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Article

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2,6-Di(Arylamino)-3-Fluoropyridine Derivatives as HIV Non-Nucleoside Reverse Transcriptase Inhibitors

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ABSTRACT: New non-nucleoside reverse transcriptase inhibitors (NNRTI), which are similar in structure to earlier described di(arylamino)pyrimidines but featuring a 2,6-di(arylamino)-3-fluoropyridine, 2,4-di(arylamino)-5-fluoropyrimidine or 1,3-di(arylamino)-4-fluorobenzene moiety instead of a 2,4-disubstituted pyrimidine moiety, are reported. The short and practical synthesis of novel NNRTI relies on two sequential Pd-catalyzed aminations as the key

steps. It is demonstrated through direct comparison with reference compounds, that the presence of a fluorine atom increases the *in vitro* anti-HIV activity, both against the wild type virus and drug-resistant mutant strains.

Introduction. At the end of 2012, an estimated 35.3 million people were living with HIV infection worldwide. There were 2.3 million new infections and 1.6 million people died of HIV/AIDS globally that same year. In the Western world, HIV/AIDS is no longer a fatal disease: life expectancy with adequate anti-retroviral treatment and care is more than 24 years after HIV-infection. Much of that success is due to the introduction of HAART (highly active antiretroviral treatment) by means of combinations of two or three compounds belonging to different classes of anti-HIV compounds.[1]

HAART consists of the combination of several active components belonging to different classes of anti-HIV compounds such as protease inhibitors (PI), integrase inhibitors (INI), nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). A major problem in the HIV treatment remains the emergence of resistance of the virus against the currently available drugs, whatever class of anti-HIV compounds they belong to. Application of HAART for the treatment of HIV infection only solves this problem in part, and HAART may become inefficient once resistance to one or more of the drugs used in combination is developed. Finally, none of the currently available anti-HIV drugs or multi-drug therapies allows for the eradication of the virus, causing the need for life-long treatment which possibly results in multidrug resistance. For this reason, there is a continuous need for the development of new anti-HIV combination therapies. In order to treat drug-resistant HIV infection, new components with novel chemical structures for such combination therapies, possessing new modes of action are necessary.

HIV-1 reverse transcriptase (RT) is one of the most important viral enzymes and plays a unique role in the HIV-1 life cycle. It has two known drug-target sites, the substrate catalytic site and an allosteric site that is distinct from, but located closely to, the substrate site.[2, 3] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) interact with the allosteric site in a non-competitive manner to distort the enzyme's active conformation and thus disrupt the function of the enzyme.[2, 4] It is demonstrated by XRD analysis, that many NNRTIs form a hydrogen bond with a K101 amino acid residue in the reverse transcriptase binding site.[5, 6] For example, in Etravirine (**1**, TMC-125, Figure 1a), which was recently approved as a next-generation NNRTI for AIDS therapy, the NH group of the arylamine and the N atom in the pyrimidine ring of the drug are involved in the hydrogen bonding with the enzyme. It was found that **1** is highly potent against wild-type and a number of mutant HIV strains with nanomolar EC_{50} values and has a high genetic barrier to delay the emergence of drug-resistance.[7, 8] A number of other NNRTIs with an azaheteroaromatic ring C featuring two arylamino substituents were

developed, such as di(arylamino)triazine (DATA)[9-11] or di(arylamino)pyrimidine (DAPY)[9, 10, 12-16] derivatives. Rilpivirine (**2**, TMC-278) was approved by the FDA in May 2011 (Figure 1a).[14, 17] It showed better potency and pharmacological profiles than **1**, and features the same hydrogen bonding sites as present in **1**.[6, 13] Another NNRTI, Dapivirine (**3**, TMC-120), is in Phase III clinical trials by the International Partnership for Microbicides for the prevention of HIV infection with aid of a vaginal ring, which can provide women with a protection for a longer period of time.[18, 19]

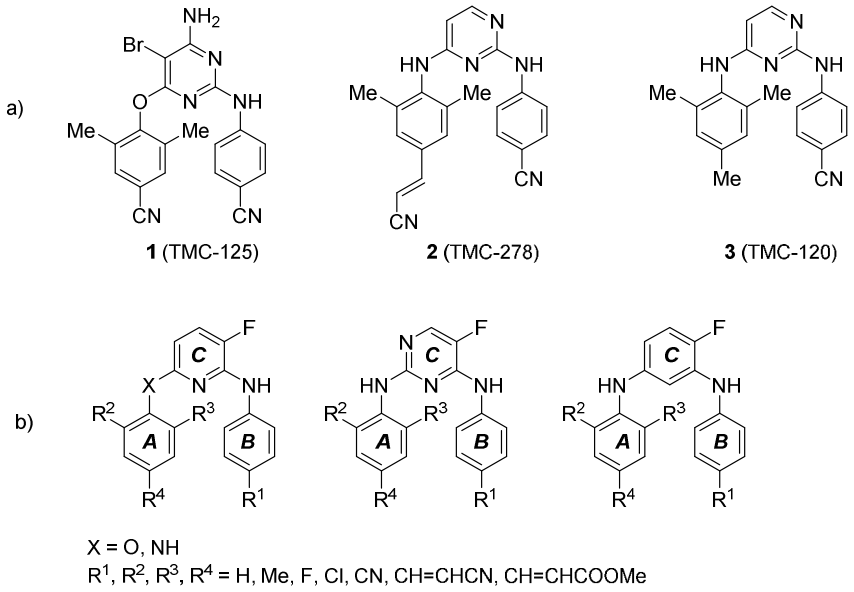


Figure 1. (a) Structures of reported NNRTI **1–3**. (b) General formula of the new NNRTI reported in this paper.

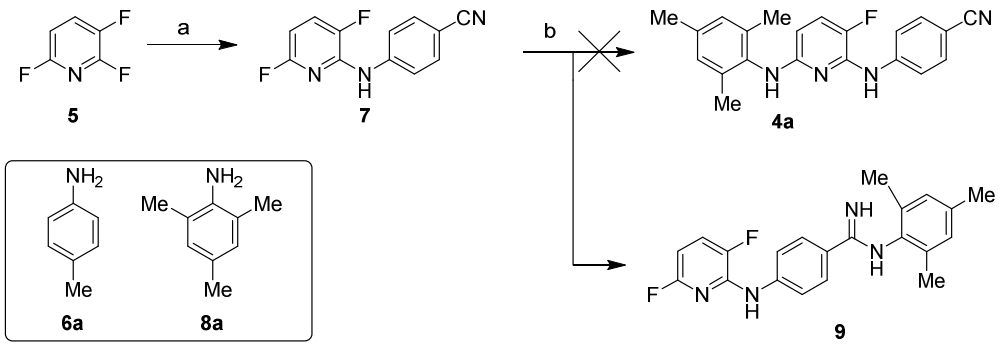
In a quest for novel NNRTI with improved activity, especially towards drug-resistant strains of HIV, we designed 2,6-di(arylamino)-3-fluoropyridine derivatives (Figure 1b). These compounds are structurally similar to **2**, **3** and analogues but feature a 2,6-disubstituted 3-fluoropyridine instead of a 2,4-disubstituted pyrimidine moiety. We hypothesized that a fluorine atom on the ring C can also participate in the interactions with the protein backbone, by way of acting as a hydrogen bond acceptor similarly to a nitrogen atom in the pyrimidine ring of **2**, and/or other weak forces which are unique for the fluorine atom such as orthogonal C=O…F–C interactions.[20] To establish the effect of the ring C on the SAR in the fluorinated series, derivatives featuring a pyrimidine and a benzene ring C were synthesized, too (Figure 1b).

Results and discussion.

Synthesis. Our initial target was **4a**, closely resembling the structure of the above-mentioned NNRTI **3**. Our original idea, which was inspired by limited information available in the patent literature,[21] was to take advantage of the commercial availability of 2,3,6-trifluoropyridine (**5**). The selective nucleophilic substitution in **5** was achieved upon

reaction with deprotonated 4-aminobenzonitrile (**6a**) and gave 46% yield of 4-[(3,6-difluoropyridin-2-yl)amino]benzonitrile (**7**) (Scheme 1). The structure of **7** was established by XRD analysis and confirmed the substitution exclusively in position 2 of the pyridine core. However, the attempted reaction between **7** and 2,4,6-trimethylaniline (**8a**) in NMP did not give the desired **4a**, but instead produced a small amount of the amidine **9** due to the competitive attack of the aniline nucleophile on the CN group.

Scheme 1. Initial attempts to synthesize 4a from 2,3,6-trifluoropyridine[a]



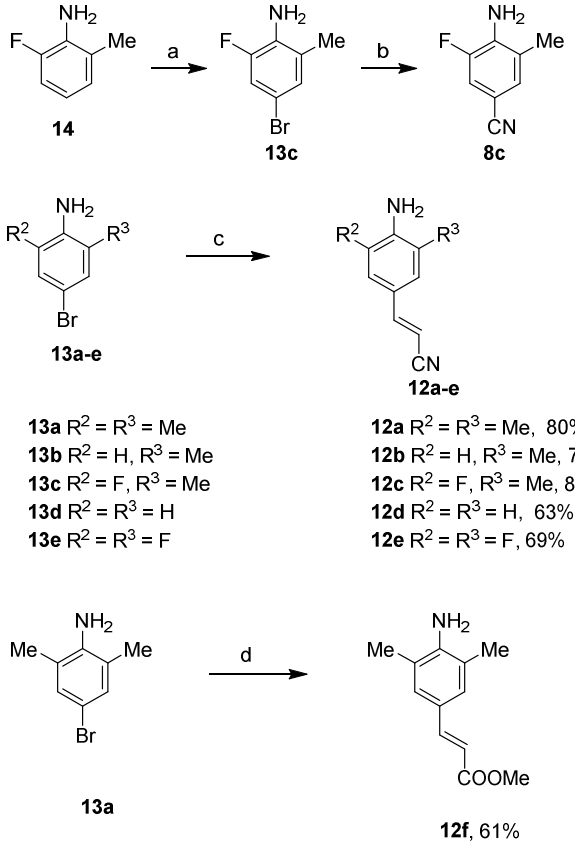
[a]Reagents and conditions: (a) **6a**, *t*-BuLi, THF, –78 °C, then 2 h at 0 °C, 46%; (b) **8a**, NMP, TsOH or MsOH, 180 °C.

We therefore turned our attention to regioselective Pd-catalyzed amination on commercially available 2,6-dichloro-3-fluoropyridine (**10**), as examples of regioselective Pd-catalyzed aminations involving halogenated pyridines were previously reported.[22-28] A reaction between **10** and **6a** in the presence of a Pd source and XPhos ligand afforded the desired 4-[(6-chloro-3-fluoropyridin-2-yl)amino]benzonitrile (**11a**), albeit in modest yield (Table SI1). Optimization of the catalytic system (Pd source, ligand, base additive) was therefore undertaken. Xantphos ligand in combination with *t*-BuONa as a base and $Pd(OAc)_2$ as a metal source proved to be the catalytic system of choice. Further, it is essential to stress that the reaction proceeds with complete regioselectivity, the substitution occurred exclusively at position 2 and no substitution at position 6 was observed, as confirmed by the single crystal XRD analysis. A second Pd-catalyzed amination reaction of the intermediate **11a** with 2,4,6-trimethylaniline (**8a**) finally provided the target compound **4a** (Table SI1 and Scheme 3). It was found that in this case, XPhos ligand provided an acceptable yield of the amination product.

With the optimized synthetic protocol in hand, we proceeded with the synthesis of a library of 2,6-di(arylamino)-3-fluoropyridine derivatives **4a–u** starting from **10** and various anilines (**6a–d, 8a–c**, **12a–f**, Scheme 3). Based on the knowledge about SAR of di(arylamino)pyrimidine NNRTI[10, 12] we envisaged variation of *para*-substituents (R^1) on the ring B and *ortho*- (R^2, R^3) and *para*-substituents (R^4) on the ring A of 2,6-di(arylamino)-3-fluoropyridine derivatives (Figure 1b).

Particular attention was given to compounds with R^4 = (*E*)-CH=CHCN, based on the high activity of **2** (Figure 1a). The anilines **12a–f** necessary for the synthesis of those compounds were prepared via a Heck reaction starting from the corresponding 4-bromoanilines **13a–e**. The latter were commercially available with the exception of 4-bromo-2-fluoro-6-methylaniline (**13c**), which was prepared by bromination of commercially available 2-fluoro-6-methylaniline (**14**) (Scheme 2). 4-Amino-3-fluoro-5-methylbenzonitrile (**8c**) was prepared following the published general method (Scheme 2).[29]

Scheme 2. Synthesis of the aniline reagents 12a–g[a]



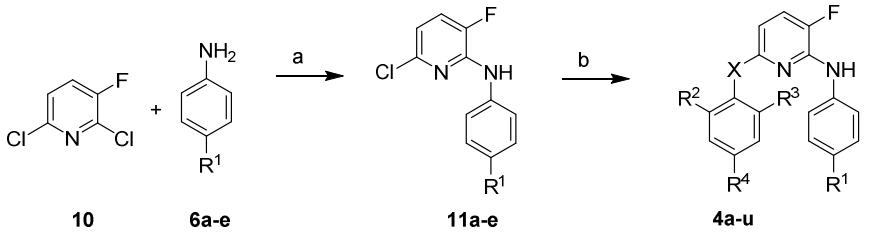
[a]Reagents and conditions: (a) Br_2, AcOH, rt, 2 h, 82%; (b) CuCN, DMF, CuI, KI, *N,N'*-dimethyl-1,2-ethanediamine, 110 °C, 16 h, 74%; (c) acrylonitrile, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, AcONa·$3H_2O$, DMA, 140 °C, 48 h; (d) methyl acrylate, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, AcONa·$3H_2O$, DMA, 140 °C, 48 h, 29%.

With the anilines in hand a series of 2,6-di(arylamino)-3-fluoropyridine derivatives **4a–k,n–u** was synthesized using our optimized two-step Pd-catalyzed amination protocol (Scheme 3). Similarly, two analogues (**4l,m**) featuring an O rather than an NH linkage between the ring A and the ring C were prepared using a Pd-catalyzed C–O bond formation reaction of **11a** with phenols **15a,b** instead of an aniline (Scheme 3).

With the aim to study the effect of the ring C on the biological activity, we prepared two analogues of **4a–u** featuring a pyrimidine or benzene ring C. Following a synthetic route similar to that used for the preparation of **4a–u**, a Pd-catalyzed amination reaction of 2,4-dichloro-5-fluoropyrimidine (**16**) with 4-aminobenzonitrile (**6a**) produced the intermediate 4-[(2-chloro-5-fluoropyrimidin-4-yl)amino]benzonitrile (**17**) as a single regioisomer. Subsequent amination of **17** with the corresponding anilines (**8b**, **12a**) provided the targets **18a,b** in modest yields (Scheme 4). Furthermore, compounds **19a–c** were prepared starting from commercially available 2-bromo-4-chloro-1-fluorobenzene (**20**) as shown in Scheme 5. The bromine atom in **20** was selectively substituted to produce 4-[(5-chloro-2-fluorophenyl)amino]benzonitrile (**21**), which was then converted to **19a–c** via Pd-catalyzed amination with anilines **12a,b,d** (Scheme 5).

Finally, in order to unambiguously evaluate the effect of the fluorine atom in the 3-position of the ring C, reference compounds **22a–d** lacking a fluorine atom were synthesized. Starting from the commercially available 2,6-dichloropyridine (**23**) the intermediate 4-[(6-chloropyridin-2-yl)amino]benzonitrile (**24**) was prepared and then used in a second Pd-catalyzed amination step to obtain **22a–d** (Scheme 6).

Scheme 3. Synthesis of 2,6-di(arylamino)-3-fluoropyridine derivatives 4a–u[a]

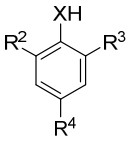


10 **6a-e** **11a-e** **4a-u**

6a R^1 = CN
6b R^1 = Cl
6c R^1 = F
6d R^1 = COOMe
12d R^1 = CH=CHCN

11a R^1 = CN, 89%
11b R^1 = Cl, 74%
11c R^1 = F, 88%
11d R^1 = COOMe, 66%
11e R^1 = CH=CHCN, 74%

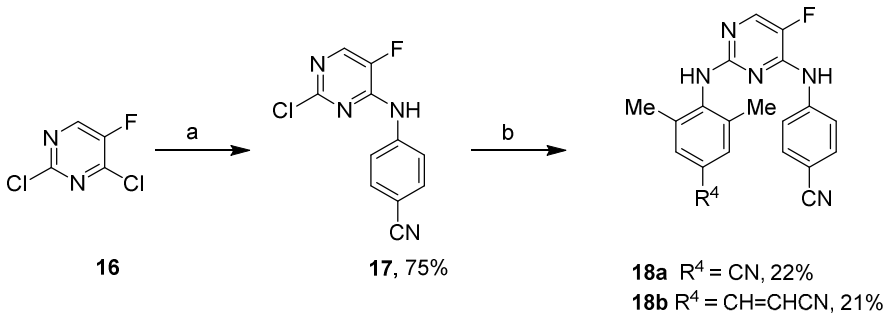
4a X = NH, R^1 = CN, R^2 = R^3 = R^4 = Me, 53%
4b X = NH, R^1 = CN, R^2 = R^3 = Me, R^4 = CN, 61%
4c X = NH, R^1 = CN, R^2 = R^3 = Me, R^4 = CH=CHCN, 62%
4d X = NH, R^1 = CN, R^2 = R^3 = Me, R^4 = CH=COOMe, 71%
4e X = NH, R^1 = F, R^2 = R^3 = Me, R^4 = CH=CHCN, 66%
4f X = NH, R^1 = CH=CHCN, R^2 = R^3 = Me, R^4 = CH=CHCN, 63%
4g X = NH, R^1 = F, R^2 = R^3 = Me, R^4 = CN, 50%
4h X = NH, R^1 = CN, R^2 = R^3 = H, R^4 = CH=CHCN, 68%
4i X = NH, R^1 = Cl, R^2 = R^3 = Me, R^4 = CN, 54%
4j X = NH, R^1 = Cl, R^2 = R^3 = Me, R^4 = CH=CHCN, 65%
4k X = NH, R^1 = CN, R^2 = Me, R^3 = F, R^4 = CH=CHCN, 79%
4l X = O, R^1 = CN, R^2 = R^3 = H, R^4 = Me, 89%
4m X = O, R^1 = CN, R^2 = R^3 = R^4 = Me, 43%
4n X = NH, R^1 = Cl, R^2 = Me, R^3 = H, R^4 = CH=CHCN, 73%
4o X = NH, R^1 = F, R^2 = R^3 = Me, R^4 = CH=COOMe, 55%
4p X = NH, R^1 = Cl, R^2 = R^3 = Me, R^4 = CH=COOMe, 71%
4q X = NH, R^1 = F, R^2 = Me, R^3 = H, R^4 = CH=CHCN, 75%
4r X = NH, R^1 = CN, R^2 = Me, R^3 = H, R^4 = CH=CHCN, 70%
4s X = NH, R^1 = CN, R^2 = Me, R^3 = F, R^4 = CN, 42%
4t X = NH, R^1 = CN, R^2 = R^3 = F, R^4 = CH=CHCN, 72%
4u X = NH, R^1 = COOMe, R^2 = R^3 = Me, R^4 = CH=CHCN, 72%



8b X = NH, R^2 = R^3 = Me, R^4 = CN
8c X= NH, R^2 = Me, R^3 = F, R^4 = CN
15a X= O, R^2 = R^3 = H, R^4 = Me
15b X= O, R^2 = R^3 = R^4 = Me

[a]Reagents and conditions: (a) $Pd(OAc)_2$, XantPhos, *t*-BuONa, dioxane, 110 °C, 16 h; (b) **8a–c** or **12a–f** or **15a,b**, $Pd(OAc)_2$, XPhos, Cs_2CO_3, dioxane, 110 °C, 16 h.

Scheme 4. Synthesis of 2,4-di(arylamino)-5-fluoropyrimidine derivatives 18a,b[a]

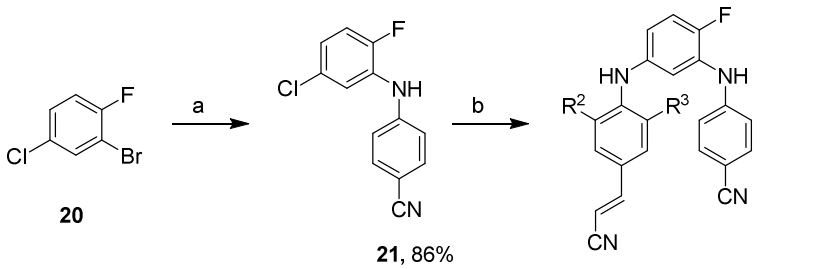


16 **17**, 75%

18a R^4 = CN, 22%
18b R^4 = CH=CHCN, 21%

[a]Reagents and conditions: (a) **6a**, $Pd_2(dba)_3$, XantPhos, Cs_2CO_3, dioxane, 110 °C, 16 h; (b) **8b** or **12a**, $Pd(OAc)_2$, XPhos, Cs_2CO_3, dioxane, 110 °C, 16 h.

Scheme 5. Synthesis of 1,3-di(arylamino)-4-fluorobenzene derivatives 19a–c[a]

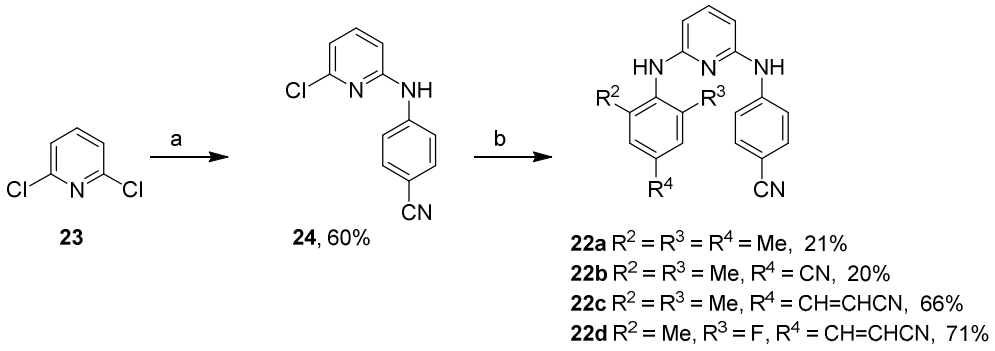


20 **21**, 86%

19a R^2 = R^3 = Me, 56%
19b R^2 = F, R^3 = Me, 41%
19c R^2 = H, R^3 = Me, 59%

[a]Reagents and conditions: (a) **6a**, $Pd(OAc)_2$, XantPhos, *t*-BuONa, dioxane, 110 °C, 16 h; (b) **12a–c**, $Pd(OAc)_2$, XPhos, Cs_2CO_3, dioxane, 110 °C, 16 h

Scheme 6. Synthesis of 2,6-di(arylamino)pyridine derivatives 22a–d



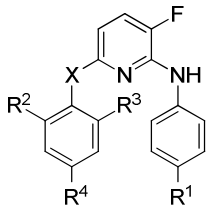
23 **24**, 60%

22a $R^2 = R^3 = R^4 = Me$, 21%
22b $R^2 = R^3 = Me$, $R^4 = CN$, 20%
22c $R^2 = R^3 = Me$, $R^4 = CH=CHCN$, 66%
22d $R^2 = Me$, $R^3 = F$, $R^4 = CH=CHCN$, 71%

[a]Reagents and conditions: (a) $Pd(OAc)_2$, *rac*-BINAP, K_2CO_3, toluene, 120 °C, 24 h; (b) **8a,b** or **12a,c**, $Pd(OAc)_2$, XPhos, Cs_2CO_3, dioxane, 110 °C, 16 h.

In vitro studies. The details on the activity against wild type HIV-1 and cytotoxicity for the new NNRTI are summarized in Tables 1–4. Reference data for **2** and **3** are included for comparison. It should be noted that for molecules containing CH=CHCN moiety, in some instances we were able to isolate pure *E* isomers, while a mixture of *E*- and *Z*- -isomers was obtained in some other cases, *E*-isomer always being a major one (see Tables 1–4). It was previously reported by Janssen and co-workers that for **2** and a few structural analogues, in vitro activity of *E*-isomers was much higher than that of the corresponding *Z*-isomers. Furthermore, also in this study by Janssen[15] mixtures of *E* and *Z* isomers were examined in some cases. In case of **4c**, we performed activity analysis both on the 9/1 mixture of *E*- and *Z*- isomers and on the pure *E*-isomer, which gave results within the experimental error (Table 1). Based on these observations, we performed screening on the mixtures of *E*- and *Z*- -isomers for majority of compounds and assumed that minor amounts of less active Z-isomer do not significantly affect the results.

Table 1. Activity and selectivity index of 2,6-di(arylamino)-3-fluoropyridine derivatives 4a–u[a]



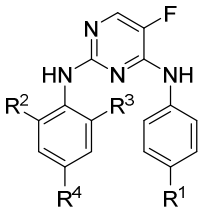
Compound	X	R^1	R^2	R^3	R^4	E/Z	EC_{50} [nM]	SI

2						100/0	0.72	10700
3							1.4	2000
4a	NH	CN	Me	Me	Me		8.3	2000
4b	NH	CN	Me	Me	CN		4.7	7100
4c	NH	CN	Me	Me	CH=CHCN	100/0	1.5	62500
4c	NH	CN	Me	Me	CH=CHCN	90/10	1.6	37500
4d	NH	CN	Me	Me	CH=CHCOOMe	100/0	4.4	13000
4e	NH	F	Me	Me	CH=CHCN	86/14	6.2	8100
4f	NH	CH=CHCN	Me	Me	CH=CHCN	88/12[b]	4.6	19000
4g	NH	F	Me	Me	CN		51	830
4h	NH	CN	H	H	CH=CHCN	70/30	480	14
4i	NH	Cl	Me	Me	CN		15	2000
4j	NH	Cl	Me	Me	CH=CHCN	93/7	6.3	6600
4k	NH	CN	Me	F	CH=CHCN	100/0	1.0	>100000
4l	O	CN	H	H	Me		260	390
4m	O	CN	Me	Me	Me		8.6	6400
4n	NH	Cl	Me	H	CH=CHCN	100/0	63	380
4o	NH	F	Me	Me	CH=CHCOOMe	100/0	84	610
4p	NH	Cl	Me	Me	CH=CHCOOMe	100/0	53	950
4q	NH	F	Me	H	CH=CHCN	100/0	400	210
4r	NH	CN	Me	H	CH=CHCN	87/13	11	24000
4s	NH	CN	Me	F	CN		8.8	4600
4t	NH	CN	F	F	CH=CHCN	79/21	3.3	4600
4u	NH	COOMe	Me	Me	CH=CHCN	100/0	23	2100

[a]The selectivity index (SI) is defined as CC_{50}/EC_{50}, where EC_{50} is the 50%-effective concentration vs. HIV virus, and CC_{50} is the concentration causing death of 50% of the cells; The EC_{50} value was determined in TZMbl cells against the subtype B R5-tropic

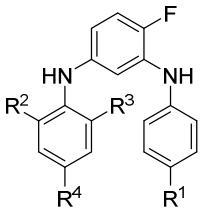
Bal virus and the CC_{50} value was determined in the same cells using the WST-1 assay. [b]Ratio (*E*,*E*)/sum of (*E*,*Z*) and (*Z*,*E*) isomers.

Table 2. Activity and selectivity index of 2,4-di(arylamino)-5-fluoropyrimidine derivatives 18a,b



Compound	R^1	R^2	R^3	R^4	E/Z	EC_{50} [nM]	SI
18a	CN	Me	Me	CN		2.8	> 36000
18b	CN	Me	Me	CH=CHCN	86/14	0.9	> 42000

Table 3. Activity and selectivity index of 1,3-di(arylamino)-4-fluorobenzene derivatives 19a–c



Compound	R^1	R^2	R^3	R^4	E/Z	EC_{50} [nM]	SI
19a	CN	Me	Me	CH=CHCN	81/19	4.5	7400
19b	CN	Me	F	CH=CHCN	75/25	11	6100
19c	CN	Me	H	CH=CHCN	89/11	58	89

From the data obtained it is clear the two ortho-substituents on the ring A (R^2, R^3)are essential, and replacement of one or both substituents by a hydrogen atom results in a significant drop in activity (e.g. **4c** vs. **4h**,**r**; **4j** vs. **4n**; **4m** vs. **4l**; **4e** vs. **4q**, Table 1). Substitution of one or both methyl groups by fluorine atoms in the ring A provided only an insignificant effect (slight increase in activity and selectivity for **4k** vs **4c**; slight decrease for **4t** vs. **4c** and for **4s** vs **4b**, Table 1). A

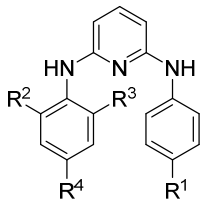
cyanovinyl group in the para-position of the ring A produced the best results (**4c** vs. **4b,d**), as was expected from the published results on **2** and analogues (Table 1).[10, 12, 16] Finally, the nature of the linker between the ring A and the ring C had no effect (**4m** vs. **4a**, Table 1).

Concerning the variation of the ring B, a cyano group was clearly superior to other alternatives (**4b** vs **4g,i**, **4c** vs **4e,f,j,u**, and **4d** vs **4o,p**, Table 1). Finally, variation of the ring C provided similar results for pyridine and pyrimidine derivatives (**4b** vs. **18a**, **4c** vs. **18b**, Table 2), while derivatives with the benzene ring C systematically show a somewhat lower activity (**4c** vs **19a**, **4k** vs. **19b**, **4r** vs **19c**, Table 3).

Overall, most successful were compounds closely resembling the known NNRTI **2**, namely **4c,k** and **18b**, all displaying EC_{50} close to 1.0 nM and a very high selectivity index (> 40000).

In order to unambiguously compare the effect of the fluorine atom on the anti-HIV activity of 2,6-di(arylamino)-3-fluoropyridine derivatives, four analogues **22a–d** lacking a fluorine atom on the pyridine ring were evaluated (Table 4). In every case (**4a** vs **22a**, **4b** vs **22b**, **4c** vs **22c** and **4k** vs **22d**) removal of a fluorine atom decreased the activity and selectivity (Table 4). In case of **4k** vs **22d** this effect was the most pronounced; an increase of activity by ca. a factor of 6 and of the SI by ca. a factor of 20 due to the presence of a F atom.

Table 4. Activity and selectivity index of compounds 22a–d.



Compound	R^1	R^2	R^3	R^4	E/Z	EC_{50} [nM]	SI
22a	CN	Me	Me	Me		30	1400
22b	CN	Me	Me	CN		25	930
22c	CN	Me	Me	CH=CHCN	80/20	3.5	11000
22d	CN	Me	F	CH=CHCN	92/8	5.5	5500

For selected molecules which displayed a high activity against WT HIV-1, data were collected for mutant HIV-1 strains, which have shown resistance against Nevirapine (Y181C) and Efavirenz (L100I, K103N), and site-directed mutants (pNL4.3-K103N, pNL4.3-K103N-Y181C) (Table 5). The activity of **4c** and **4k** is close to or slightly higher than that of earlier reported **3**, but lower than that of **2** for all strains (WT, single and double mutant). Further comparison of three 2,6-di(arylamino)-3-fluoropyridine derivatives with their analogues lacking fluorine clearly reveals for every case (**4b** vs. **22b**, **4c** vs **22c** and **4k** vs. **22d**) higher activity of the fluorinated derivatives and thus further underlines the advantages of a F atom on the ring C.

Table 5. Antiviral activity of selected compounds vs mutant HIV-1[a]

Compound	Y181C EC_{50} [nM]	L100I, K103N EC_{50} [nM]	pNL4.3-K103N EC_{50} [nM]	pNL4.3-K103N-Y181C EC_{50} [nM]
2	2.5	3.6	0.7	3.1
3	11	> 1000	2.8	92
4a	130	> 10000		
4b	91	> 10000		
22b	1500	6600		
4c	8.1	540	7.8	554
22c	91	> 1000		
4k	25	272	36	> 1000
22d	255	1100		

[a]The EC_{50} values were determined in TZMbl cells against Nevirapine-resistant VI829 (carrying Y181C) and Efavirenz-resistant VI829 (carrying L100I and K103N). Both viruses are subtype C and R5-tropic. Site-directed mutants (SDMs) carrying K103N and K103N+Y181C were used to further evaluate **2**, **3**, **4c** and **4k**. Construction of the SDMs is described elsewhere.[30]

Docking studies. Docking of the **4a** and **22a** ligands in the crystal structure of RT in complex with **3**[13] was performed using the Gromacs molecular dynamics and mechanics software.[31] A comparison between the docked poses of **3**, **4a** and **22a** shows little variation between the three ligands. In all cases, a hydrogen bond between the backbone oxygen of Lys-101 of the RT and the aniline nitrogen bridging the central aromatic ring with the nitrile-substituted ring is observed. The

main difference between the binding of **4a** on the one hand, and **3** and **22a** on the other hand, is the presence of a weak interaction between the fluorine substituent of **4a** and the Cε hydrogen of Lys-103 (Figure SI5, see Supporting Information). A corresponding interaction is not found in **3** due to the fact that this compound does not contain a fluorine atom at this position and that the corresponding pyrimidine nitrogen of **3** is located too far away from the corresponding Cε hydrogen of Lys-103. Similarly, in **22a** this fluorine atom is substituted with a hydrogen atom, bearing a partially positive charge (Figure B, supporting information) and therefore incapable of forming a favorable electrostatic interaction with the Cε hydrogen of Lys-103. These docking experiments corroborate the experimental findings, as the differences in EC_{50} between the three molecules in question are comparatively small.

Conclusions

In summary, we have developed a short and practical synthesis of new NNRTI, which are similar in structure to earlier described di(arylamino)pyrimidines but feature a 2,6-disubstituted 3-fluoropyridine instead of a 2,4-disubstituted pyrimidine moiety. The in vitro studies of a synthesized library confirmed a SAR similar to that observed earlier for the di(arylamino)pyrimidines series, as well as for the recently published 3-aminopyridine derivatives.[32] An important observation is that the presence of a fluorine atom on the central pyridine ring is essential for the antiviral activity, both against the wild type HIV and the drug-resistant mutant strains. The activity of the best molecules **4c,k** was, for all studied HIV strains, close to or slightly higher than that of a well-known NNRTI API **3**.

Experimental part

Instrumentation and Chemicals. All reagents, chemicals and solvents were obtained from commercial sources and used without extra purification unless stated otherwise. Melting points were determined on a Büchi apparatus and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3COCD_3, CD_3OD or DMSO-d_6 on a Bruker Avance II 400 spectrometer with TMS as the internal standard. Coupling constants are given in Hertz and the chemical shifts are given in ppm. For mass spectrometric analysis, samples were dissolved in CH_3OH containing 0.1% formic acid and diluted to a concentration of approximately 10^{-5} mol/L. Injections (1 µL) were directed to the mass spectrometer at a flow rate of 5 µL/min (CH_3OH and 0.1% formic acid), using a CapLC HPLC system (Waters-Micromass). High resolution mass data were acquired on a Q-TOF 2 mass spectrometer (Waters-Micromass) equipped with a standard electrospray ionisation (ESI) interface. Column chromatography was performed on Kieselgel 60 (ROCC *SI 1721*, 40-60 mm), or on an automated chromatography system with silica flash cartridges (Grace). Purities of final compounds were determined with

a UHPLC system based on MS and UV detection. A Waters Aquity UPLC system coupled to a Waters PDA detector and a Waters Micromass ZQ ESI mass spectrometer was used. A Halo C18 fused core 2.7µm, 2.1mm × 30mm column was used. Solvent A: water with 0.1% formic acid; solvent B: methanol with 0.1% formic acid. Method: 0.5 mL/min, 0.5 min 99% A, 1% B then in 5.6 min from 99% A, 1% B to 5% A, 95% B then 0.4min, 5% A, 95% B, then in 0.1min to 99% A, 1% B holding this for 4.4min before the next analysis. The wavelength for UV detection was 254 nm. All final products had a purity of at least 95%, with the exception of compounds **4r** (94%), **4t** (94%) and **18a** (93%).

Structural data. X-ray data were collected on a Bruker platform goniometer equipped with sealed Mo (λ= 0.71073 Å) X-ray tube, pyrrolithic graphite monochromator, and Smart 1000 CCD detector. For data collection and reduction, the Bruker SAINT software, V7.66A (Bruker Corporation, Madison, USA, 2010) was employed. Data were corrected for absorption with the multi-scan method with SADABS 2008/1 (Bruker Corporation, Madison, USA, 2008). Structures were solved with direct methods with SHELXS-97,[33] and refined with SHELXL-2014/7 (George M. Sheldrick, Universität Göttingen, 2014) and the shelXle graphical interface.[34] CIF files were deposited at the CCDC, reference numbers: 1410424 (**7**), 1410427 (**11a**), 1410425 (**4a**), 1410426 (**4b**). Ellipsoid plots of all structures were made with ORTEP-3 for Windows[35] and can be found in the Supporting Information.

Biological Assays. ***Cells.*** The TZM-bl cell line (NIH AIDS Research and Reference Reagent Program, Germantown, USA) was used for the evaluation of drug susceptibility and cytotoxicity. TZM-bl cells were cultured in Dulbecco's Minimum Essential Medium (DMEM) (Lonza) containing 10% heat-inactivated FBS and 50 µg gentamycin/mL at 37 °C in a humidified 5% CO_2, 95% air environment. Twice a week the cells were treated with 0.25% trypsin – 1 mM EDTA (Lonza) for 10 minutes. The resulting cell suspension was washed with an equivalent amount of TZM-bl medium and subsequently seeded in a T75 culture flask (Greiner Bio-One, Germany) at 10^6 cells in 20 mL medium.

Antiviral assay. The antiviral activity of the newly designed compounds was measured by pre-incubating 10^4 TZM-bl cells (at 10^5 cells/mL in culture medium supplemented with 30µg/mL DEAE dextran) in a 96-well plate for 30 minutes at 37 °C, 5% CO_2 in the presence or absence of serial dilutions of the each compound. Subsequently, 200 $TCID_{50}$ of wild type (Bal) or NNRTI-resistant HIV-1 (Y181C, L100I + K103N) was added to each well and cultures were incubated for 48 hours before quantifying luciferase activity. Each condition was evaluated in triplicate wells and in at least three independent experiments. The antiviral activity of the compound was expressed as the percentage of viral inhibition compared to the untreated controls and subsequently plotted against the compound concentration. Non-linear regression analysis was

used to calculate the 50% effective concentration (EC_{50}) based on at least three independent measurements and using GraphPad Prism version 5.03 for Windows (GraphPad Software, San Diego, CA, USA).

WST-1 cytotoxicity assay. The Water Soluble Tetrazolium-1 (WST-1) Cell Proliferation Assay is a colorimetric assay for the measurement of cell proliferation and viability. The assay is based on the cleavage of the tetrazolium salt WST-1 ((4-[3-(4-iodophenyl)-2-(4-nitrophenyl)- 2H-5-tetrazolio]-1,3-benzene disulfonate)) to a formazan dye by a complex cellular mechanism. This bioreduction is largely dependent on the glycolytic production of NAD(P)H in viable cells. Therefore, the amount of formazan dye formed correlates directly to the number of viable cells in the culture, and can be quantified by measuring the absorbance at 450nm in a multiwell plate reader. The greater the number of viable cells, the greater the amount of formazan dye produced following the addition of WST-1. Cytotoxicity of each compound was evaluated using this WST-1 viability assay, according to the manufacturer's instructions (Roche, Vilvoorde, Belgium). Briefly, 10^4 TZM-bl cells were seeded in a 96-well plate and cultured for 2 days in the presence of a serial dilution of each compound. After 48h exposure, Cell Proliferation Reagent was added and absorbance at 450 nm was quantified after 90 min using a microplate reader (BioRad, Tokio, Japan). Each compound was tested in three replicate wells and in at least three independent experiments. The percentage cell viability, compared to untreated controls, was plotted against the compound concentration and non-linear regression analysis was performed using GraphPad Prism version 5.02 for Windows (GraphPad Software, San Diego, CA, USA) to calculate the 50% cytotoxic concentration (CC_{50}).

Computational methods. ***Docking of 4a and 22a.*** The crystal structure of RT in complex with **3**[13] was taken as the starting structure and both compounds were positioned in the pocket by superimposing their aromatic ring atoms onto the corresponding atoms of **3**. Positions were refined by energy minimization of both ligand and protein using the GROMOS 53A6 force-field[36] within the Gromacs software suite[31] and until the maximum force dropped below 10 kJ/mol. Force-field parameters and atomic partial charges for **4a** and **22a** were generated with the online ATB tool (version 2.2).[37]

Electrostatic potential surface of 4a and 22a. The electrostatic potential surfaces of both compounds after geometry optimization were calculated with Spartan 14 using Hartree-Fock 6-31G** basis set.[38]

Synthetic procedures.

4-[(3,6-Difluoropyridin-2-yl)amino]benzonitrile (7). To a solution of 4-aminobenzonitrile (0.156 g, 1.320 mmol) in THF (4.5 mL) a solution of *t*-BuLi (1.6 M in pentane; 0.763 mL, 1.22 mmol) was added dropwise at −78 °C. Next, a solution of 2,3,6-trifluoropyridine (0.266 g, 2.0 mmol) in THF (1.5 mL) was added and the mixture was stirred for 5 min at −78 °C. The reaction mixture was warmed to room temperature and stirred for 2 h, then aq. NH_4Cl (10 mL) was added and the

mixture was extracted with EtOAc (2 x 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified by column chromatography to give **7** as a white solid (128 mg, 46%); mp 120–122 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (ddd, *J* = 8.5 Hz, 3.3 Hz, 2.3 Hz, 1H), 6.86 (br, 1 H), 7.43 (ddd, *J* = 9.6 Hz, 8.5 Hz, 6.1 Hz, 1H), 7.62 (d, *J* = 8.9 Hz, 2 H), 7.77 (d, *J* = 8.9 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.1 (dd, *J* = 40.8 Hz, 3.6 Hz), 105.2, 118.4 (2 C), 119.2, 126.0 (dd, *J* = 19.1 Hz, 9.4 Hz), 133.5 (2 C), 141.6 (dd, *J* = 19.1 Hz, 9.4 Hz), 143.0, 144.2 (dd, *J* =243.6 Hz, 5.4 Hz), 157.2 (d, *J* = 236.8 Hz). HRMS (ESI) m/z calcd. for $C_{12}H_7F_2N_3$ ($[M+H]^+$): 231.0608, found: 231.0618. Single crystals for XRD analysis were grown by the slow evaporation from a dichloromethane solution. CCDC Nr. 1410424.

4-[(3,6-Difluoropyridin-2-yl)amino]-*N*-mesitylbenzimidamide (9). A mixture of nitrile **7** (0.231 g, 1.0 mmol), $MeSO_3H$ (0.065 mL, 1.0 mmol) and 2,4,6-trimethylaniline (0.281 mL, 2 mmol) in *N*-methyl-2-pyrrolidinone (0.5 mL) was placed in a 10 mL microwave vial and heated in the microwave oven (300 W output) for 1 h at 180 °C. The mixture was cooled to room temperature, a solution of Na_2CO_3 (10% in H_2O, 10 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The residue was purified by column chromatography to give **9** (33 mg, 9%) as a brownish solid; mp >240 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 6H), 2.25 (s, 3H), 4.53 (br, 2 H), 6.26 (ddd, *J* = 8.5 Hz, 3.1 Hz, 2.4 Hz, 1H), 6.85 (s, 2 H), 6.88 (br, 1 H), 7.33 (ddd, *J* = 9.5 Hz, 8.5 Hz, 6.2 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 2 H), 7.84 (d, *J* = 8.9 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7 (2 C), 20.7, 97.5 (dd, *J* = 41.2 Hz, 3.4 Hz), 118.6 (2 C), 125.4 (dd, *J* = 18.1 Hz, 9.4 Hz), 127.7 (2 C), 128.77 (2 C), 128.84, 129.9, 131.9, 140.9 (2 C), 142.5 (dd, *J* = 18.1 Hz, 12.9 Hz), 143.7, 144.1 (dd, *J* =252.5 Hz, 5.5 Hz), 153.0, 157.3 (dd, *J* = 235.0 Hz, 1.5 Hz); HRMS (ESI) m/z calcd. for $C_{21}H_{21}F_2N_4$ ($[M+H]^+$): 367.1734, found: 367.1720.

4-Bromo-2-fluoro-6-methylaniline (13c).[39] A round bottomed flask was charged with 2-fluoro-6-methylaniline (12 mmol, 1.5 g) and acetic acid (20 mL). Bromine (12 mmol, 0.616 mL) was added dropwise, and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was evaporated, neutralized with saturated aq. Na_2CO_3 solution, and extracted with CH_2Cl_2 (3 x 50 mL). Combined organic phases were dried over Mg_2SO_4 and evaporated in vacuo. The residue was purified with an automated chromatography system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 35 min, 35 mL/min). Obtained as red liquid; yield 82% (2.0 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3H), 3.63 (s, 2H), 6.98 (s, 1H), 7.02 (dd, *J* = 10.1 Hz, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4, 108.8 (d, *J* = 10.1 Hz), 116.7 (d, *J* = 23.1 Hz), 126.7 (d, *J* = 4.1 Hz), 128.8 (d, *J* = 2.9 Hz), 132.7 (d, *J* = 12.4 Hz), 151.8 (d, *J* = 240.5 Hz).

4-Amino-3-fluoro-5-methylbenzonitrile (8c).[40] A 50 mL round bottomed flask was charged with CuCN (2.95 mmol, 264 mg), CuI (0.25 mmol, 47 mg), KI (0.52 mmol, 86 mg), *N,N'*-dimethyl-1,2-ethanediamine (2.46 mmol, 217 mg), 4-bromo-2-fluoro-6-methylaniline (2.45 mmol, 500 mg) and dry DMF (20 mL). The resulting mixture was heated to 110 °C (oil bath temperature) for 16 h. After the reaction, DMF was evaporated and aqueous 28% NH_3 solution (50 mL) was added. The resulting mixture was extracted with dichloromethane, washed with brine solution and dried over $MgSO_4$. The product was purified with an automated chromatography system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 80% ethylacetate in 35 min, 35 mL/min). Obtained as white solid; yield 74% (0.272 g); mp 119–120 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19 (s, 3H), 4.20 (brs, 2H), 7.10–7.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.0 (d, J = 3.1 Hz), 99.3 (d, J = 9.7 Hz), 116.7 (d, J = 22.0 Hz), 119.3 (d, J = 3.0 Hz), 124.6 (d, J = 4.2 Hz), 130.2 (d, J = 2.4 Hz), 138.1 (d, J = 11.9 Hz), 149.8 (d, J = 240.6 Hz).

General Procedure for synthesis of anilines 12a–f (General Procedure A): A solution of Pd catalyst in DMA was prepared first. A flask was charged with $Pd(OAc)_2$ (0.2 mmol, 45 mg) and tri(*o*-tolyl)phosphine (0.4 mmol, 0.122 g), dry DMA (4 mL) was added and the resulting solution was stirred for 15 min under an argon atmosphere. Next, a 100 mL round bottomed flask was charged with a 4-bromoaniline **9a–e** (4 mmol), acrylonitrile (6.0 mmol, 0.32 g), tetrabutylammonium chloride (4.0 mmol, 1.12 g) and $CH_3COONa{\cdot}3H_2O$ (4.0 mmol, 0.54 g). The freshly prepared Pd catalyst solution was added, the resulting mixture was stirred for 2 min under an argon atmosphere, and then heated to reflux (oil bath temperature 140 °C) for 48 h. The reaction mixture was allowed to cool down to room temperature and filtered through Celite. The Celite cake was washed with toluene (100 mL), combined filtrates were washed with water (100 mL), brine (50 mL), dried with $MgSO_4$ and evaporated in vacuo. The residue was separated with an automated chromatography system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 80% ethylacetate in 35 min, 35 mL/min). Compounds **12a**,[41] **12b**,[42] and **12d**[41] were reported earlier. Data for compounds **12c,e,f** are given below.

3-(4-Amino-3-fluoro-5-methylphenyl)acrylonitrile (12c). Prepared according to the General Procedure A from $Pd(OAc)_2$ (0.16 mmol, 36 mg), tri(*o*-tolyl)phosphine (0.32 mmol, 97 mg), 4-bromo-2-fluoro-6-methylaniline (3.19 mmol, 0.65 g), acrylonitrile (4.78 mmol, 0.25 g), tetrabutylammonium chloride (3.19 mmol, 0.86 g) and $AcONa{\cdot}3H_2O$ (3.19 mmol, 0.43 g). Obtained as a mixture of geometrical isomers (*Z:E* 1:3.13), light yellow solid; yield 89% (0.0.49 g); mp 98-100 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): signals of major (*E*)-isomer: δ 2.19 (s, 3H), 4.03 (brs, 2H), 5.60 (d, J = 16.5 Hz, 1H), 6.94 (s, 1H), 6.99 (dd, J = 11.4 Hz, 1.6 Hz, 1H), 7.19 (d, J = 16.5 Hz, 1H); signals of minor (*Z*)-isomer: δ 2.21 (s, 3H), 5.19 (d, J =

12.1 Hz, 1H), 6.88 (d, *J* = 12.1 Hz, 1H), 7.29 (s, 1H), 7.47 (dd, *J* = 11.8 Hz, 1.6 Hz, 1H), signal of NH overlapped with the signal of major isomer; ^{13}C NMR (100 MHz, $CDCl_3$): signals of major (*E*)-isomer: δ 16.9 (d, *J* = 3.2 Hz), 92.3, 111.3 (d, *J* = 19.8 Hz), 118.9, 123.2 (d, *J* = 7.7 Hz), 124.2 (d, *J* = 3.8 Hz), 125.9 (d, *J* = 2.0 Hz), 136.2 (d, *J* = 12.5 Hz), 149.9 (d, *J* = 2.8 Hz), 151.0 (d, *J* = 239.5 Hz); signals of minor (Z)-isomer: δ 90.7, 113.3 (d, *J* = 20.1 Hz), 118.1, 123.2 (d, *J* = 7.7 Hz), 123.9 (d, *J* = 3.9 Hz), 127.7 (d, *J* = 2.1 Hz), 136.1 (d, *J* = 12.5 Hz), 147.7 (d, *J* = 2.8 Hz), 150.6 (d, *J* = 239.2 Hz), signal of CH_3 overlapped with the signal of major isomer. HRMS (ESI) *m/z* calcd. for $C_{10}H_{10}FN_2$ ($[M+H]^+$): 177.0828, found: 177.0832.

3-(4-Amino-3,5-difluorophenyl)acrylonitrile (12e). Prepared according to the General Procedure A from $Pd(OAc)_2$ (0.25 mmol, 56 mg), tri(*o*-tolyl)phosphine (0.5 mmol, 152 mg), 4-bromo-2,6-difluoroaniline (5.0 mmol, 1.04 g), acrylonitrile (7.5 mmol, 0.398 g), tetrabutylammonium chloride (5.0 mmol, 1.39 g) and $AcONa{\cdot}3H_2O$ (5.0 mmol, 0.680 g). Obtained as a mixture of geometrical isomers (*Z*:*E* 1:3.13), white solid; yield 69% (0.62 g); mp 173-174 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): signals of major (*E*)-isomer: δ 4.09 (brs, 2H), 5.64 (d, *J* = 16.5 Hz, 1H), 6.95 (dd, *J* = 7.0 Hz, 2.2 Hz, 2H), 7.18 (d, *J* = 16.5 Hz, 1H); signals of minor (*Z*)-isomer: δ 5.29 (d, *J* = 12.1 Hz, 1H), 6.87 (d, *J* = 12.1 Hz, 1H), 7.36 (dd, *J* = 7.3 Hz, 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): signals of major (*E*)-isomer: δ 94.2, 110.3 (dd, *J* = 14.9 Hz, 7.4 Hz, 2 C), 118.2, 122.2 (t, *J* = 8.7 Hz), 127.1 (t, *J* = 16.4 Hz), 148.6 (t, *J* = 3.0 Hz), 151.4 (dd, *J* = 242.0 Hz, 8.5 Hz, 2 C); signals of minor (*Z*)-isomer: δ 92.6, 112.1 (dd, *J* = 15.2 Hz, 7.4 Hz, 2 C), 117.5, 146.5 (t, *J* = 3.0 Hz), 150.93 (dd, *J* = 241.3 Hz, 8.7 Hz, 2 C); other signals are overlapped with signals of major isomer. HRMS (ESI) *m/z* calcd. for $C_9H_7F_2N_2$ ($[M+H]^+$): 181.0577, found: 181.0574.

(*E*)-Methyl 3-(4-amino-3,5-dimethylphenyl)acrylate (12f). Prepared according to the General Procedure A from $Pd(OAc)_2$ (0.2 mmol, 45 mg), tri(*o*-tolyl)phosphine (0.4 mmol, 122 mg), 4-bromo-2,6-dimethylaniline (4.0 mmol, 0.800 g), methyl acrylate (6.0 mmol, 0.52 g), tetrabutylammonium chloride (4.0 mmol, 1.11 g) and $AcONa{\cdot}3H_2O$ (4.0 mmol, 0.544 g). Analytical data correspond to those found in literature. White solid; yield 61% (0.49 g); mp 83-84 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 3H), 3.77 (s, 3H), 3.86 (brs, 2H), 6.23 (d, *J* = 15.9 Hz, 1H), 7.14 (s, 2H), 7.57 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5 (2 C), 51.4, 112.8, 121.5 (2 C), 124.1, 128.8 (2 C), 145.4, 145.6, 168.2. HRMS (ESI) *m/z* calcd. for $C_{12}H_{16}NO_2$ ($[M+H]^+$): 206.1181, found: 206.1188.

General Procedure B for the Synthesis of intermediates 11a–e. A solution of Pd catalyst in dioxane was prepared first. A flask was charged with $Pd(OAc)_2$ (0.025 mmol, 5.6 mg) and Xantphos (0.03 mmol, 17 mg), dry dioxane (5 mL) was added and the resulting solution was stirred for 15 min under an argon atmosphere. Next, a 50 mL round bottomed flask was charged with 2,6-dichloro-3-fluoropyridine (0.5 mmol, 83 mg), an aniline **2a–d** or **8d** (0.6 mmol) and *t*-BuONa (0.7 mmol, 67 mg). The freshly prepared solution of Pd catalyst was added, the resulting mixture was stirred for 2 min under

an argon atmosphere, and then heated to reflux (oil bath temperature 110 °C) for 16 h. The reaction mixture was allowed to cool down to room temperature and filtered through Celite. The Celite cake was washed with CH_2Cl_2 (100 mL), combined organic phases were evaporated in vacuo. The residue was separated with an automated chromatography system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 35 min, 35 mL/min).

4-[(6-Chloro-3-fluoropyridin-2-yl)amino]benzonitrile (11a). Prepared according to the General Procedure B from $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), Xantphos (0.03 mmol, 17 mg), 2,6-dichloro-3-fluoropyridine (0.5 mmol, 83 mg), 4-aminobenzonitrile (0.6 mmol, 71 mg) and *t*-BuONa (0.7 mmol, 67 mg). Obtained as white solid, yield 89% (0.11 g); mp 171–172 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (dd, J = 8.4 Hz, 2.8 Hz, 1H), 6.87 (brs, 1H), 7.31 (dd, J = 10.0 Hz, 8.4 Hz, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 105.3, 115.5 (d, J = 3.2 Hz), 118.4 (2 C), 119.2, 124.2 (d, J = 18.0 Hz), 133.4 (2 C), 143.0, 143.1 (d, J = 3.5 Hz), 143.2 (d, J = 11.4 Hz), 146.0 (d, J= 253.6 Hz); HRMS (ESI) m/z calcd. for $C_{12}H_8ClFN_3$ ([M+H]$^+$): 248.0391, found: 248.0397. Single crystals for XRD analysis were grown by the slow evaporation from a dichloromethane solution. CCDC Nr. 1410427.

6-Chloro-*N*-(4-chlorophenyl)-3-fluoropyridin-2-amine (11b). Prepared according to the General Procedure B from $Pd(OAc)_2$ (0.30 mmol, 68 mg), Xantphos (0.36 mmol, 0.21 g), 2,6-dichloro-3-fluoropyridine (6.02 mmol, 1.0 g), 4-chloroaniline (7.23 mmol, 0.92 g) and *t*-BuONa (8.43 mmol, 0.81 g). Obtained as white solid; yield 74% (1.12 g); mp 89–90 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.63 (brs, 1H), 6.74 (dd, J = 8.0 Hz, 2.7 Hz, 1H), 7.26 (dd, J = 10.0 Hz, 8.0 Hz, 1H), 7.32 (d, J = 8.9 Hz, 2H), 7.61 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 113.9 (d, J = 3.2 Hz), 120.2 (2 C), 123.5 (d, J = 17.9 Hz), 127.7 (2 C), 129.0, 137.5, 142.9 (d, J = 3.5 Hz), 144.1 (d, J = 11.5 Hz), 145.7 (d, J = 252.6 Hz); HRMS (ESI) m/z calcd. for $C_{11}H_8C_{l2}FN_2$ ([M+H]$^+$): 257.0049, found: 257.0038.

6-Chloro-3-fluoro-*N*-(4-fluorophenyl)pyridin-2-amine (11c). Prepared according to the General Procedure B from $Pd(OAc)_2$ (0.25 mmol, 56 mg), Xantphos (0.30 mmol, 0.17 g), 2,6-dichloro-3-fluoropyridine (5.0 mmol, 0.83 g), 4-fluoroaniline (6.0 mmol, 0.58 mL) and *t*-BuONa (7.0 mmol, 0.67 g). Obtained as white solid; yield 88% (1.06 g); mp 87–88 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (brs, 1H), 6.69 (dd, J = 8.2 Hz, 2.7 Hz, 1H), 7.06 (t, J = 9.1 Hz, 2H), 7.22 (dd, J = 10.2 Hz, 8.2 Hz, 1H), 7.58 (dd, J = 9.1 Hz, 4.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3COCD_3): δ 113.5 (d, J = 3.2 Hz), 115.7 (d, J = 22.6 Hz, 2 C), 121.0 (d, J = 7.8 Hz, 2 C), 123.4 (d, J = 17.9 Hz), 134.9 (d, J = 2.6 Hz), 143.0 (d, J = 3.4 Hz), 144.6 (d, J = 11.7 Hz), 145.7 (d, J = 252.2 Hz), 158.7 (d, J = 242 Hz); HRMS (ESI) m/z calcd. for$C_{11}H_8ClF_2N_2$ ([M+H]$^+$): 241.0344, found: 241.0335.

Methyl 4-[(6-chloro-3-fluoropyridin-2-yl)amino]benzoate (11d). Prepared according to the General Procedure B from $Pd(OAc)_2$ (0.1 mmol, 22 mg), Xantphos (0.120 mmol, 0.069 g), 2,6-dichloro-3-fluoropyridine (2.0 mmol, 0.332 g), methyl 4-aminobenzoate (2.0 mmol, 0.302 g) and Cs_2CO_3 (10.0 mmol, 3.26 g). white solid; yield 66% (0.367 g); mp 159–160 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.78 (dd, J = 8.2 Hz, 2.8 Hz, 1H), 6.83 (brs, 1H), 7.27 (dd, J = 8.2 Hz, 9.9 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.9, 114.8 (d, J = 2.9 Hz), 117.7 (2 C), 123.8 (d, J = 18.0 Hz), 124.0, 131.0 (2 C), 143.0 (d, J = 3.6 Hz), 143.2, 143.6 (d, J = 11.3 Hz), 145.9 (d, J = 253.7 Hz), 166.8; HRMS (ESI) m/z calcd. for $C_{13}H_{11}ClFN_2O_2$ ($[M+H]^+$): 281.0493, found: 281.0497.

3-{4-[(6-Chloro-3-fluoropyridin-2-yl)amino]phenyl}acrylonitrile (11e). Prepared according to the General Procedure B from $Pd(OAc)_2$ (0.05 mmol, 11.0 mg), Xantphos (0.06 mmol, 34 mg), 2,6-dichloro-3-fluoropyridine (1.0 mmol, 166 mg), 3-(4-aminophenyl)acrylonitrile (1.0 mmol, 144 mg) and *t*-BuONa (1.4 mmol, 135 mg). Obtained as a mixture of geometrical isomers (*Z*:*E* 1:9), light yellow solid; yield 74% (0.15 g); mp 169–170 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): signals of major (*E*)-isomer: δ 5.76 (d, J = 16.6 Hz, 1H), 6.78 (dd, J = 8.2 Hz, 2.8 Hz, 1H), 6.83 (brs, 1H), 7.28 (dd, J = 9.9 Hz, 8.2 Hz, 1H), 7.34 (d, J = 16.6 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.71 (d,J = 8.7 Hz, 2H);); signals of minor (*Z*)-isomer: δ 5.32 (d, J = 12.1 Hz, 1H), 7.05 (d, J = 12.1 Hz, 1H), 7.83 (d, J = 8.8 Hz, 2H); other signals are overlapped with signals of major isomer. ^{13}C NMR (100 MHz, $CDCl_3$): signals of major (*E*)-isomer: δ 93.8, 114.8 (d, J = 3.1 Hz), 118.67, 118.71 (2 C), 123.8 (d, J = 18.0 Hz), 127.9, 128.6 (2 C), 141.8, 143.0 (d, J = 3.5 Hz), 143.6 (d, J = 11.4 Hz), 145.9 (d, J = 252 Hz), 149.9; HRMS (ESI) m/z calcd. for $C_{14}H_{10}ClFN_3$ ($[M+H]^+$): 274.0547, found: 274.0540.

4-[(2-Chloro-5-fluoropyrimidin-4-yl)amino]benzonitrile (17). Prepared according to the General Procedure B from $Pd(OAc)_2$ (0.25 mmol, 56 mg), Xantphos (0.3 mmol, 0.17 g), 2,4-dichloro-5-fluoropyrimidine (5 mmol, 0.84 g), 4-aminobenzonitrile (5 mmol, 0.59 g) and Cs_2CO_3 (25 mmol, 0.84 g). Obtained as white solid; yield 75% (0.93 g); mp 235-236 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 2.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 106.0, 119.5, 121.3 (2 C), 133.5 (2 C), 142.9, 143.2 (d, J = 21.2 Hz), 145.9 (d, J = 260 Hz), 150.1 (d, J = 12.4 Hz), 153.1 (d, J = 3.5 Hz); HRMS (ESI) m/z calcd. for $C_{11}H_7ClFN_4$ ($[M+H]^+$): 249.0343, Found: 249.0341.

4-[(5-Chloro-2-fluorophenyl)amino]benzonitrile (21). Prepared according to the General Procedure B from $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), Xantphos (0.03 mmol, 17 mg), 2-bromo-4-chloro-1-fluorobenzene (0.5 mmol, 110 mg), 4-aminobenzonitrile (0.5 mmol, 59 mg) and *t*-BuONa (0.7 mmol, 67 mg). Obtained as white solid; yield 86% (107 mg); mp 141-142 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (brs, 1H), 6.96 (ddd, J = 8.8 Hz, 4.3 Hz, 2.5 Hz, 1H), 7.00–7.10 (m, 3H), 7.35 (dd, J = 7.2 Hz, 2.5 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 103.9, 116.5 (2 C), 117.0 (d, J =

21.2 Hz), 119.3, 120.0 (d, *J* = 1.5 Hz), 123.2 (d, *J* = 7.4 Hz), 129.7 (d, *J* = 3.5 Hz), 129.9 (d, *J* = 12.7 Hz), 133.9 (2 C), 145.9, 152.7 (d, *J* = 243.7 Hz); HRMS (ESI) *m*/*z* calcd. for $C_{13}H_9ClFN_2$ ($[M+H]^+$): 247.0438, found: 247.0432.

4-[(6-Chloropyridin-2-yl)amino]benzonitrile (24). A solution of Pd catalyst in dioxane was prepared first. A flask was charged with $Pd(OAc)_2$ (0.1 mmol, 22 mg) and *rac*-BINAP (0.1 mmol, 62 mg), dry toluene (10 mL) was added and the resulting solution was stirred for 15 min under an argon atmosphere. Next, a 100 mL round bottomed flask was charged with 2,6-dichloropyridine (5 mmol, 0.74 g), 4-aminobenzonitrile (5 mmol, 0.71 g) and K_2CO_3 (0.1 mol, 13.8 g). The freshly prepared Pd catalyst solution was added, the resulting mixture was stirred for 2 min under an argon atmosphere, and then heated to reflux (oil bath temperature 120 °C) for 24 h. The mixture was allowed to cool down to room temperature and filtered through Celite. Celite cake was washed with dichloromethane (100 mL), combined organic phases were evaporated in vacuo and the residue was separated with an automated chromatography system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 35 min, 35 mL/min). Obtained as white solid; yield 60% (0.28 g); mp 182-183 °C (AcOEt); ^{1}H NMR (400 MHz, $DMSO_{d6}$): δ 6.87 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.69 (d, *J*= 8.9 Hz, 2H), 7.77 (d, *J* = 8.9 Hz, 2H), 9.85 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 102.5, 110.9, 115.4, 118.1 (2 C), 120.0, 133.7 (2 C), 141.2, 145.5, 148.1, 155.1; HRMS (ESI) *m*/*z* calcd. for $C_{13}H_{10}ClN_2$ ($[M+H]^+$): 229.0533, found: 229.0533.

General Procedure C for the Synthesis of Compounds 4a–u. A solution of Pd catalyst in dioxane was prepared first. A flask was charged with $Pd(OAc)_2$ (0.025 mmol, 5.61 mg) and XPhos (0.03 mmol, 14 mg), dry dioxane (5 mL) was added and the resulting solution was stirred for 15 min under an argon atmosphere. Next, a 50 mL round bottomed flask was charged with the intermediate **7a–e** (0.5 mmol, 124 mg), an aniline **8a–c** or **12a–f** or a phenol **15a,b** (0.6 mmol) and Cs_2CO_3 (1.25 mmol, 0.41 g). The freshly prepared solution of Pd catalyst was added, the resulting mixture was stirred for 2 min under an argon atmosphere, and then heated to reflux (oil bath temperature 110 °C) for 16 h. The mixture was allowed to cool down to room temperature and filtered through Celite. Celite cake was washed with dichloromethane (100 mL), combined organic phases were evaporated in vacuo and the residue separated with an automated chromatography system using Silica Flash Cartridges applying a heptane-ethyl acetate gradient (from 100% heptane to 100% ethylacetate in 35 min, 35 mL/min).

4-{[6-(Mesitylamino)-3-fluoropyridin-2-yl]amino}benzonitrile (4a). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), XPhos (0.03 mmol, 14 mg), intermediate **11a** (0.5 mmol, 124 mg), aniline **8a** (0.6 mmol, 81 mg) and Cs_2CO_3 (1.25 mmol, 408 mg). Obtained as white solid; yield 53% (91 mg); mp 201–202 °C

(AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 6H), 2.33 (s, 3H), 5.59 (dd, J = 8.6 Hz, 2.0 Hz, 1H), 5.72 (s, 1H), 6.69 (br, 1H), 6.94 (s, 2H), 7.09 (dd, J = 10.2 Hz, 8.6 Hz, 1H), 7.47 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.6, 21.0, 98.1 (br), 101.4, 118.2 (2 C), 120.2, 125.4 (d, J = 18.0 Hz), 129.0 (2 C), 132.8 (2 C), 135.1, 136.1, 136.4 (2 C), 140.0 (d, J = 240.0 Hz), 141.5 (d, J = 11.2 Hz), 146.1, 153.3; HRMS (ESI) m/z calcd. for $C_{21}H_{20}FN_4$ ($[M+H]^+$): 347.1672, found: 347.1688. HUPLC: t_r 5.26 min. Single crystals for XRD analysis were grown by the slow evaporation of an acetone solution. CCDC Nr. 1410425.

4-{[6-(4-Cyanophenyl)amino-5-fluoropyridin-2-yl]amino}-3,5-dimethylbenzonitrile (4b). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), XPhos (0.03 mmol, 14 mg), intermediate **11a** (0.5 mmol, 124 mg), aniline **8b** (0.6 mmol, 88 mg) and Cs_2CO_3 (1.25 mmol, 408 mg). Obtained as white solid; yield 61% (109 mg); mp 235–236 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 6H), 5.70 (dd, J = 8.6 Hz, 2.2 Hz, 1H), 5.91 (s, 1H), 6.78 (brs, 1H), 7.19 (dd, J = 10.2 Hz, 8.6 Hz, 1H), 7.45 (s, 2H),7.49 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 97.6 (d, J = 2.5 Hz), 104.1, 109.7, 117.9 (2 C), 118.8, 119.4, 124.3 (d, J = 18.0 Hz), 132.2 (2 C), 133.1 (2 C), 137.1 (2 C), 141.4 (d, J = 242.7 Hz), 141.8, 142.0 (d, J = 10.8 Hz), 143.9, 150.7 (d, J = 2.4 Hz); HRMS (ESI) m/z calcd. for $C_{21}H_{17}FN_5$ ($[M+H]^+$): 358.1468, found: 358.1486. HUPLC: t_r 4.60 min. Single crystals for XRD analysis were grown by the slow evaporation from an acetone solution. CCDC Nr. 1410426.

(*E*)-4-({6-[4-(2-Cyanovinyl)-2,6-dimethylphenylamino]-3-fluoropyridin-2-yl}amino)benzonitrile (4c). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), XPhos (0.03 mmol, 14 mg), intermediate **11a** (0.5 mmol, 124 mg), aniline **12a** (0.6 mmol, 103 mg) and Cs_2CO_3 (1.25 mmol, 408 mg). Obtained as white solid; yield 62% (0.119 g); mp 211-212 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 6H), 5.67 (dd, J = 8.6 Hz, 2.2 Hz, 1H), 5.86 (brs, 1H), 5.88 (d, J = 16.6 Hz, 1H), 6.75 (brs, 1H), 7.18 (dd, J = 10.2 Hz, 8.6 Hz, 1H), 7.26 (s, 2H), 7.39 (d, J = 16.6 Hz, 1H), 7.51 (d, J = 8.9 Hz, 2H), 7.67 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 18.9, 96.5, 99.2 (d, J = 2.0 Hz), 103.6, 118.9 (2 C), 119.4, 120.1, 125.5 (d, J = 18.2 Hz), 128.5 (2 C), 132.5, 133.4 (2 C), 138.0 (2 C), 141.4 (d, J = 240.8 Hz), 142.5, 142.7 (d, J = 11.2 Hz), 146.3, 151.2, 153.3 (d, J = 2.0 Hz); HRMS (ESI) m/z calcd. for $C_{23}H_{19}FN_5$ ($[M+H]^+$): 384.1624, found: 384.1629. HUPLC: t_r 4.76 min.

***(E)*-Methyl 3-(4-{6-[(4-cyanophenyl)amino]-5-fluoropyridin-2-ylamino}-3,5-dimethyl-phenyl)acrylate (4d).** Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), XPhos (0.03 mmol, 14 mg), intermediate **11a** (0.5 mmol, 124 mg), aniline **12f** (0.6 mmol, 123 mg) and Cs_2CO_3 (1.25 mmol, 408 mg). Obtained as white solid; yield 71% (0.15 g); mp 189–190 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 6H), 3.82 (s, 3H), 5.68 (dd, J = 8.6

Hz, 2.2 Hz, 1H), 5.86 (s, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.76 (d, J = 3.2 Hz, 1H), 7.15 (dd, J = 10.2 Hz, 8.6 Hz, 1H), 7.31 (s, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6 (2C), 51.8, 97.1 (d, *J* = 2.0 Hz), 103.7, 117.5, 117.8 (2 C), 119.6, 124.3 (d, *J* = 17.9 Hz), 128.3 (2 C), 132.4, 133.1 (2 C), 136.7 (2 C), 139.2, 141.0 (d, *J* = 10.8 Hz), 141.8 (d, *J* = 241.4 Hz), 144.1, 144.4, 151.5 (d, *J* = 2.0 Hz), 167.5; HRMS (ESI) *m/z* calcd. for $C_{24}H_{22}FN_4O_2$ ([M+H]$^+$): 417.1727, found: 417.1732. HUPLC: t_r 5.04 min.

3-(4-{6-[(4-Fluorophenyl)amino]-5-fluoropyridin-2-ylamino}-3,5-dimethylphenyl)acrylo-nitrile (4e). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), XPhos (0.03 mmol, 14 mg), intermediate **11c** (0.5 mmol, 120 mg), aniline **12a** (0.6 mmol, 103 mg) and Cs_2CO_3 (1.25 mmol, 408 mg). Obtained as a mixture of geometrical isomers (*Z:E* 1:6.3), white solid; yield 66% (0.123 g); mp 189–190 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): signals of major (*E*)-isomer: δ 2.24 (s, 6H), 5.51 (dd, *J* = 8.5 Hz, 2.1 Hz, 1H), 5.78 (brs, 1H), 5.84 (d, *J* = 16.6 Hz, 1H), 6.43 (brs, 1H), 6.90 (t, *J* = 8.8 Hz, 2H), 7.08 (dd, *J* = 10.4 Hz, 8.5 Hz, 1H), 7.21 (s, 2H), 7.35 (d, *J* = 16.6 Hz, 1H), 7.47 (dd, *J* = 9.1 Hz, 4.7 Hz, 2H); signals of minor (*Z*)-isomer: δ 5.39 (d, *J* = 12.1 Hz, 1H), 7.57 (s, 2H), other signals are overlapped with signals of major isomer; ^{13}C NMR (100 MHz, $CDCl_3$) of major (*E*)-isomer: δ 18.6 (2C), 95.2 (d, *J* = 2.1 Hz), 95.5, 115.3 (d, *J* = 22.3 Hz, 2C), 118.4, 120.2 (d, *J* = 7.5 Hz, 2C), 123.5 (d, *J* = 17.5 Hz), 127.6 (2C), 131.1, 136.1 (d, *J* = 2.5 Hz), 136.8 (2 C), 140.6, 140.9 (d, *J* = 240.7 Hz), 143.3 (d, *J* = 11.1 Hz), 150.2, 151.1 (d, *J* = 2.2 Hz), 158.1 (d, *J* = 240.8 Hz); HRMS (ESI) *m/z* calcd. for $C_{22}H_{19}F_2N_4$ ([M+H]$^+$): 377.1578, found: 377.1585. HUPLC: t_r 4.94 min, 5.03 min.

3-[4-(6-{4-[(2-Cyanovinyl)-2,6-dimethylphenyl]amino}-3-fluoropyridin-2-yl)aminophenyl]acrylonitrile (4f). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), XPhos (0.03 mmol, 14 mg), intermediate **11e** (0.5 mmol, 137 mg), aniline **12a** (0.6 mmol, 103 mg) and Cs_2CO_3 (1.25 mmol, 408 mg). Obtained as a mixture of geometrical isomers (*Z,E:E,Z:E,E* 1:1:14.7), yellow solid; yield 63% (0.129 g); mp 269–270 °C (AcOEt); ^{1}H NMR (400 MHz, CD_3COCD_3): signals of major (*E,E*)-isomer: δ 2.26 (s, 6H), 5.97 (d, *J* = 16.6 Hz, 1H), 6.02 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H); 6.30 (d, *J* = 16.7 Hz, 1H), 7.30 (dd, *J* = 10.9 Hz, 8.5 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 16.6 Hz, 1H), 7.46-7.52 (m, 3H), 7.59 (d, *J* = 16.7 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 2H), 8.16 (brs, 1H); signals of minor (Z,*E*)- and (*E,Z*)-isomers: δ 5.47 (d, *J* = 12.1 Hz, 1H), 5.73 (d, *J* = 12.1 Hz, 1H), 6.25 (d, *J* = 16.6 Hz, 1H), 7.15 (d, *J* = 12.1 Hz, 1H), other signals are overlapped with signals of major isomer; ^{13}C NMR (100 MHz, CD_3COCD_3) of major (*E,E*)-isomer: δ 18.9, 93.3, 96.5, 101.0, 118.9, 119.0, 119.4, 119.7, 125.2 (d, *J* = 18.2 Hz), 127.3, 128.5, 129.1, 132.4, 138.0, 142.6, 145.0, 144.0 (d, *J* = 240.6 Hz), 151.0, 151.2, 153.3 (d, *J* = 1.8 Hz); HRMS (ESI) *m/z* calcd. for $C_{25}H_{21}FN_5$ ([M+H]$^+$): 410.1781, found: 410.1793. HUPLC: t_r 4.87 min, 4.92 min.

4-{6-[(4-Fluorophenyl)amino]-5-fluoropyridin-2-ylamino}-3,5-dimethylbenzonitrile (4g). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), XPhos (0.03 mmol, 14 mg), intermediate **11c** (0.5 mmol, 120 mg), aniline **8b** (0.6 mmol, 88 mg), and Cs_2CO_3 (1.25 mmol, 408 mg). Obtained as colorless solid; yield 50% (88 mg); mp 135-136 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 6H), 5.58 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 5.86 (brs, 1H), 6.47 (brs, 1H), 6.91 (t, J = 8.7 Hz, 2H), 7.11 (dd, J = 10.4 Hz, 8.4 Hz, 1H), 7.39–7.45 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5 (2 C), 95.6 (d, J = 2.3 Hz), 109.1, 115.3 (d, J = 22.3 Hz, 2 C), 119.1, 120.2 (d, J = 7.5 Hz, 2 C), 123.5 (d, J = 18.2 Hz), 132.1 (2 C), 135.9 (d, J = 2.5 Hz), 136.9(2 C), 141.1 (d, J = 241.6 Hz), 142.3, 143.3 (d, J = 11.1 Hz), 150.5 (d, J = 2.3 Hz), 158.1 (d, J = 241 Hz); HRMS (ESI) m/z calcd. for $C_{20}H_{17}F_2N_4$ ($[M+H]^+$): 351.1421, found: 351.1404. HUPLC: t_r 4.89 min.

4-{6-[4-(2-Cyanovinyl)phenylamino]-3-fluoropyridin-2-ylamino}benzonitrile (4h). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), XPhos (0.03 mmol, 14 mg), intermediate **11a** (0.5 mmol, 124 mg), aniline **12d** (0.6 mmol, 87 mg) and Cs_2CO_3 (1.25 mmol, 408 mg). Obtained as a mixture of geometrical isomers (*Z:E* 1:2.33), white solid; yield 68% (0.12 g); mp 285-286 °C (AcOEt); ^{1}H NMR (400 MHz, DMSO-d_6): signals of major (*E*)-isomer: δ 6.22 (d, J = 16.6 Hz, 1H), 6.44-6.52 (m, 1H), 7.50-7.60 (m, 6H), 7.69 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 9.31 (s, 1H), 9.39 (s, 1H), signals of minor (*Z*)-isomer: δ 5.60 (d, J = 12.0 Hz, 1H), 7.28 (d, J = 12.0 Hz, 1H), 7.62 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 8.6 Hz, 2H), 9.45 (s, 1H), other signals are overlapped with the signals of major (*E*)-isomer; ^{13}C NMR (100 MHz, DMSO-d_6): signals of major (*E*)-isomer: δ 92.7, 102.4, 103.6 (br), 117.7 (2 C), 118.9 (2 C), 120.2, 125.7 (d, J = 18.1 Hz), 126.2, 129.3 (2 C), 133.3 (2 C), 141.1 (d, J = 11.7 Hz), 141.9 (d, J = 244 Hz), 144.7, 145.6, 149.6 (d, J = 2.2 Hz), 150.8, 1 signal is missing because of overlap; signals of minor (*Z*)-isomer: δ 91.2, 102.5, 119.1 (2 C), 119.2, 120.1, 126.2, 130.4 (2 C), 133.2 (2 C), 144.5, 148.9, other signals are overlapped with the signals of major isomer; HRMS (ESI) m/z calcd. for $C_{21}H_{15}FN_5$ ($[M+H]^+$): 356.1311, found: 356.1308. HUPLC: t_r 4.60 min, 4.65 min.

4-[6-(4-Chlorophenyl)amino-5-fluoropyridin-2-ylamino]-3,5-dimethylbenzonitrile (4i). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.1 mg), XPhos (0.03 mmol, 14 mg), intermediate **11b** (0.5 mmol, 129 mg), aniline **8b** (0.6 mmol, 88 mg), and Cs_2CO_3 (1.25 mmol, 408 mg). Obtained as colorless solid; yield 54% (99 mg); mp 197-198 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 6H), 5.60 (dd, J = 8.5 Hz, 2.1 Hz, 1H), 5.85 (brs, 1H), 6.52 (brs, 1H), 7.13 (dd, J = 10.4 Hz, 8.5 Hz, 1H), 7.17 (d, J = 8.8 Hz, 2H), 7.43 (s, 2H), 7.44 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5 (2 C), 96.0 (d, J = 2.3 Hz), 109.3, 119.0, 119.7 (2 C), 123.6 (d, J = 18.2 Hz), 126.7, 128.7 (2 C), 132.1 (2 C), 136.9 (2 C), 138.5, 141.2 (d, J = 241.9 Hz), 142.2, 143.0 (d, J = 11.0 Hz), 150.6 (d, J = 2.3 Hz); HRMS (ESI) m/z calcd. for $C_{20}H_{17}ClFN_4$ ($[M+H]^+$): 367.1126, found: 367.1142. HUPLC: t_r 5.16 min.

3-{4-[6-(4-Chlorophenyl)amino-5-fluoropyridin-2-ylamino]-3,5-dimethylphenyl}acrylonitrile (4j). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), XPhos (0.03 mmol, 14 mg), intermediate **11b** (0.5 mmol, 129 mg), aniline **12a** (0.6 mmol, 103 mg) and Cs_2CO_3 (1.25 mmol, 408 mg). Obtained as a mixture of geometrical isomers (*Z*:*E* 1:13.5), brown solid; yield 65% (128 mg); mp 156-157 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): signals of major (*E*)-isomer: δ 2.23 (s, 6H), 5.56 (dd, *J* =8.5 Hz, 2.1 Hz, 1H), 5.83 (d, *J* = 16.6 Hz, 1H), 5.84 (brs, 1H), 6.50 (brs, 1H), 7.09 (dd, *J* = 10.4 Hz, 8.5 Hz, 1H), 7.13 (d, *J* = 8.9 Hz, 2H), 7.21 (s, 2H), 7.34 (d, *J* = 16.6 Hz, 1H), 7.45 (d, *J* = 8.9 Hz, 2H); signals of minor (*Z*)-isomer: δ 5.42 (d, *J* = 12.1 Hz, 1H), 7.60 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5 (2 C), 95.4, 95.6 (d, *J* = 2.2 Hz), 118.4, 119.6 (2 C), 123.6 (d, *J* = 17.8 Hz), 126.3, 128.2 (2 C), 129.0 (2 C), 131.1, 136.7 (2 C), 138.6, 140.4, 140.9 (d, *J* = 241.0 Hz), 142.8 (d, *J* = 11.0 Hz), 150.1, 151.1 (d, *J* = 2.2 Hz); HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{19}ClFN_4$ ($[M+H]^+$): 393.1282, found: 393.1296. HUPLC: t_r 5.24 min.

(*E*)-4-{6-[4-(2-Cyanovinyl)-2-fluoro-6-methylphenylamino]-3-fluoropyridin-2-ylamino}benzonitrile (4k). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), XPhos (0.03 mmol, 14 mg), intermediate **11a** (0.5 mmol, 124 mg), aniline **12c** (0.6 mmol, 110 mg) and Cs_2CO_3 (1.25 mmol, 408 mg). Obtained as brown solid; yield 79% (150 mg); mp 235-236 °C (AcOEt); ^{1}H NMR (400 MHz, CD_3COCD_3): δ 2.29 (s, 3H), 6.26 (dd, *J* = 8.6 Hz, 2.2 Hz, 1H), 6.34 (d, *J* = 16.4 Hz, 1H), 7.33-7.38 (m, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.45-7.48 (m, 2H), 7.59 (d, *J* = 16.6 Hz, 1H), 7.68 (br s, 1H), 7.75 (d, *J* = 8.8 Hz, 2H), 8.32 (brs, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 17.5, 96.9, 99.5 (d, *J* = 2.0 Hz), 102.9, 111.8 (d, *J* = 22.5 Hz), 117.9, 118.1 (2 C), 119.1, 124.5 (d, *J* = 18.3 Hz), 125.8 (d, *J* = 2.7 Hz), 130.4 (d, *J* = 13.1 Hz), 131.8 (d, *J* = 8.6 Hz), 132.5 (2 C), 138.2 (d, *J* = 2.0 Hz), 141.1 (d, *J* = 242.1 Hz), 141.7 (d, *J* = 11.4 Hz), 145.2, 149.1 (d, *J* = 2.7 Hz), 151.5 (d, *J* = 2.1 Hz), 158.5 (d, *J* = 245.2 Hz); HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{16}F_2N_5$ ($[M+H]^+$): 388.1374, found: 388.1368. HUPLC: t_r 4.55 min.

4-[3-Fluoro-6-(*p*-tolyloxy)pyridin-2-ylamino]benzonitrile (4l). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **11a** (0.5 mmol, 124 mg), phenol **15a** (0.6 mmol, 65 mg) and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as white solid; yield 89% (0.142 g); mp 153-154 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 6.41 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 6.76 (brs, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.38 (m, 1H), 7.42 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 101.0 (d, *J* = 2.9 Hz), 104.2, 118.0 (2 C), 119.7, 122.1 (2 C), 125.5 (d, *J* = 18.9 Hz), 130.3 (2 C), 133.2 (2 C), 134.8, 141.1 (d, *J* = 11.8 Hz), 142.7 (d, *J* = 244.8 Hz), 143.7, 152.3, 158.4 (d, *J* = 1.8 Hz); HRMS (ESI) *m*/*z* calcd. for $C_{19}H_{15}FN_3O$ ($[M+H]^+$): 320.1199, found: 320.1197. HUPLC: t_r 5.23 min.

4-[3-Fluoro-6-(mesityloxy)pyridin-2-ylamino]benzonitrile (4m). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **11a** (0.5 mmol, 124 mg), phenol **15b** (0.6 mmol, 82 mg) and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as yellow solid; yield 43% (0.074 g); mp 201-202 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 6H), 2.38 (s, 3H), 6.39 (dd, J = 8.4 Hz, 2.2 Hz, 1H), 6.70 (brs, 1H), 6.95 (s, 2H), 7.28 (s, 4H), 7.36 (dd, J = 10 Hz, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4 (2 C), 20.9, 99.6 (d, J = 2.8 Hz), 103.8, 117.6 (2 C), 119.6, 125.5 (d, J = 18.1 Hz), 129.2 (2 C), 131.0 (2 C), 132.9 (2 C), 134.6, 140.9 (d, J = 11.7 Hz), 142.1 (d, J = 244 Hz), 143.6, 148.9, 157.3 (d, J = 1.4 Hz); HRMS (ESI) m/z calcd. for $C_{21}H_{19}FN_3O$ ($[M+H]^+$): 348.1512, found: 348.1509. HUPLC: t_r 5.61 min.

(*E*)-3-{4-[6-(4-Chlorophenyl)amino-5-fluoropyridin-2-ylamino]-3-methylphenyl}acrylonitrile (4n). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **11b** (0.5 mmol, 129 mg), aniline **12b** (0.6 mmol, 95 mg) and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as yellow solid; yield 73% (0.137 g); mp 189-190 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 5.74 (d, J = 16.6 Hz, 1H), 6.16 (brs, 1H), 6.24 (dd, J = 8.4 Hz, 2.2 Hz, 1H), 6.54 (brs, 1H), 7.19-7.29 (m, 5H), 7.32 (d, J = 16.6 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 93.1, 99.4 (d, J = 2.4 Hz), 118.8, 118.9, 120.5 (2 C), 123.6 (d, J = 17.9 Hz), 126.3, 127.13, 127.17, 127.4, 128.8 (2 C), 129.9, 138.1, 141.7 (d, J = 243.3 Hz), 142.3, 143.0 (d, J = 18.1 Hz), 148.7 (d, J = 2.7 Hz), 150.1; HRMS (ESI) m/z calcd. for $C_{21}H_{17}{}^{35}ClFN_4$ ($[M+H]^+$): 379.1126, found: 379.1109. HUPLC: t_r 4.65 min.

(*E*)-Methyl 3-{4-[6-(4-fluorophenyl)amino-5-fluoropyridin-2-ylamino]-3,5-dimethylphenyl}acrylate (4o). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **11c** (0.5 mmol, 120 mg), aniline **12f** (0.6 mmol, 123 mg) and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as brown solid; yield 55% (0.113 g); mp 162-163 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 6H), 3.82 (s, 3H), 5.51 (dd, J = 8.5 Hz, 2.1 Hz, 1H), 5.77 (s, 1H), 6.42 (d, J = 16.0 Hz, 1H), 6.43 (brs, 1H), 6.92 (t, J = 8.8 Hz, 2H), 7.07 (dd, J = 10.5 Hz, 8.5 Hz, 1H), 7.30 (s, 2H), 7.49 (dd, J = 9.1 Hz, 4.7 Hz, 2H), 7.66 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6 (2 C), 51.7, 95.0 (d, J = 2.2 Hz), 115.3 (d, J = 22.3 Hz, 2 C), 117.2, 120.1 (d, J = 7.4 Hz, 2 C), 123.5 (d, J = 17.6 Hz), 128.3 (2 C), 132.1, 136.0 (br), 136.6 (2 C), 139.5, 140.8 (d, J = 240.2 Hz), 143.2 (d, J = 11.2 Hz), 144.5 (2 C), 151.3 (br), 158.0 (d, J = 240.6 Hz), 167.5; HRMS (ESI) m/z calcd. for $C_{23}H_{22}F_2N_3O_2$ ($[M+H]^+$): 410.1680, found: 410.1686. HUPLC: t_r 5.36 min.

(*E*)-Methyl 3-{4-[6-(4-chlorophenyl)amino-5-fluoropyridin-2-ylamino]-3,5-dimethylphenyl}acrylate (4p). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.018 mmol, 4.10 mg), XPhos (0.022 mmol, 10.46 mg), intermediate **11b** (0.366 mmol, 94 mg), aniline **12f** (0.44 mmol, 90 mg) and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as brown solid; yield 71% (0.067 g); mp 162-163 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 6H), 3.82 (s, 3H), 5.53 (dd, J = 8.6

Hz, 2.1 Hz, 1H), 5.77 (brs, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.48 (brs, 1H), 7.09 (dd, *J* = 10.5 Hz, 8.5 Hz, 1H), 7.17 (d, *J* = 8.9 Hz, 2H), 7.30 (s, 2H), 7.49 (d, *J* = 8.9 Hz, 2H), 7.66 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 51.7, 95.4 (d, *J* = 2.1 Hz), 117.3, 119.6 (2 C), 123.6 (d, *J* = 17.9 Hz), 126.4, 128.3 (2 C), 128.7 (2 C), 132.1, 136.6 (2 C), 138.6, 139.4, 140.9 (d, *J* = 234.7 Hz), 142.8 (d, *J* = 11.0 Hz), 144.5, 151.4 (d, *J* = 2.0 Hz), 167.5; HRMS (ESI) *m*/*z* calcd. for $C_{23}H_{22}{}^{35}ClFN_3O_2$ ([M+H]$^+$): 426.1385, found: 426.1383. HUPLC: t_r 5.52 min.

(*E*)-3-(4-{5-Fluoro-6-[4-(fluorophenyl)amino]pyridin-2-ylamino}-3-methylphenyl)acrylonitrile (4q). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **11c** (0.5 mmol, 120 mg), aniline **12b** (0.6 mmol, 95 mg) and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as yellow solid; yield 75% (0.135 g); mp 150-151 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 5.72 (d, *J* = 16.6 Hz, 1H), 6.16 (brs, 1H), 6.21 (dd, *J* = 8.4 Hz, 2.2 Hz, 1H), 6.48 (brs, 1H), 7.00 (t, *J* = 8.7 Hz, 2H), 7.19-7.28 (m, 3H), 7.31 (d, *J* = 16.6 Hz, 1H), 7.50-7.53 (dd, *J* = 9.0 Hz, 4.7 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.0, 93.1, 99.1 (d, *J* = 2.3 Hz), 115.4 (d, *J* = 22.4 Hz, 2 C), 118.7, 118.9, 121.4 (d, *J* = 7.7 Hz, 2 C), 123.5 (d, *J* = 17.8 Hz), 126.4, 127.1, 127.2, 129.9, 135.6 (d, *J* = 2.6 Hz), 141.6 (d, *J* = 243.8 Hz), 142.4, 143.5 (d, *J* = 11.2 Hz), 148.8 (d, *J* = 2.7 Hz), 150.2, 158.5 (d, *J* = 241.6 Hz); HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{17}F_2N_4$ ([M+H]$^+$): 363.1421, found: 363.1424. HUPLC: t_r 5.02 min.

4-{6-[4-(2-Cyanovinyl)-2-methylphenylamino]-3-fluoropyridin-2-ylamino}benzonitrile (4r). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **11a** (0.5 mmol, 124 mg), aniline **12b** (0.6 mmol, 0.95 mg) and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as mixture of geometrical isomers (Z:*E* 1:6.9), yellow solid; yield 70% (0.13 g); mp 239-240 °C (AcOEt); ^{1}H NMR (400 MHz, CD_3COCD_3): signals of major (*E*)-isomer: δ 2.26 (s, 3H), 6.29 (d, *J* = 16.6 Hz, 1H), 6.50 (dd, *J* = 8.6 Hz, *J* = 2.2 Hz, 1H), 7.46 (dd, *J* = 8.4 Hz, J = 1.9 Hz, 1H), 7.49-7.59 (m, 5H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 8.29 (s, 1H), 9.20 (s, 1H); signals of minor (*Z*)-isomer: δ 5.68 (d, *J* = 12.0 Hz, 1H), 7.31 (d, *J* = 12.0 Hz, 1H), 8.35 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): signals of major (*E*)-isomer: δ 17.4, 93.5, 101.7 (d, *J* = 2.5 Hz), 103.3, 118.5 (2 C), 118.7, 119.1, 121.1, 124.5 (d, *J* = 18.2 Hz), 126.1, 128.1, 129.9, 132.7 (2 C), 141.5 (d, *J* = 243.6 Hz), 141.6 (d, *J* = 11.3 Hz), 142.6, 145.1, 148.2, 150.1, 150.3 (d, *J* = 2.5 Hz); signals of minor (Z)-isomer: 17.5, 91.9, 118.4, 120.9, 121.0, 127.4, 129.4, 131.5, other signals are overlapped with signals of major isomer. HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{17}FN_5$ ([M+H]$^+$): 370.1468, found: 370.1455. HUPLC: t_r 4.69 min, 4.75 min.

4-[6-(4-Cyanophenyl)amino-5-fluoropyridin-2-ylamino]-3-fluoro-5-methylbenzonitrile (4s). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **11a** (0.5 mmol, 124), aniline **8c** (0.6 mmol, 90 mg), and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as brown solid; yield 42% (75

mg); mp 253-254 °C (AcOEt); ^{1}H NMR (400 MHz, CD_3COCD_3): δ 2.36 (s, 3H), 6.38 (dd, J = 8.6 Hz, 2.2 Hz, 1H), 7.43 (dd, J = 10.7, 8.6 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.63-7.67 (m, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.93 (s, 1H), 8.44 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 17.4 (d, J = 2.6 Hz), 100.2 (d, J = 2.3 Hz), 103.1, 108.2 (d, J = 10.3 Hz), 117.1 (d, J = 25.1 Hz), 117.7 (d, J = 3.0 Hz), 118.1 (2 C), 119.1, 124.6 (d, J = 18.3 Hz), 130.1 (d, J = 3.2 Hz), 132.5, 133.2 (d, J = 12.3 Hz), 138.6 (d, J = 2.3 Hz), 141.5 (d, J = 242.3 Hz), 141.7 (d, J = 11.6 Hz), 145.0, 150.8 (d, J = 2.2 Hz), 157.5 (d, J = 247.3 Hz); HRMS (ESI) m/z calcd. for $C_{20}H_{14}F_2N_5$ ($[M+H]^+$): 362.1217, found: 362.1233. HUPLC: t_r 4.46 min.

4-{6-[4-(2-Cyanovinyl)-2,6-difluorophenylamino]-3-fluoropyridin-2-ylamino}benzonitrile (4t). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **11a** (0.5 mmol, 124 mg), aniline **12e** (0.6 mmol, 108 mg) and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as mixture of geometrical isomers (Z:*E* 1:6.9), brown solid; yield 72% (140 mg); mp 223-224 °C (AcOEt); ^{1}H NMR (400 MHz, CD_3COCD_3), signals of major (*E*)-isomer: δ 6.38-6.44 (m, 2H), 7.38-7.46 (m, 3H), 7.51 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 16.7 Hz, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.96 (brs, 1H), 8.38 (brs, 1H); signals of minor (*Z*)-isomer δ 5.87 (d, J = 12.1 Hz, 1H), 7.68 (d, J = 9.0 Hz, 2H), 8.01 (brs, 1H), other signals are overlapped with signals of major isomer; ^{13}C NMR (100 MHz, CD_3COCD_3) signals of major (*E*)-isomer: δ 99.0, 101.5 (d, J = 2.2 Hz), 104.0, 111.9 (dd, J = 18.5, J = 6.8 Hz), 118.7, 119.0 (2 C), 120.1, 121.9 (t, J = 16.3 Hz), 125.5 (d, J = 18.3 Hz), 132.0 (t, J = 9.7 Hz), 133.5 (2 C), 142.6 (d, J = 243.2 Hz), 142.7 (d, J = 11.6 Hz), 145.9, 149.0 (t, J = 2.8 Hz), 151.0 (d, J = 2.2 Hz), 158.6 (dd, J = 247.2 Hz, J = 6.5 Hz). HRMS (ESI) m/z calcd. for $C_{21}H_{13}F_3N_5$ ($[M+H]^+$): 392.1123, found: 392.1127. HUPLC: t_r 4.35 min, 4.42 min.

(*E*)-Methyl 4-{6-[4-(2-cyanovinyl)-2,6-dimethylphenylamino]-3-fluoropyridin-2-ylamino}benzoate (4u). Synthesized according to the general procedure C using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **11d** (0.5 mmol, 140 mg), aniline **12a** (0.6 mmol, 103 mg) and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as white solid; yield 72% (0.149 g); mp 233-234 °C (AcOEt); ^{1}H NMR (400 MHz, CD_3COCD_3): δ 2.23 (s, 6H), 3.81 (s, 3H), 6.05 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 6.27 (d, J = 16.7 Hz, 1H), 7.27 (dd, J = 10.8 Hz, 8.5 Hz, 1H), 7.45 (brs, 1H), 7.47 (s, 2H), 7.56 (d, J = 16.7 Hz, 1H), 7.61 (d, J = 9.2 Hz, 2H), 7.65 (d, J = 9.2 Hz, 2H), 8.14 (brs, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 17.9 (2 C), 51.0, 95.6, 97.8 (d, J = 2.0 Hz), 117.2 (2 C), 118.4, 121.9, 124.3 (d, J = 18.2 Hz), 127.5 (2 C), 130.0 (2 C), 131.5, 137.1 (2 C), 140.6 (d, J = 240.9 Hz), 141.7, 142.1 (d, J = 10.8 Hz), 145.5, 150.2, 152.3 (d, J = 1.9 Hz), 166.1; HRMS (ESI) m/z calcd. for $C_{24}H_{22}FN_4O_2$ ($[M+H]^+$): 417.1727, found: 417.1732. HUPLC: t_r 4.96 min.

General Procedure D for the Synthesis of Compounds 18a,b. Same as the General Procedure C but starting from the intermediate **17** (0.5 mmol, 124 mg), and an aniline **8b** or **12a** (0.6 mmol).

4-[4-(4-Cyanophenyl)amino-5-fluoropyrimidin-2-ylamino]-3,5-dimethylbenzonitrile (18a). Synthesized according to the general procedure D using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **17** (0.5 mmol, 124 mg), aniline **8b** (0.6 mmol, 80 mg) and Cs_2CO_3 (2.50 mmol, 0.82 g). Obtained as light yellow solid; yield 22% (0.039 g); mp 268-269 °C (AcOEt); ^{1}H NMR (400 MHz, CD_3COCD_3): δ 2.29 (s, 6H), 7.51 (d, J = 8.8 Hz, 2H), 7.58 (s, 2H), 7.82 (d, J = 8.8 Hz, 2H), 8.00 (m, 2H), 8.85 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 17.7, 105.1, 109.6, 118.6, 118.7, 119.5, 119.6, 131.5, 132.6, 138.2, 140.8 (d, J = 246 Hz), 142.0 (d, J = 11.4 Hz), 143.7, 149.6 (d, J = 10.4 Hz), 157.1 (d, J = 2.9 Hz); HRMS (ESI) m/z calcd. for $C_{20}H_{16}FN_6$ ($[M+H]^+$): 359.1420, found: 359.1411. HUPLC: t_r 3.96 min.

4-{2-[4-(2-Cyanovinyl)-2,6-dimethylphenylamino]-5-fluoropyrimidin-4-ylamino}-benzonitrile (18b). Synthesized according to the general procedure D using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **17** (0.5 mmol, 124 mg), aniline **12a** (0.6 mmol, 86 mg) and Cs_2CO_3 (2.50 mmol, 0.82 g). Obtained as a mixture of geometrical isomers (*Z*:*E* 1:6.0), light yellow solid; yield 21% (0.040 g); mp 232-233 °C (AcOEt); ^{1}H NMR (400 MHz, CD_3COCD_3): signals of major (*E*)-isomer: δ 2.25 (s, 3H), 6.27 (d, J = 16.7 Hz, 1H), 7.44-7.49 (m, 4H), 7.56 (d, J = 16.7 Hz, 1H), 7.81-7.87 (m, 3H), 7.99 (s, 1H), 8.80 (s, 1H); signals of minor (*Z*)-isomer: δ 5.72 (d, J = 12.1 Hz, 1H), 7.38 (d, J = 12.1 Hz, 1H), other signals are overlapped with signals of major isomer; ^{13}C NMR (100 MHz, CD_3COCD_3) of major (*E*)-isomer: δ 17.8, 95.9, 104.9, 118.3, 118.7, 119.5, 127.3, 128.6, 131.9, 132.5, 137.2, 140.3, 140.6 (d, J = 246 Hz), 142.0 (d, J = 10.4 Hz), 149.5 (d, J = 10.5 Hz), 150.2, 157.4 (d, J = 2.7 Hz); HRMS (ESI) m/z calcd. for $C_{22}H_{18}FN_6$ ($[M+H]^+$): 385.1577, found: 385.1572. HUPLC: t_r 3.82 min, 3.98 min.

General Procedure E for the Synthesis of Compounds 19a–c. Same as the General Procedure C but starting from the intermediate **21** (0.5 mmol, 123 mg) and an aniline **12a–c** (0.6 mmol).

4-{5-[4-(2-Cyanovinyl)-2,6-dimethylphenylamino]-2-fluorophenylamino}benzonitrile (19a). Synthesized according to the general procedure E using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **21** (0.5 mmol, 123 mg), aniline **12a** (0.6 mmol, 103 mg) and Cs_2CO_3 (2.50 mmol, 0.82 g). Obtained as a mixture of geometrical isomers (*Z*:*E* 1:4.2), yellow solid; yield 56% (0.11 g); mp 219-220 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): signals of major (*E*)-isomer: δ 2.21 (s, 6H), 5.23 (s, 1H), 5.79 (d, J = 16.6 Hz, 1H), 5.95 (s, 1H), 6.15-6.19 (m, 1H), 6.54 (dd, J = 6.7 Hz, 2.5 Hz, 1H), 6.92-6.97 (m, 3H), 7.18 (s, 2H), 7.31 (d, J = 16.6 Hz, 1H), 7.48 (d, J = 8.5 Hz, 2H); signals of minor (*Z*)-isomer: δ 5.25 (s, 1H), 5.37 (d, J = 12.2 Hz, 1H), 7.01 (d, J = 12.2 Hz, 1H), other signals are overlapped with signals of major isomer; ^{13}C NMR (100 MHz, CD_3COCD_3) of major (*E*)-isomer: δ 18.7, 96.1, 101.9, 109.2, 110.9 (d, 7.0 Hz), 116.0, 117.5 (d, J = 21.3 Hz), 119.3, 120.3, 128.9, 129.6 (d, J = 12.9 Hz), 131.7, 134.2, 135.4, 142.9, 144.1, 148.6, 148.8 (d, J = 236.4 Hz), 151.0; HRMS (ESI) m/z calcd. for $C_{24}H_{20}FN_4$ ($[M+H]^+$): 383.1672, found: 383.1690. HUPLC: t_r 4.85 min.

4-{5-[4-(2-Cyanovinyl)-2-fluoro-6-methylphenylamino]-2-fluorophenylamino}benzo-nitrile (19b). Synthesized according to the general procedure E using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **21** (0.5 mmol, 123 mg), aniline **12c** (0.6 mmol, 106 mg) and Cs_2CO_3 (2.50 mmol, 0.82 g). Obtained as a mixture of geometrical isomers (*Z:E* 1:3.13), light yellow solid; yield 59% (0.12 g); mp 173-174 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): signals of major (*E*)-isomer: δ 2.20 (s, 3H), 5.49 (br, 1H), 5.77 (d, *J* = 16.6 Hz, 1H), 5.98 (br, 1H),6.35-6.38 (m, 1H), 6.73 (dd, *J* = 6.8 Hz, 2.4 Hz, 1H), 6.97-7.02 (m, 3H), 7.05-7.10 (m, 2H), 7.27 (d, *J* = 16.6 Hz, 1H), 7.49 (d, *J* = 8.6 Hz, 2H); signals of minor (*Z*)-isomer: δ 5.40 (d, *J* = 12.1 Hz, 1H), 5.51 (br, 1H), other signals are overlapped with signals of major isomer; ^{13}C NMR (100 MHz, CD_3COCD_3) of major (*E*)-isomer: δ 18.4 (J = 2.7 Hz), 97.0, 102.1, 110.8, 112.4 (J = 6.8 Hz), 113.3 (d, J = 22.0 Hz), 116.1, 117.2 (d, J = 21.0 Hz), 119.1, 120.3, 127.3 (d, J = 2.5 Hz), 129.5 (d, J = 13.1 Hz), 131.0 (d, J = 8.5 Hz), 132.2 (d, J = 12.1 Hz), 134.3, 136.2 (d, J = 2.4 Hz), 142.6 (d, J = 1.7 Hz), 149.4, 149.9 (d, J = 2.4 Hz), 150.5 (d, J = 236.7 Hz), 157.8 (d, J = 244.8 Hz); HRMS (ESI) *m/z* calcd. for $C_{23}H_{17}F_2N_4$ ($[M+H]^+$): 387.1421, found: 387.1414. HUPLC: t_r 4.69 min.

4-{5-[4-(2-Cyanovinyl)-2-methylphenylamino]-2-fluorophenylamino}benzonitrile (19c). Synthesized according to the general procedure E using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **21** (0.5 mmol, 123 mg), aniline **12b** (0.55 mmol, 87 mg) and Cs_2CO_3 (2.50 mmol, 0.82 g). Obtained as a mixture of geometrical isomers (*Z:E* 1:8.3), light yellow solid; yield 41% (0.076 g); mp 170-171 °C (AcOEt); ^{1}H NMR (400 MHz, CD_3COCD_3): signals of major (*E*)-isomer: δ 2.28 (s, 3H), 5.99 (d, *J* = 16.6 Hz, 1H), 6.88-6.94 (m, 1H), 7.08 (br, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 7.15-7.24 (m, 3H), 7.36-7.42 (m, 2H), 7.46 (br, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.85 (br, 1H); signals of minor (*Z*)-isomer: δ 5.41 (d, *J* = 12.1 Hz, 1H), 7.96 (br, 1H), other signals are overlapped with signals of major isomer; ^{13}C NMR (100 MHz, CD_3COCD_3) of major (*E*)-isomer: δ 17.2, 92.0, 101.5, 114.5 (d, *J* = 1.6 Hz), 114.9, 115.5, 116.5 (d, *J* = 7.0 Hz), 116.5 (d, *J* = 21.1 Hz), 118.9, 119.2, 126.0, 126.2, 126.8, 129.2 (d, *J* = 13.0 Hz), 130.3, 133.4, 139.4 (d, *J* = 1.6 Hz), 145.7, 148.2, 150.1, 150.7 (d, *J* = 240.9 Hz); HRMS (ESI) *m/z* calcd. for $C_{23}H_{18}FN_4$ ($[M+H]^+$): 369.1516, found: 369.1505. HUPLC: t_r 4.80 min.

General procedure F for the synthesis of Compounds 22a–d. Same as the General Procedure C but starting from the intermediate **24** (0.5 mmol, 115 mg) and an aniline **8a,b** or **12a,c** (0.6 mmol).

4-(6-Mesitylaminopyridin-2-ylamino)benzonitrile (22a). Synthesized according to the general procedure F using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **24** (0.5 mmol, 115 mg), aniline **8a** (0.6 mmol, 81 mg) and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as white solid; yield 21% (35 mg); mp 216-217 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 6H), 2.33 (s, 3H), 5.67 (d, *J* = 8.0 Hz, 1H), 5.92 (s, 1H), 6.20 (d, *J* = 7.8 Hz, 1H), 6.59 (s, 1H), 6.96 (s, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.44 (d, *J* =8.9 Hz, 2H), 7.50 (d, *J* =8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 21.0, 95.8,

99.2, 103.4, 117.8 (2 C), 119.7, 129.2 (2 C), 133.3 (2 C), 134.4, 136.6 (2 C), 136.7, 140.1, 144.9, 152.2, 156.8; HRMS (ESI) *m/z* calcd. for $C_{21}H_{21}N_4$ ($[M+H]^+$): 329.1766, found: 329.1765. HUPLC: t_r 5.06 min.

4-{6-[4-(Cyanophenyl)amino]pyridin-2-ylamino}-3,5-dimethylbenzonitrile (22b). Synthesized according to the general procedure F using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **24** (0.5 mmol, 115 mg), aniline **8b** (0.6 mmol, 88 mg) and Cs_2CO_3 (1.25 mmol, 0.41 g). Brown solid; yield 20% (34 mg); mp 223-224 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 6H), 5.75 (d, J = 8.1 Hz, 1H), 5.93 (s, 1H), 6.28 (d, J = 7.9 Hz, 1H), 6.54 (s, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.42-7.46 (m, 4H), 7.50 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 99.1, 101.0, 103.5, 109.7, 117.6 (2C), 118.9, 119.6, 132.2 (2 C), 133.3 (2 C), 137.3 (2 C), 139.8, 141.9, 144.9, 153.2, 155.4; HRMS (ESI) *m/z* calcd. for $C_{21}H_{18}N_5$ ($[M+H]^+$): 340.1562, found: 340.1579. HUPLC: t_r 4.51 min.

4-{6-[4-(2-Cyanovinyl)-2,6-dimethylphenylamino]pyridin-2-ylamino}benzonitrile (22c). Synthesized according to the general procedure F using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **24** (0.5 mmol, 115 mg), aniline **12a** (0.6 mmol, 0.10 g) and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as a mixture of geometrical isomers (*Z:E* 1:4.1), light yellow solid; yield 66% (0.12 g); mp 229-230 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) of major (*E*)-isomer: δ 2.27 (s, 6H), 5.73 (d, J = 8.0 Hz, 1H), 5.86 (d, J = 16.6 Hz, 1H), 5.96 (s, 1H), 6.26 (d, J = 7.6 Hz, 1H), 6.61 (s, 1H), 7.24 (s, 2H), 7.32-7.38 (m, 2H), 7.42-7.49 (m, 4H); signals of minor (*Z*)-isomer: 5.78 (d, J = 8.0, 1H), 6.25 (d, J = 7.8, 1 H), 7.09 (d, J = 12.1, 1 H), other signals are overlapped with signals of the major (*E*)-isomer. ^{13}C NMR (100 MHz, $CDCl_3$) of major (*E*)-isomer: δ 18.6, 95.9, 98.9, 100.5, 103.4, 117.6 (2 C), 118.3, 119.6, 127.6 (2 C), 129.2, 131.6, 133.3 (2 C), 136.8, 137.1 (2 C), 139.7, 145.1, 153.2, 156.1; HRMS (ESI) *m/z* calcd. for $C_{23}H_{20}N_5$ ($[M+H]^+$): 366.1719, found: 366.1731. HUPLC: t_r 4.50 min, 4.61 min.

4-{6-[4-(2-cyanovinyl)-2-fluoro-6-methylphenylamino]pyridin-2-ylamino}benzonitrile (22d). Synthesized according to the general procedure F using $Pd(OAc)_2$ (0.025 mmol, 5.61 mg), XPhos (0.03 mmol, 14 mg), intermediate **24** (0.5 mmol, 115 mg), aniline **12c** (0.6 mmol, 0.106 g) and Cs_2CO_3 (1.25 mmol, 0.41 g). Obtained as a mixture of geometrical isomers (*Z:E* 1:10.8), white solid; yield 71% (0.132 g); mp 261-262 °C (AcOEt); ^{1}H NMR (400 MHz, CD_3COCD_3): signals of major (*E*)-isomer: δ 2.30 (s, 3H), 6.26 (d, J = 7.9 Hz, 2H), 6.34 (d, J = 16.7 Hz, 1H), 7.32 (d, J = 8.8 Hz, 2H), 7.41 (t, J = 7.9 Hz, 1H), 7.44-7.50 (m, 2H), 7.56-7.68 (m, 4H), 8.57 (s, 1H); signals of minor (*Z*)-isomer: δ 5.78 (d, J = 12.1 Hz, 1H), 7.84 (s, 1H), other signals are overlapped with signals of major isomer; ^{13}C NMR (100 MHz, CD_3COCD_3) of major (*E*)-isomer: δ 17.6 (d, J = 2.7 Hz), 96.9, 100.0, 101.1, 101.8, 111.8 (d, J = 22.5 Hz), 117.3, 118.0, 119.3, 125.8 (d, J = 2.6 Hz), 130.3 (d, J = 13.3 Hz), 132.0 (d, J = 8.5 Hz), 132.5, 138.5, 139.1, 146.1, 149.1 (d), 154.0, 156.0, 158.6 (d, J = 245.4 Hz); HRMS (ESI) *m/z* calcd. for $C_{22}H_{17}FN_5$ ($[M+H]^+$): 370.1468, found: 370.1481. HUPLC: t_r 4.33 min, 4.44 min.

Associated Content

SUPPORTING INFORMATION

Supporting Information Available: spectra of synthesized compounds; experimental data on the optimization of synthetic protocols; crystallographic data; figures illustrating docking studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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Abbreviations used

HAART, highly active antiretroviral treatment; PI, protease inhibitor; INI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RT, reverse transcriptase; DATA, di(arylamino)triazine; DAPY, di(arylamino)pyrimidine; SDM, site-directed mutant; WST, water-soluble tetrazolium; TCID, tissue culture infective dose; CC, cytotoxic concentration; EC, effective concentration; DEAE, diethylaminoethyl.

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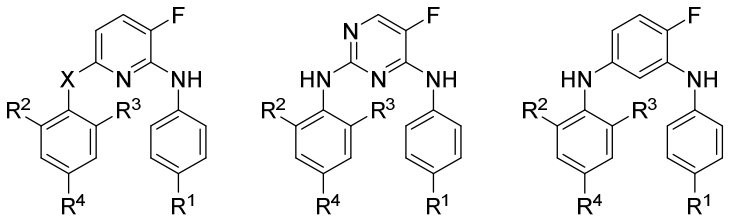

X = O, NH

R^1, R^2, R^3, R^4 = H, Me, F, Cl, CN, CH=CHCN, CH=CHCOOMe

4k (R^1 = CN, R^2 = F, R^3 = H, R^4 = CH=CHCN)

EC_{50} = 1.0 [nM] (WT HIV)