5O_3$ (M + H$^+$): 450.1374, found: 450.1397.

*4.1.7.4. N-(4-(6-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**13d**).* Flash chromatography using 2%–3% Ethanol/DCM as eluent affords the desired product with 68% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.03 (s, 1H), 8.57 (d, $J = 7$ Hz, 1H), 8.19–7.98 (m, 2H), 7.90 (d, $J = 12$ Hz, 1H), 7.71–7.51 (m, 2H), 7.41 (t, $J = 8$ Hz, 3H), 7.26 (t, $J = 8$ Hz, 1H), 6.90 (s, 2H), 6.71 (t, $J = 7$ Hz, 1H), 5.83 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 168.4, 165.9, 163.4, 161.7, 161.4, 160.2, 158, 155.3, 152, 144.9, 144.1, 136.4, 136.2, 136.1, 129.3, 129.2, 124.4, 120.1, 116.2, 116, 115.8, 108.3, 108, 106.9, 85.7. MS (EI) ES$^+$: 458 ([M$^+$ + H], 100). MS (EI) ES$^-$: 434 ([M$^-$ + H], 100). HRMS-ESI (m/z) calcd for $C_{22}H_{16}F_2N_5O_3$ (M + H$^+$): 436.1218, found: 436.1216.

*4.1.7.5. N-(4-(6-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-1-(2-fluoro-4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**13e**).* Flash chromatography using 1%–3% Ethanol/DCM as eluent affords the desired product with 91% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 11.94 (s, 1H), 8.59 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 8.12 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 8.04 (d, $J = 1$ Hz, 1H), 7.91 (dd, $J = 12$ Hz, $J = 2$ Hz, 1H), 7.53 (t, $J = 9$ Hz, 1H), 7.45–7.35 (m, 1H), 7.27 (t, $J = 9$ Hz, 1H), 7.12 (dd, $J = 12$ Hz, $J = 2$ Hz, 1H), 7.00–6.84 (m, 3H), 6.78–6.67 (m, 1H), 5.85 (d, $J = 1$ Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 168.4, 166, 161.4, 161.3, 161.2, 161.1, 158.7, 158, 155.4, 155.3, 152, 145.2, 144.6, 136.5, 136.4, 135.4, 135.2, 129.5, 124.4, 120, 119.8, 116.1, 110.7, 108.4, 108.1, 107.1, 102.4, 102.1, 85.7, 56, 55.9, 54.8, 18.5. MS (EI) ES$^+$: 466 ([M$^+$ + H], 100). MS (EI) ES$^+$: 466 ([M$^+$ + H], 100). HRMS-ESI (m/z) calcd for $C_{23}H_{18}F_2N_5O_4$ (M + H$^+$): 466.1323, found: 466.1313.

*4.1.8. N-(3-Fluoro-4-(6-(2-Morpholinoethylamino)pyrimidin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**14**)*

In a dry flask under argon, to a solution of the benzotriazol **11d** (0.1 g, 0.18 mmol), and cesium carbonate (0.11 g, 0.36 mmol) in DME (3 mL) was added 2-aminoethyl-morpholine (0.03 mL, 0.21 mmol) and the mixture was heated at reflux during 6 h. The solvent was removed, the residue was extracted with EtOAc, washed with water, brine, dried over $MgSO_4$ and filtered. The solvent was evaporated to give the crude product which was purified by flash chromatography using 1% Ethanol/DCM as eluent to afford the desired product with 76% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.04 (s, 1H), 8.57 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 8.11 (dd, $J = 7$ Hz, $J = 2$ Hz, 2H), 7.91 (d, $J = 12$ Hz, 1H), 7.60 (dd, $J = 9$ Hz, $J = 4$ Hz, 2H), 7.33 (dt, $J = 47$ Hz, $J = 9$ Hz, Hz, 5H), 6.71 (t, $J = 7$ Hz, 1H), 5.95 (s, 1H), 3.55 (d, $J = 4$ Hz, 4H), 2.60–2.23 (m, 8H). ^{13}C NMR

(DMSO-d_6, 75 MHz) δ (ppm): 164.5, 163.4, 161.7, 161.4, 160.2, 155.3, 152, 144.9, 144.1, 136.2, 135.4, 135.2, 129.3, 129.2, 124.4, 120, 116.2, 116, 115.8, 112.1, 108.3, 108, 106.9, 66.1, 53.2. MS (EI) ES$^+$: 549 ([M$^+$ + H], 50); 571 ([M$^+$ + Na], 100). HRMS-ESI (m/z) calcd for $C_{28}H_{27}F_2N_6O_3$ (M + H$^+$): 549.2056, found: 549.2053.

4.1.9. N-(3-Fluoro-4-(6-(methylaminopyrimidin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide) (**15**)

In a dry flask under argon, to a solution of the benzotriazol **11d** (0.08 g, 0.17 mmol), and cesium carbonate (0.114 g, 0.35 mmol) in DME (1.5 mL) was added methylamine $NH_2Me \cdot HCl$ (0.018 g, 0.26 mmol) and the mixture was heated at reflux during 6 h. The solvent was removed, the residue was extracted with EtOAc, washed with water, brine, dried over $MgSO_4$ and filtered. The solvent was evaporated to give the crude product which was purified by flash chromatography using Cyclohexane/Ethyl Acetate 40:60 as eluent to afford the desired product with 55% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.04 (s, 1H), 8.58 (d, J = 6 Hz, 1H), 8.21–7.98 (m, 2H), 7.91 (d, J = 12 Hz, 1H), 7.72–7.51 (m, 2H), 7.51–7.17 (m, 5H), 6.72 (t, J = 6 Hz, 1H), 5.91 (s, 1H), 2.78 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 165.2, 163.4, 161.7, 161.4, 160.1, 160.2, 155.3, 152, 144.9, 144.1, 136.4, 136.2, 135.4, 135.2, 129.3, 129.2, 124.3, 120.1, 116.2, 115.9, 108.3, 108, 106.9, 95.2, 93.4, 28.9. MS (EI) ES$^+$: 472 ([M$^+$ + Na], 100). HRMS-ESI (m/z) calcd for $C_{23}H_{18}F_2N_5O_3$ (M + H$^+$): 450.1374, found: 450.1366.

4.1.10. 2-Chloro-4-(2-fluoro-4-nitrophenoxy)pyrimidine (**17**)

This compound was obtained with 58% yield according to the method described for compound **5a**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.76 (d, J = 6 Hz, 1H), 8.43 (dd, J = 9 Hz, J = 3 Hz, 1H), 8.23 (ddd, J_1 = 9 Hz, J = 3 Hz, J = 2 Hz, 1H), 7.80 (dd, J = 9 Hz, J = 8 Hz, 1H), 7.48 (d, J = 6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 168.4, 160.9, 160.4, 155.3, 151.9, 144.4, 144.2, 124.2, 120.5, 120.4, 113.4, 113.1, 106.8 MS (EI) ES$^+$: 270 ([M$^+$ + H], 90); 282 ([M$^+$ + Na], 100).

4.1.11. 4-(2-Fluoro-4-nitrophenoxy)-N-(4-methoxybenzyl) pyrimidin-2-amine (**18a**)

In a dry sealed tube under argon were placed the compound **17** (0.9 g, 3.3 mmol), 4-methoxy-benzylamine (0.6 mL, 4 mmol), potassium carbonate (0.54 g, 4 mmol) in DMF (15 mL) and the mixture was heated at 60 °C for 30 min. The mixture was then cooled at room temperature and the solvent evaporated under high vacuum. The residue was extracted with EtOAc, washed with a saturated solution of $NaHCO_3$, water and brine. The organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated to give the crude product as a yellow solid. This residue was purified by flash chromatography using Cyclohexane/Ethyl acetate 90:10 as eluent to afford the desired product as a light yellow solid with 26% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.43–8.08 (m, 2H), 7.66 (s, 1H), 7.16 (s, 1H), 6.79 (s, 3H), 6.37 (s, 1H), 4.34 (s, 1H), 3.96 (s, 1H), 3.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 168.2, 161.9, 161.2, 158.8, 155.6, 152.3, 145.7, 145.5, 145.2, 130.5, 128.6, 124.5, 124.4, 120, 119.9, 113.8, 112.9, 112.6, 99.9, 55.2, 44.8. MS (EI) ES$^+$: 370 ([M$^+$ + H], 100).

4.1.12. 4-(4-Amino-2-fluorophenoxy)-N-(4-methoxybenzyl) pyrimidin-2-amine (**19a**)

In a dry flask under argon, the compound **18a** (0.2 g, 0.54 mmol) was dissolved in a mixture of THF/MeOH 1:1 (15 mL), then Zn (0.35 g, 5.4 mmol) and NH_4Cl (0.28, 5.4 mmol) were added. The mixture was stirred at room temperature during 1 h. The crude was then filtered over a pad of celite, rinsed with EtOAc and the filtrate was evaporated. The brown residue was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and filtered. The solvent was evaporated to give the crude product as a brown solid. This residue was purified by flash chromatography using Cyclohexane/Ethyl Acetate 65:35 as eluent to afford the desired product as a white solid with 96% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.09 (d, J = 6 Hz, 1H), 6.93 (t, J = 9 Hz, 1H), 6.79 (s, 1H), 6.55–6.25 (m, 2H), 6.11 (d, J = 6 Hz, 1H), 5.34 (s, 2H), 4.33 (s, 1H), 3.69 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 169.3, 162.1, 157.9, 148, 132, 128.4, 124.1, 113.3, 109.4, 54.9, 43.3, 40.2, 40.1, 39.1, 38.9, 38.6. MS (EI) ES$^+$: 341 ([M$^+$ + H], 100); 363 ([M$^+$ + Na], 40).

4.1.13. 4-(2-Fluoro-4-nitrophenoxy)-N-methylpyrimidin-2-amine (**18b**)

In a dry sealed tube under argon were placed the compound **17** (0.67 g, 2.4 mmol), $MeNH_2 \cdot HCl$ (0.2 g, 2.9 mmol), potassium carbonate (0.68 g, 4.9 mmol) in DMF (11 mL) and the mixture was heated at 60 °C during 15 h. The mixture was then cooled at room temperature and the solvent evaporated under high vacuum. The residue was extracted with EtOAc, washed with a saturated solution of $NaHCO_3$, water and brine. The organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated to give the crude product as a yellow solid. This residue was purified by flash chromatography using Cyclohexane/Ethyl acetate 90:10 as eluent to afford the desired product as a light yellow solid with 16% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.45–8.07 (m, 3H), 7.69 (t, J = 9 Hz, 1H), 6.36 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 167.6, 162.5, 160.5, 155, 151.6, 145.2, 145, 125, 120.7, 112.9, 112.6, 96, 27.7. MS (EI) ES$^+$: 265 ([M$^+$ + H], 100).

4.1.14. 4-(4-Amino-2-fluorophenoxy)-N-methylpyrimidin-2-amine (**19b**)

This compound was obtained with a quantitative yield according to the method described for compound **19a**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.11 (s, 1H), 7.0 (s, 1H), 6.93 (t, J = 9 Hz, 1H), 6.39 (dd, J = 24 Hz, J = 9 Hz, 2H), 6.08 (s, 1H), 5.31 (s, 2H), 2.66 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 169.9, 163.1, 159.4, 156.6, 153.3, 145.4, 145.3, 131.4, 131.3, 124.3, 124.2, 110.5, 110.4, 103.4, 103.1, 28.2. MS (EI) ES$^+$: 265 ([M$^+$ + H], 100).

4.1.15. N-(3-Fluoro-4-(2-(4-Methoxybenzylamino)pyrimidin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**20a**)

This compound was obtained with 85% yield according to the general procedure C. ^{1}H NMR (CD_2Cl_2, 300 MHz) δ (ppm): 12.04 (s, 1H), 8.72 (d, J = 7 Hz, 1H), 8.17 (s, 1H), 7.95 (d, J = 12 Hz, 1H), 7.67 (d, J = 5 Hz, 1H), 7.45–7.41 (m, 2H), 7.31–7.26 (m, 3H), 7.17 (t, J = 8 Hz, 2H), 6.83 (d, J = 8 Hz, 2H), 6.65 (t, J = 8 Hz, 1H), 6.24 (d, J = 5 Hz, 1H), 5.39 (m, 2H), 3.78 (s, 3H), 2.80 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 169.3, 164.4, 162.4, 162.1, 161.3, 161, 159.5, 158.7, 156, 152.7, 145.1, 141.6, 136.7, 136.6, 135.8, 135.7, 130.9, 129, 128.4, 128.3, 123.9, 122.1, 117, 116.7, 115.8, 113.8, 109.2, 108.9, 107.2, 55.2, 44.8. MS (EI) ES$^+$: 556 ([M$^+$ + H], 100). HRMS-ESI (m/z) calcd for $C_{30}H_{24}F_2N_5O_4$ (M + H$^+$): 556.1791, found: 556.1781.

4.1.16. N-(4-(2-Aminopyrimidin-4-yloxy)-3-fluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**21**)

This compound was obtained with 85% yield according to the general procedure E. ^{1}H NMR (CD_2Cl_2, 300 MHz) δ (ppm): 12.04 (s, 1H), 8.74 (dd, J = 7 Hz, J = 2 Hz, 1H), 8.16 (d, J = 6 Hz, 1H), 7.92 (dd, J = 12 Hz, J = 2 Hz, 1H), 7.67 (dd, J = 7 Hz, J = 2 Hz, 1H), 7.46–7.37 (m, 2H), 7.33–7.21 (m, 4H), 7.18 (t, J = 8 Hz, 1H), 6.65 (t, J = 7 Hz, 1H), 6.29 (d, J = 6 Hz, 1H), 4.96 (s, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 168.8, 163.5, 161.7, 161.5, 160.2, 160.1, 155.2, 151.9, 144.9, 144.1, 136.6, 136.2, 135.1, 129.3, 129.2, 124.4, 120.1, 116.2, 116.1, 115.9, 108.4, 108.1, 106.9, 95.3 MS (EI) ES$^+$: 436 ([M$^+$ + H], 100). HRMS-ESI (m/z) calcd for $C_{22}H_{16}F_2N_5O_3$ (M + H$^+$): 436.1218, found: 436.1228.

4.1.17. N-(3-Fluoro-4-(2-(methylamino)pyrimidin-4-yloxy) phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**20b**)

This compound was obtained with 40% yield according to the general procedure C. ^{1}H NMR (CD_2Cl_2, 300 MHz) δ (ppm): 12.03 (s, 1H), 8.72 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 8.16 (d, $J = 5$ Hz, 1H), 7.92 (dd, $J = 12$ Hz, $J = 2$ Hz, 1H), 7.67 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 7.44 (dd, $J = 9$ Hz, $J = 5$ Hz, 2H), 7.30 (dd, $J = 14$ Hz, $J = 6$ Hz, 3H), 7.16 (t, $J = 9$ Hz, 1H), 6.63 (t, $J = 7$ Hz, 1H), 6.18 (d, $J = 5$ Hz, 1H), 2.85 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 168.5, 163.4, 162.5, 161.7, 161.5, 161.3, 160.2, 159.9, 155.2, 152, 144.8, 144.1, 136.7, 136.5, 136.2, 136.1, 129.3, 129.2, 124.4, 120.1, 116.2, 115.9, 108.1, 106.9, 99.4, 27.7. MS (EI) ES$^+$: 450 ([M$^+$ + H], 100). HRMS-ESI (m/z) calcd for $C_{23}H_{18}F_2N_5O_3$ (M + H$^+$): 450.1374, found: 450.1371.

4.1.18. N-(4-(6-(1H-Benzo[d][1,2,3]triazol-1-yloxy)pyrimidin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**22**)

This compound was obtained with 72% yield according to the general procedure C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 11.92 (s, 1H), 8.80–8.71 (m, 1H), 8.34 (s, 1H), 8.08 (d, $J = 9$ Hz, 1H), 7.80 (d, $J = 9$ Hz, 2H), 7.61 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 7.58 (d, $J = 7$ Hz, 1H), 7.47 (dd, $J = 8$ Hz, $J = 5$ Hz, 2H), 7.49–7.45 (m, 2H), 7.25 (dd, $J = 12$ Hz, $J = 5$ Hz, 2H), 7.14 (d, $J = 9$ Hz, 2H), 6.58 (dd, $J = 12$ Hz, $J = 5$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 172.1, 171.2, 164.3, 162.4, 161.3, 161, 158.4, 148, 145.1, 143.3, 141.6, 136.5, 135.9, 135.8, 128.9, 128.4, 128.3, 122.1, 121.8, 121.7, 116.9, 116.6, 108.5, 107.2, 90.3. MS (EI) ES$^+$: 558 ([M$^+$ + H], 30). MS (EI) ES$^-$: 534 ([M$^-$ − H], 30).

4.1.19. N-(4-(6-Aminopyrimidin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (**23**)

This compound was obtained according to the general procedure D (62% yield) and E (96% yield). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 11.94 (s, 1H), 8.58 (dd, $J = 7$ Hz, $J = 2$ Hz, 1H), 8.19–7.98 (m, 2H), 7.74 (d, $J = 9$ Hz, 2H), 7.66–7.55 (m, 2H), 7.48–7.35 (m, 2H), 7.13 (d, $J = 9$ Hz, 2H), 6.84 (s, 2H), 6.71 (t, $J = 7$ Hz, 1H), 5.71 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 169.4, 165.9, 163.4, 161.7, 161.1, 160.2, 158.1, 148.5, 144.7, 143.8, 136.2, 135.3, 129.3, 129.2, 122, 120.9, 120.4, 116.1, 115.8, 106.9, 86.2. MS (EI) ES$^+$: 418 ([M$^+$ + H], 100). HRMS-ESI (m/z) calcd for $C_{22}H_{17}FN_5O_3$ (M + H$^+$): 418.1312, found: 418.1335.

4.2. Kinase assays

TYRO3 kinase activity was performed in presence of potential inhibitors in 96-well plates pre-coated with 1 μg/well Poly (Glu, Ala, Tyr) peptide (Sigma, France) as substrate. 50 μl of inhibitor at various concentrations (2×) in 0.2% DMSO and 50 μl of recombinant human TYRO3 kinase domain (60 ng/ml) (Invitrogen, France) diluted in 2× reaction buffer (100 mM TRIS pH 7.4, 10 mM $MgCl_2$, 10 mM $MnCl_2$, 2 mM DTT, 0.4% BSA, 10 μM ATP) were added to each well and incubated for 1.5 h at 37 °C. Background signal was evaluated in absence of ATP in reaction buffer. Experiments at each concentration were performed in triplicate. The pan kinase inhibitor, Sunitinib, was used as positive control. After incubation, the plate was then washed three times with PBS containing 0.05% Tween-20 (PBS-T). 300 μl of PBS-T containing 3% BSA were added in each well and plate was incubated for 1 h at 37 °C. Plate was washed twice with PBS-T and 100 μl of anti-phosphotyrosine antibody (PY99, 1:1000 dilution in PBS-T-1% BSA) was added. After overnight incubation at 4 °C, the plate was washed three times with PBS-T and goat anti-mouse antibody (100 μl, 1:2000 dilution in PBS-T-1% BSA) was added. The plate was incubated for 1 h at room temperature and washed three times with PBS. Finally, 100 μl of TMB substrate (Thermoscientific, France) was added and the plate was incubated at room temperature until the blue color emerged. The reaction was stopped by adding 100 μl of 2 M H_2SO_4 and the absorbance was read at 450 nm using a multi-well spectrophotometer.

Kinase assays on a small panel of kinases for a subset of synthesized molecules were carried out at KinomScan, a division of DiscoveRex, 11180 Roselle St. Suite D, San Diego, CA 92121.

Compound **1** (BMS-777607) was purchased from Selleckchem (München, Germany).

4.3. Molecular modeling

Experimental crystallographic coordinates of human Met (PDB ID: 3F82, resolution 2.50 Å) and a DFG-out model of Tyro3 were used in the docking studies.

Docking experiments were performed with FRED version 2.2.5 [26], OpenEye Scientific Software, Santa Fe, NM. http://eyesopen.com, using Chemgauss3 scoring function [27]. A conformational database of listed compounds was generated with OMEGA version 2.3.2 [28] and subsequently used as input to FRED. The required receptor file was built with FRED_Receptor using multiple molecular probes detection. No constraint was used in order not to restrict the pose selection. The best ranked pose for each compound was retained and analyzed in order to clarify the interactions involved in the ligand binding.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.10.037.

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