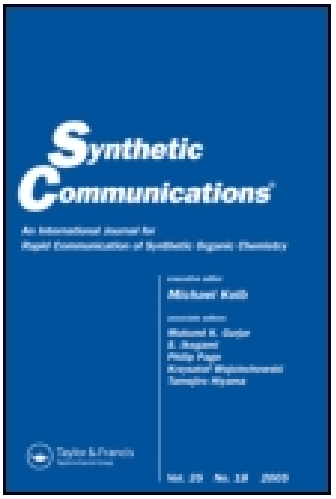

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TWO-DIRECTIONAL APPROACH FOR THE RAPID SYNTHESIS OF 2,4-BIS-AMINOARYL PYRIDINE DERIVATIVES

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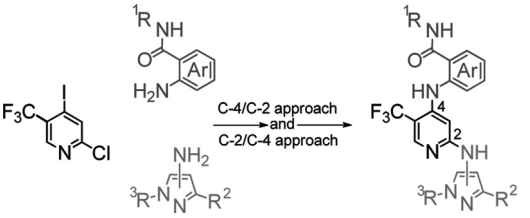
GRAPHICAL ABSTRACT



Abstract *We have developed two different approaches in parallel to rapidly access 2,4-bis aminoaryl pyridine compounds from a common starting material. The C-4/C-2 approach uses palladium-mediated coupling reactions to sequentially functionalize C-4 and then C-2. An alternative C-2/C-4 route uses a regioselective SNAr reaction to first substitute at C-2 then subsequently at C-4 by a palladium-mediated reaction. Both approaches have been used successfully to provide a range of 2,4-bis-aminoaryl pyridine compounds.*

Keywords Nucleophilic substitution; palladium; pyridine; regioselectivity; strategy

INTRODUCTION

As part of our continuing interest in promising new scaffolds as inhibitors of kinases, we focused our research on 5-substituted 2,4-bis-aminoaryl pyridines (BAPyds). Very few synthetic methods have been reported in the literature,[1,2] and the most straightforward synthesis of such compounds involves the successive displacements of halogens by amino derivatives at the C-2 and C-4 positions of the pyridine ring.[2] The main drawback of this approach is control of the mixture of regioisomers; this can be achieved by using two different halogens (e.g., iodo vs. chloro) to exploit their difference in reactivity. Iodo arenes are prone to react

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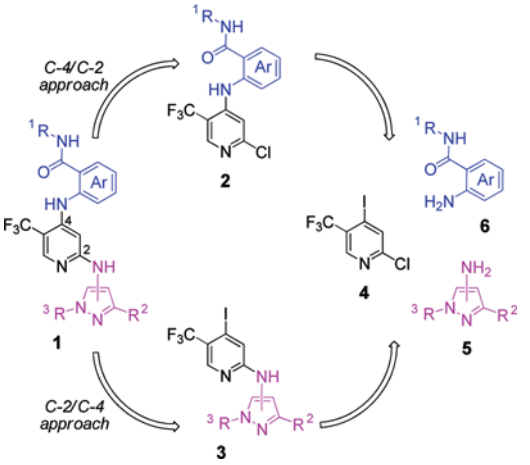


Scheme 1. Retrosynthetic analysis showing the C-2/C-4 and C-4/C-2 approaches from common reagents. (Figure is provided in color online.)

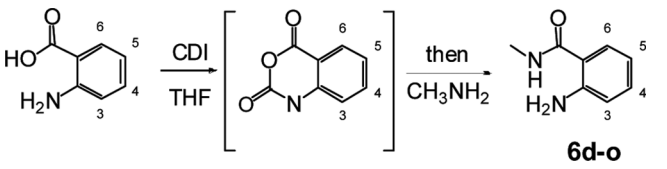
via a Buchwald–Hartwig coupling reaction, whereas chloro arenes can react via either palladium-catalyzed reaction or aromatic nucleophilic substitution (S_NAr). Iodo arenes undergo palladium-mediated amination quicker than chloro arenes under standard conditions and similar electronic effects.[3] Because we wanted to shorten the time spent to identify the best druglike compounds, we faced an additional challenge to control the order of functionalization (C-2/C-4 vs. C-4/C-2). Although synthetic routes to 5-substituted 2-chloro,4-iodo pyridines are known,[4] access to the 2-iodo,4-chloro pyridine analogs is more limited.[5] Thus, we fixed the pyridine substitution pattern to 2-chloro,4-iodo pyridine to have a common key intermediate for the two approaches and developed several conditions that allow control of regioselectivity (C-2/C-4 and C-4/C-2 in parallel) to rapidly increase diversity and then make the best combinations. We describe this strategy applied to the synthesis of a representative number of compounds in one of our series: 2-(pyrazolylamino)-4-(anilino)-5-(trifluoromethyl)pyridine derivatives **1** (Scheme 1).

RESULTS AND DISCUSSION

Access to the Precursors

The retrosynthetic analysis shows the three required parts to be assembled (Scheme 1). 2-Chloro-4-iodo-5-(trifluoromethyl) pyridine (**4**) and the aminopyrazoles **5** described here are readily available from commercial sources. The required anilines **6** were synthesized from the corresponding commercially available anthranilic acids. In the first method, anthranilic acids were treated with carbodiimidazole (CDI) to give the corresponding 1H-benzo[d][1,3]oxazine-2,4-dione, which was ring-opened in situ with 1 N methylamine in tetrahydrofuran (THF) to give the desired anilines **6** in good yield (Table 1). This one-pot method gave lower yields (~15%) when the corresponding 1H-benzo[d][1,3]oxazine-2,4-dione was treated with

Table 1. Synthesis of starting 2-amino-N-methylbenzamides **6**

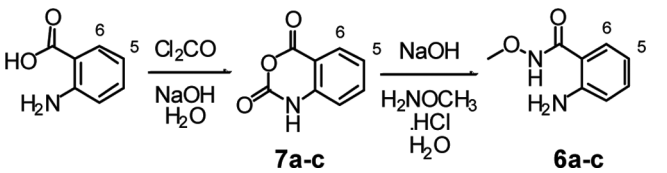


Entry	Anthranilic acid	Yield (%)	Product
1	6-OMe	75[a]	**6d**
2	4-F	62	**6e**
3	4-Cl	74	**6f**
4	4-OMe	33	**6g**
5	3-F	77	**6h**
6	5-Cl	89	**6i**
7	5-OMe	61	**6j**
8	4-SO_2Me	69	**6k**
9	5-SMe	51	**6l**
10	—	87	**6m**[b]

[a]Ring opening of **7b** by methylamine gave 76% yield.
[b]Synthesized from ring opening of commercially available **7a**.

methoxyamine hydrochloride and base. A solution of methoxyamine in an organic solvent would have been the best option to get good yields, but there are no commercial sources. Instead, a two-step synthesis was developed where anthranilic acids were treated with phosgene to give the corresponding cyclized intermediates **7**, which were isolated in good yields. Caution: Phosgene is a very toxic substance. A commerically available solution in toluene was used. It could be efficiently replaced by di- or triphosgen, which are easier to handle. The ring opening was then performed using an aqueous solution of methoxyamine hydrochloride and sodium hydroxide to give the desired N-alkoxyamide anilines **6a–c** in good yields (Table 2). The ring opening of 1H-benzo[d][1,3]oxazine-2,4-dione (respectively **7b** and **7a**) was also

Table 2. Synthesis of starting 2-amino-N-methoxybenzamide **6**



Entry	Anthranilic acid	Yield (%) (**7** / **6**)	Product
1	—	—/63[a]	**7a/6a**
2	6-OMe	88/90	**7b/6b**
3	5-F	88/97	**7c/6c**

[a]Compound **7a** is commercially available.

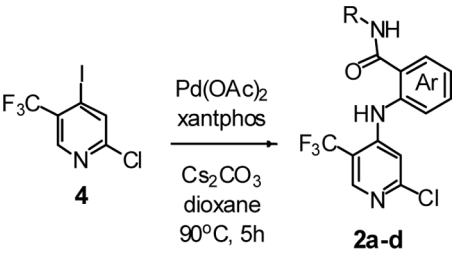
successfully carried out to make the methylamide substituted anilines **6d** and **6m** when methylamine was used instead of methoxyamine.

C-4/C-2 Approach

Starting from 2-chloro-4-iodo-5-(trifluoromethyl)pyridine (**4**), the C-4/C-2 approach[6,7] required that the 4-iodo of starting material 4 would react first in palladium-mediated amination, compared to the 2-chloro.[3] As expected, the reaction displayed excellent regioselectivity for C-4 amination with moderate to good yields (Table 3). No product arising from a possible competing reaction with the aniline **6** at the 2-chloro position of the starting material **4** was observed, and the slow overreaction (double arylation) at the 2-chloro position of the intermediate **2** was minimized by using a stoichiometric amount of the required anilines **6**. Any attempts to use S_NAr conditions with the pyridine **4** led to a loss of regioselectivity (see the C-2/C-4 approach section).

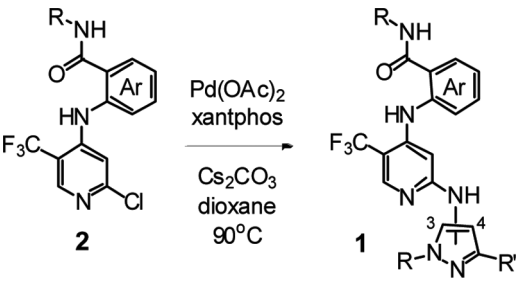
The final C-2 functionalization of 2-chloro-4-anilino pyridines has been reported but was limited to anilines.[6] For the first time, we have successfully coupled aminopyrazoles using palladium-mediated conditions by treating the intermediates **2** and aminopyrazoles **5** with palladium acetate, xantphos, and Cs_2CO_3 in dioxane at 90 °C (Table 4). The reaction of aminoheteroarenes on intermediates **2** worked moderately well for both substituted 3- and 4-aminopyrazoles **5**, with little difference in reactivity or obtained yields (Table 4, entries 1 and 12; entries 4, 6, and 8; entries 13 and 14). Some traces of a by-product were also observed, formed by reaction of the final products **1** with the pyridine C2 position of the starting materials **2**. We successfully used Josiphos SL-J009-1[8] as an alternative ligand with NaOtBu and $Pd(OAc)_2$ in dimethoxyethane (DME), to suppress the formation of this by-product because of its chemoselectivity for primary amines over secondary amines.[9] For parallel synthesis, however, we preferred to use xantphos and Cs_2CO_3 because of the drawbacks of weighing out hygroscopic NaOtBu and the ease of removal of the trace by-products in the examples presented in Table 4.

Table 3. Buchwald–Hartwig functionalization at C-4 with anilines



Entry	Aniline	Yield (%)	Product
1	**6m**	67	**2a**
2	**6d**	69	**2b**
3	**6e**	69	**2c**
4	**6c**	40	**2d**

Table 4. Buchwald–Hartwig functionalization at C-2 with various amino-pyrazoles

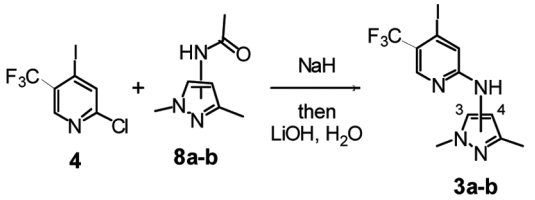


Entry	Pyrazole	Starting material	Yield (%)[a]	Product
1	2,5-Dimethylpyrazol-3-amine (**5b**)	**2a**	40	**1a**
2	1,5-Dimethylpyrazol-4-amine	**2a**	20	**1b**
3	1-Ethyl-3-methyl-pyrazol-4-amine	**2a**	34	**1c**
4	1-Ethylpyrazol-4-amine	**2a**	32	**1d**
5	2-Methylpyrazol-3-amine	**2a**	52	**1e**
6	1-Ethylpyrazol-3-amine	**2a**	28	**1f**
7	5-Cyclopropyl-2-methyl-pyrazol-3-amine	**2a**	26	**1g**
8	2-Ethylpyrazol-3-amine	**2a**	51	**1h**
9	1-Isobutylpyrazol-4-amine	**2a**	23	**1i**
10	2,5-Dimethylpyrazol-3-amine (**5b**)	**2b**	59	**1j**
11	2,5-Dimethylpyrazol-3-amine (**5b**)	**2c**	55	**1k**
12	1,3-Dimethylpyrazol-4-amine (**5a**)	**2a**	34	**1l**
13	2,5-Dimethylpyrazol-3-amine (**5b**)	**2d**	38	**1m**
14	1,3-Dimethylpyrazol-4-amine (**5a**)	**2d**	40	**1n**

[a]Yields are unoptimized.

C-2/C-4 Approach

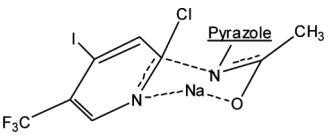
In addition to the C-4/C-2 approach, we looked for reaction conditions that would allow substitution of the C-2 position of the 2,4-dihalopyridine derivative by an aminoheteroarene. Very few examples have been reported in the literature and were not applicable to our 2-chloro-4-iodo-5-(trifluoromethyl)pyridine substrate (**4**).[2b,6b,10] The C-4/C-2 approach showed that the 4-iodo of starting material **4** reacted first in palladium-mediated amination compared to the 2-chloro (see the C-4/C-2 approach section). This was confirmed when **4** was reacted with 3-amino pyrazole **5b** under palladium-mediated amination conditions. As the only product formed came from the C-4 coupling reaction, we turned our attention to the S_NAr reaction. Free-palladium conditions were screened: NaH/dimethylformamide (DMF), NaH/THF, NaH/toluene (solvent effect), K_2CO_3/DMF (base effect), cat. HCl/ACN. None of them led to either consumption of **4** or clean reaction except for the NaH/DMF condition, which was not regioselective and led to a 4:1 mixture in favor of 4-iodo-displacement by **5b**. Based on precedent from in-house work, the pyridine **4** was reacted with the anion of acetylamino pyrazoles **8**, and surprisingly an efficient and highly regioselective substitution at the C-2 position occurred (Scheme 2). The electron-withdrawing inductive effect of the C-5 trifluoromethyl group would be expected to have a greater activating effect on C-4 compared to



Scheme 2. S_NAr at C-2 with N-(1,3-dimethyl-1H-pyrazol-4-yl)acetamide (**8a**) and N-(1,4-dimethyl-1H-pyrazol-3-yl)acetamide (**8b**). Conditions: **Ba**, NaH, THF, 25 °C, 1 h, 69%, or **8b**, NaH, DMF/THF (1/9), 75°C, o/n, 72%.

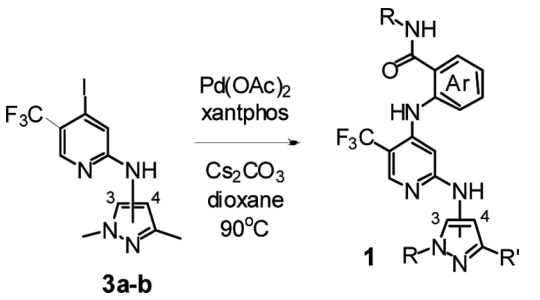
C-2. Nevertheless, recent work[11] has shown that CF_3 favors *para*-direct S_NAr nucleophile substitution in polar solvent on 2,4-dihaloaromatic compounds as this activating group affords little stabilization of the *ortho* transition state. In our case, even though chloride is a better leaving group than iodide, the 4-iodo displacement of our substrate **4** is favored by aminopyrazole **5b** compared to the 2-Cl displacement under basic conditions in polar solvent. When acetyl pyrazoles **8** are used, we postulated that a cyclic six-membered transition state could be envisaged, with chelation of the sodium cation to the pyridine N-1 of **4** resulting in activation of the C-2 position and overcoming the activating effect of CF_3 at C-4 (Scheme 3). To help understand whether the sodium cation was playing a role, the anion of acetyl pyrazole **8b** formed with NaH in THF was treated with 15-crown-5 before the addition of the pyridine **4**; the reaction gave the product **3b** in 60% yield and no product arising from 4-iodo substitution was observed, countering our hypothesis. So we assumed that steric hindrance of the C-4 position is the predominant factor affecting the regioselectivity and the use of a bulkier anion favors C-2 attack. Some acetyl deprotection occurred during the reaction, and deacylation was completed in situ by addition of lithium hydroxide and water. N-Acetylated intermediates of **3** were also isolated and reacted further successfully in palladium-mediated amination.

The final C-4 functionalization was achieved by treating the intermediate **3** with different anilines in parallel syntheses using the standard palladium-mediated amination conditions. The desired compounds **1** were obtained in good to excellent yields after purification. Few by-products resulting from overreaction with a second molecule of **3** were observed. The results are summarized in Table 5. The reaction does not seem to be strongly dependant on the nature of the aniline and the position of the electron-donating group does not affect the yield (Table 5, entries 4, 8, and 11). Anilines substituted with electron-withdrawing groups also gave good results (Table 5, entries 5, 9, and 12), and similar yields were obtained when the amide portion was modified (Table 5, entries 3 vs. 4, 1 vs. 7). Not surprisingly, the anilines **6f**



Scheme 3. Postulated cyclic six-membered transition state between **4** and **8**.

Table 5. Buchwald–Hartwig functionalization at C-4 with anilines **6**



Entry	Starting material	Aniline	Yield (%)	Product
1	**3a**	**6m**	87	**1l**
2	**3a**	**6c**	59	**1n**
3	**3a**	**6b**	74	**1o**
4	**3a**	**6d**	75	**1p**
5	**3a**	**6e**	78	**1q**
6	**3a**	**6f**	88	**1r**
7	**3a**	**6a**	75	**1s**
8	**3a**	**6g**	79	**1t**
9	**3a**	**6h**	64	**1u**
10	**3a**	**6i**	88	**1v**
11	**3a**	**6j**	85	**1w**
12	**3a**	**6k**	78	**1x**
13	**3a**	**6l**	46	**1y**
14	**3b**	**6b**	66	**1z**
15	**3b**	**6d**	46	**1j**
16	**3b**	**6e**	33	**1k**

and **6i** bearing a chlorine atom did not undergo any palladium-mediated amination side reaction (Table 5, entries 6 and 10). Only the aniline bearing a thiomethyl group **6l** (Table 5, entry 13) showed a lower conversion rate to give **1y** in 46% yield. On the other hand, the reaction seems to slightly depend on the nature of **3** as the yields drop when the 3-aminopyrazole derivative **3b** is used in place of the 4-aminopyrazole derivative **3a** (Table 5, entries 3 vs. 14, 4 vs. 15, 5 vs. 16).

Carrying Out Both Approaches

Using a two-directional approach allowed us to quickly increase diversity but more importantly allowed us to have the flexibility of using either route (C-2/C-4 vs. C-4/C-2), depending on the desired substitution pattern, costs of starting materials/reagents, and speed of access to the required amount of compound. Both approaches have advantages and drawbacks: the C-4/C-2 approach required only two palladium-mediated coupling reactions, but large-scale purification can be problematic. The C-2/C-4 approach required three steps (pyrazole acetylation and 2-chloro and 4-iodo displacements) and excess reagents (2 eq. of acetylated pyrazole **8** for 2-Cl displacement and 1.5 eq. of aniline **6** for 4-I displacement). Compounds **1l**, **1j**, **1n**,

Table 6. Comparison of the two approaches

Entry	Product	Overall (yield)% (C-4/C-2)	Overall (yield)% (C-2/C-4)
1	**1j**	40	26
2	**1k**	36	18
3	**1l**	23	50
4	**1n**	16	32

and **1k** illustrate both approaches (Table 6). The 4-aminopyrazole compounds **1l** and **1n** were synthesized in greater overall yields using the C-2/C-4 approach, whereas the best overall yields were obtained for 3-amino pyrazole compounds **1j** and **1k** using the C-4/C-2 route.

In conclusion, we have developed approaches for the rapid synthesis of 2,4-bis-aminoaryl pyridine compounds starting from a common 2-chloro, 4-iodo, 5-CF_3 pyridine derivative. The desired products could be obtained either via a double Pd-mediated coupling reaction (C-4/C-2) or a S_NAr/Pd-mediated reaction sequence (C-2/C-4) from the 2-chloro-4-iodo-5-(trifluoromethyl)pyridine (**4**) substrate. Based exclusively on the overall yields, the C-2/C-4 approach seemed preferable to access 4-aminopyrazole compounds (e.g., **1l** and **1n**), whereas the C-4/C-2 approach gave the best results for the 3-aminopyrazole derivatives (e.g., **1j** and **1k**).

EXPERIMENTAL

All compounds are known in the literature.[11] All reagents were purchased from commercial sources and used without further purification. Flash chromatography was carried out on Merck Kieselgel 50 (Art. 9385). Preparative high-performance liquid chromatography/mass specrometry (HPLC/MS) was carried out on a Waters auto-purification system (injector/collector 2767, pump 2525 MS detector ZQ) using a Waters × Bridge 5 microns, reverse-phase column (19 × 100 mm mm or 30 × 150 mm) and decreasingly polar mixtures of water (containing 0.2% ammonium carbonate) and acetonitrile as eluent. NMR spectra were recorded on either a Bruker Avance 500 (500 MHz) spectrometer or a NMR spectrometer Jeol Eclipse 270 (269.72 MHz). Chemical shifts are expressed in δ (ppm) units, and peak multiplicities are expressed as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quadruplet; br s, broad singlet; and m, multiplet. Mass spectrometry and purity assessment at two wavelengths (254 nm and 310 nm) were carried out on an analytical Waters HPLC/MS system with positive and negative ion data collected automatically. Purity of isolated compounds was more than 95%. NMR and mass spectra were run on isolated products and were consistent with the proposed structures. The following abbreviations have been used: Ac, acetyl; ACN, acetonitrile; BAPyds, bis-aminoaryl pyridines; CDI, carbodiimidazole; DCM, dichloromethane; DMSO, dimethyl sulfoxide; DME, 1,2-dimethoxyethane; DMF, N,N-dimethylformamide; Josiphos SLJ002-1, (R)-(−)-1-[(S)-2-(diphenylphosphino) ferrocenyl] ethyldi-t-butylphosphine; PE, petroleum ether; S_NAr, aromatic nucleophilic substitution; TBME, *ter*-butyl methyl ether; tBu, *ter*-butyl; TFA, trifluoracetic acid;

TLC, thin-layer chromatography; TMSCl, chlorotrimethylsilane; and xantphos, 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

Synthesis of Compounds 1 from Intermediate 2 (C-4/C-2 Approach)

Argon was passed through a suspension of the appropriate intermediate **2** (1 eq.), the appropriate aminopyrazole **5** (1.2 eq.), $Pd(OAc)_2$ (0.08 eq.), xantphos (0.16 eq.), and cesium carbonate (1.2 eq.) in dioxane (0.25 M) for 10 min at room temperature. The reaction mixture was heated at 90 °C for 5 h, allowed to cool to room temperature, and concentrated in vacuo. The crude product was purified by either flash chromatography on silica gel (0–5% MeOH/EtOAc) or preparative HPLC/MS, depending on the reaction scale and synthesis method (parallel synthesis or large-scale reaction). The solvent was evaporated in vacuo. The residue was triturated in either TBME or DCM, collected by filtration, and dried to afford the expected product **1** as a white solid.

2-[[2-[(2,5-Dimethylpyrazol-3-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-benzamide (1a). Yield 40%; δ_H (500 MHz, DMSO-d_6) 2.08 (s, 3H), 2.76 (d, 3H), 3.54 (s, 3H), 6.01 (s, 1H), 6.70 (s, 1H), 7.13 (dd, 1H), 7.50 (dd, 1H), 7.56 (d, 1H), 7.71 (d, 1H), 8.24 (s, 1H), 8.68 (q, 1H), 8.99 (s, 1H), 10.19 (s, 1H); MS (ESI) m/z 405 (MH^+).

2-[[2-[(1,5-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-benzamide (1b). Yield 20%; δ_H (500 MHz, DMSO-d_6) 2.11 (s, 3H), 2.76 (d, 3H), 3.69 (s, 3H), 6.46 (bs, 1H), 7.08 (dd, 1H), 7.43 (s, 1H), 7.46 (d, 1H), 7.50 (d, 1H), 7.69 (d, 1H), 8.16 (s, 1H), 8.35 (s, 1H), 8.65 (q, 1H), 10.08 (s, 1H); MS (ESI) m/z 405 (MH^+).

2-[[2-[(1-Ethyl-3-methyl-pyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-benzamide (1c). Yield 34%; δ_H (500 MHz, DMSO-d_6) 1.31 (t, 3H), 2.07 (s, 3H), 2.76 (d, 3H), 3.99 (q, 2H), 6.62 (bs, 1H), 7.09 (dd, 1H), 7.47 (dd, 1H), 7.52 (d, 1H), 7.70 (d, 1H), 7.88 (s, 1H), 8.20 (s, 1H), 8.41 (s, 1H), 8.66 (q, 1H), 10.11 (s, 1H); MS (ESI) m/z 419 (MH^+).

2-[[2-[(1-Ethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-benzamide (1d). Yield 32%; δ_H (500 MHz, DMSO-d_6) 1.34 (t, 3H), 2.77 (d, 3H), 4.07 (q, 2H), 6.61 (s, 1H), 7.10 (dd, 1H), 7.39 (s, 1H), 7.48 (dd, 1H), 7.56 (d, 1H), 7.71 (d, 1H), 7.90 (s, 1H), 8.24 (s, 1H), 8.67 (q, 1H), 9.03 (bs, 1H), 10.13 (s, 1H); MS (ESI) m/z 405 (MH^+).

N-Methyl-2-[[2-[(2-methylpyrazol-3-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]benzamide (1e). Yield 52%; δ_H (500 MHz, DMSO-d_6) 2.77 (d, 3H), 3.63 (s, 3H), 6.21 (d, 1H), 6.70 (s, 1H), 7.13 (ddd, 1H), 7.32 (d, 1H), 7.49 (ddd, 1H), 7.55 (d, 1H), 7.71 (dd, 1H), 8.25 (s, 1H), 8.68 (q, 1H), 9.03 (s, 1H), 10.20 (s, 1H); MS (ESI) m/z 391 (MH^+).

2-[[2-[(1-Ethylpyrazol-3-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-benzamide (1f). Yield 28%; δ_H (500 MHz, DMSO-d_6) 1.27 (t, 3H), 2.77 (d, 3H), 3.95 (q, 2H), 6.09 (s, 1H), 7.11 (ddd, 1H), 7.49 (ddd, 1H), 7.54 (d, 1H), 7.62

(d, 1H), 7.63 (bs, 1H), 7.70 (dd, 1H), 8.23 (s, 1H), 8.68 (q, 1H), 9.52 (s, 1H), 10.28 (s, 1H); MS (ESI) m/z 405 (MH^+).

2-[[2-[(5-Cyclopropyl-2-methyl-pyrazol-3-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-benzamide (1g). Yield 26%; δ_H (500 MHz, DMSO-d_6) 0.54–0.60 (m, 2H), 0.76–0.84 (m, 2H), 1.72–1.80 (m, 1H), 2.75 (d, 3H), 3.52 (s, 3H), 5.91 (s, 1H), 6.66 (s, 1H), 7.13 (ddd, 1H), 7.48 (ddd, 1H), 7.55 (d, 1H), 7.70 (dd, 1H), 8.23 (s, 1H), 8.67 (q, 1H), 8.97 (s, 1H), 10.17 (s, 1H); MS (ESI) m/z 431 (MH^+).

2-[[2-[(2-Ethylpyrazol-3-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-benzamide (1h). Yield 51%; δ_H (500 MHz, DMSO-d_6) 1.24 (t, 3H), 2.76 (d, 3H), 3.96 (q, 2H), 6.19 (s, 1H), 6.66 (s, 1H), 7.11 (dd, 1H), 7.35 (d, 1H), 7.47 (dd, 1H), 7.53 (d, 1H), 7.70 (d, 1H), 8.23 (s, 1H), 8.68 (q, 1H), 8.96 (s, 1H), 10.20 (s, 1H); MS (ESI) m/z 405 (MH^+).

2-[[2-[(1-Isobutylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-benzamide (1i). Yield 23%; δ_H (500 MHz, DMSO-d_6) 0.81 (d, 6H), 2.01–2.12 (m, 1H), 2.76 (d, 3H), 3.84 (d, 2H), 6.59 (s, 1H), 7.09 (ddd, 1H), 7.39 (s, 1H), 7.46 (ddd, 1H), 7.54 (d, 1H), 7.70 (dd, 1H), 7.87 (s, 1H), 8.24 (s, 1H), 8.66 (q, 1H), 9.02 (bs, 1H), 10.14 (s, 1H); MS (ESI) m/z 433 (MH^+).

2-[[2-[(2,5-Dimethylpyrazol-3-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-6-methoxy-N-methyl-benzamide (1j). Yield 59%; δ_H (500 MHz, DMSO-d_6) 2.08 (s, 3H), 2.73 (d, 3H), 3.54 (s, 1H), 3.82 (s, 1H), 5.97 (s, 1H), 6.48 (s, 1H), 6.88 (d, 1H), 7.08 (d, 1H), 7.41 (dd, 1H), 8.19 (s, 1H), 8.28 (q, 1H), 8.83 (s, 1H), 8.95 (s, 1H); MS (ESI) m/z 435 (MH^+).

2-[[2-[(2,5-Dimethylpyrazol-3-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-4-fluoro-N-methyl-benzamide (1k). Yield 55%; δ_H (500 MHz, DMSO-d_6) 2.08 (s, 3H), 2.76 (d, 3H), 3.55 (s, 3H), 6.04 (s, 1H), 6.76 (s, 1H), 6.95 (ddd, 1H), 7.39 (dd, 1H), 7.79 (dd, 1H), 8.27 (s, 1H), 8.69 (q, 1H), 10.65 (s, 1H); MS (ESI) m/z 423 (MH^+).

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-benzamide (1l). Yield 34%; δ_H (500 MHz, DMSO-d_6) 2.05 (s, 3H), 2.69–2.77 (m, 3H), 3.70 (s, 3H), 6.62 (s, 1H), 7.06–7.11 (m, 1H), 7.48–7.50 (m, 2H), 7.69 (dd, 1H), 7.82 (s, 1H), 8.19 (s, 1H), 8.38 (s, 1H), 8.63 (q, 1H), 10.09 (s, 1H); MS (ESI) m/z 405 (MH^+).

2-[[2-[(2,5-Dimethylpyrazol-3-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-5-fluoro-N-methoxy-benzamide (1m). Yield 38%; δ_H (500 MHz, DMSO-d_6) 2.07 (s, 3H), 3.53 (s, 3H), 3.58 (s, 3H), 5.98 (s, 1H), 5.49 (s, 1H), 7.42 (dd. 1H), 7.46 (dd, 1H), 7.60 (dd, 1H), 8.22 (s, 1H), 8.96 (s, 1H), 9.20 (bs, 1H), 11.94 (bs, 1H); MS (ESI) m/z 439 (MH^+).

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-5-fluoro-N-methoxy-benzamide (1n). Yield 40%; δ_H (500 MHz, DMSO-d_6) 2.05 (s, 3H), 32.69 (s, 3H), 3.70 (s, 3H), 6.45 (bs, 1H), 7.42 (dd, 1H), 7.45 (d, 1H), 7.56 (dd, 1H), 7.83 (s, 1H), 8.18 (s, 1H), 8.40 (s, 1H), 9.15 (s, 1H), 11.95 (bs, 1H); MS (ESI) m/z 439 (MH^+).

Synthesis of Compounds 1 from Intermediate 3 (C-2/C-4 Approach)

Argon was passed through a suspension of the appropriate intermediate **3** (1 eq.), the appropriate aniline **6** (1.7 eq.), $Pd(OAc)_2$ (0.05 eq.), xantphos (0.1 eq.), and cesium carbonate (1.2 eq.) in dioxane (0.3 M) for 10 min at room temperature. The reaction mixture was heated at 90 °C overnight and then allowed to cool to room temperature. The reaction mixture was diluted with DCM and filtered through celite, and the solvent evaporated in vacuo to give the crude product, which was purified by either flash chromatography on silica gel (0–5% MeOH/EtOAc) or preparative HPLC/MS, depending on the reaction scale, and synthesis method (parallel synthesis or large scale reaction). The solvent was evaporated in vacuo. The residue was triturated in either TBME or DCM, collected by filtration, and dried to afford the expected product **1** as a white solid.

2-[[2-[(2,5-Dimethylpyrazol-3-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-6-methoxy-N-methyl-benzamide (1j). Yield 46%.

2-[[2-[(2,5-Dimethylpyrazol-3-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-4-fluoro-N-methyl-benzamide (1k). Yield 33%.

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-benzamide (1l). Yield 87%.

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-5-fluoro-N-methoxy-benzamide (1n). Yield 59%.

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N,6-dimethoxy-benzamide (1o). Yield 74%; δ_H (500 MHz, DMSO-d_6) 2.04 (s, 3H), 3.62 (s, 3H), 3.69 (s, 3H), 3.81 (s, 3H), 6.31 (bs, 1H), 6.89 (d, 1H), 7.06 (d, 1H), 7.43 (dd, 1H), 7.79 (s, 1H), 7.86 (s, 1H), 8.14 (s, 1H), 8.38 (s, 1H), 11.38 (s, 1H); MS (ESI) m/z 451 (MH^+).

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-6-methoxy-N-methyl-benzamide (1p). Yield 75%; δ_H (500 MHz, $CDCl_3$) 2.14 (s, 3H), 2.95 (d, 3H), 3.72 (s, 3H), 3.90 (s, 3H), 5.94 (s, 1H), 6.31 (s, 1H), 6.54 (d, 1H), 7.03 (d, 1H), 7.19 (dd, 1H), 7.34 (s, 1H), 7.44 (q, 1H), 8.22 (s, 1H), 10.57 (s, 1H); MS (ESI) m/z 451 (MH^+).

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-4-fluoro-N-methyl-benzamide (1q). Yield 78%; δ_H (500 MHz, $CDCl_3$) 2.15 (s, 3H), 2.96 (d, 3H), 3.81 (s, 3H), 5.97 (s, 1H), 6.02 (bs, 1H), 6.34 (bs, 1H), 6.65 (ddd, 1H), 7.10 (dd, 1H), 7.39 (s, 1H), 7.44 (dd, 1H), 8.26 (s, 1H), 10.11 (bs, 1H); MS (ESI) m/z 423 (MH^+).

4-Chloro-2-[[2-[(1,3-dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-benzamide (1r). Yield 88%; δ_H (500 MHz, DMSO-d_6) 2.06 (s, 3H), 2.74 (d, 3H), 3.70 (s, 3H), 7.12 (dd, 1H), 7.51 (d, 1H), 7.70 (d, 1H), 7.83 (s, 1H), 8.22 (s, 1H), 8.51 (s, 1H), 8.75 (q, 1H), 10.39 (s, 1H); MS (ESI) m/z 439 and 441 (MH^+).

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methoxy-benzamide (1s). Yield 75%; δ_H (500 MHz, DMSO-d_6) 2.05

(s, 3H), 3.68 (s, 3H), 3.69 (s, 3H), 6.60 (bs, 1H), 7.07 (ddd, 1H), 7.45–7.60 (m, 3H), 7.83 (s, 1H), 8.19 (s, 1H), 8.45 (s, 1H), 9.52 (bs, 1H), 11.93 (bs, 1H); MS (ESI) m/z 421 (MH^+).

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-4-methoxy-N-methyl-benzamide (1t). Yield 79%; δ_H (500 MHz, $CDCl_3$) 2.13 (s, 3H), 2.94 (d, 3H), 3.72 (s, 3H), 3.79 (s, 3H), 5.93 (s, 1H), 6.03 (q, 1H), 6.39 (s, 1H), 6.49 (dd, 1H), 6.89 (d, 1H), 7.37 (s, 1H), 7.39 (d, 1H), 8.24 (s, 1H), 10.09 (bs, 1H); MS (ESI) m/z 435 (MH^+).

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-3-fluoro-N-methyl-benzamide (1u). Yield 64%; δ_H (500 MHz, DMSO-d_6) 2.01 (s, 3H), 2.74 (d, 3H), 3.68 (s, 3H), 5.87 (bs, 1H), 7.24–7.40 (m, 1H), 7.43–7.62 (m, 2H), 7.78 (bs, 1H), 8.14 (s, 1H), 8.39 (s, 1H), 8.73 (q, 1H), 9.19 (s, 1H); MS (ESI) m/z 423 (MH^+).

5-Chloro-2-[[2-[(1,3-dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-benzamide (1v). Yield 88%; δ_H (500 MHz, DMSO-d_6) 2.05 (s, 3H), 2.74 (d, 3H), 3.69 (s, 3H), 6.61 (bs, 1H), 7.23 (s, 2H), 7.77 (s, 1H), 7.84 (s, 1H), 8.20 (s, 1H), 8.45 (s, 1H), 8.80 (q, 1H), 10.07 (s, 1H); MS (ESI) m/z 439 and 441 (MH^+).

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-5-methoxy-N-methyl-benzamide (1w). Yield 85%; δ_H (500 MHz, $CDCl_3$) 2.11 (s, 3H), 2.92 (d, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 5.86 (s, 1H), 5.99 (s, 1H), 6.30 (q, 1H), 6.93 (dd, 1H), 7.09 (d, 1H), 7.26 (d, 1H), 7.37 (s, 1H), 8.18 (s, 1H), 8.34 (bs, 1H); MS (ESI) m/z 435 (MH^+).

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-4-methylsulfonyl-benzamide (1x). Yield 78%; δ_H (500 MHz, DMSO-d_6) 2.01 (s, 3H), 2.77 (s, 3H), 3.26 (s, 3H), 3.68 (s, 3H), 6.49 (bs, 1H), 7.57 (d, 1H), 7.74 (bs, 1H), 7.85–8.01 (m, 2H), 8.24 (s, 1H), 8.51 (s, 1H), 8.92 (q, 1H), 10.24 (s, 1H); MS (ESI) m/z 483 (MH^+).

2-[[2-[(1,3-Dimethylpyrazol-4-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N-methyl-5-methylsulfanyl-benzamide (1y). Yield 46%; δ_H (500 MHz, $CDCl_3$) 2.14 (s, 3H), 2.48 (s, 3H), 2.96 (d, 3H), 3.79 (s, 3H), 6.14 (q, 1H), 6.18 (s, 1H), 6.50 (bs, 1H), 7.31 (s, 1H), 7.33–7.37 (m, 2H), 7.40 (d, 1H), 8.18 (s, 1H), 9.48 (bs, 1H); MS (ESI) m/z 451 (MH^+).

2-[[2-[(2,5-Dimethylpyrazol-3-yl)amino]-5-(trifluoromethyl)-4-pyridyl]amino]-N,6-dimethoxy-benzamide (1z). Yield 66%; δ_H (500 MHz, DMSO-d_6) 2.06 (s, 3H), 3.52 (s, 3H), 3.62 (s, 3H), 3.81 (s, 3H), 5.96 (s, 1H), 6.34 (s, 1H), 6.93 (d, 1H), 7.08 (d, 1H), 7.45 (dd, 1H), 7.95 (s, 1H), 8.17 (s, 1H), 8.94 (s, 1H), 11.36 (s, 1H); MS (ESI) m/z 451 (MH^+).

Synthesis of Intermediate 2

Argon was passed through a suspension of 2-chloro-4-iodo-5-(trifluoromethyl) pyridine (**4**) (1 eq.), the appropriate aniline **6** (1.05 eq.), $Pd(OAc)_2$ (0.08 eq.),

xantphos (0.16 eq.), and cesium carbonate (1.2 eq.) in dioxane (0.3 M) for 10 min at room temperature. The reaction mixture was heated at 90 °C for 5 h and then allowed to cool to room temperature. The reaction mixture was diluted with DCM and filtered through celite, and the solvent evaporated in vacuo to give the crude product, which was purified by flash chromatography on silica gel (10–60% EtOAc/PE) to give the expected product **2**.

2-(2-Chloro-5-(trifluoromethyl)pyridin-4-ylamino)-N-methylbenzamide (2a). Yield 67%; δ_H (500 MHz, DMSO-d_6) 2.75 (d, 3H), 7.21 (dt, 1H), 7.51 (dt, 1H), 7.59 (dd, 1H), 7.73 (dd, 1H), 8.48 (s, 1H), 8.72 (q, 1H), 10.52 (s, 1H); MS (ESI) m/z 330 and 332 (MH^+).

2-(2-Chloro-5-(trifluoromethyl)pyridin-4-ylamino)-6-methoxy-N-methylbenzamide (2b). Yield 69%; δ_H (500 MHz, DMSO-d_6) 2.68 (d, 3H), 3.82 (s, 3H), 6.81 (s, 1H), 7.06 (d, 1H), 7.08 (d, 1H), 7.55 (t, 1H), 8.18 (q, 1H), 8.51 (s, 1H), 9.13 (s, 1H); MS (ESI) m/z 360 and 362 (MH^+).

2-(2-Chloro-5-(trifluoromethyl)pyridin-4-ylamino)-4-fluoro-N-methylbenzamide (2c). Yield 69%; δ_H (500 MHz, DMSO-d_6) 2.77 (d, 3H), 7.06 (dt, 1H), 7.45 (s, 1H), 7.52 (dd, 1H), 7.82 (dd, 1H), 8.54 (s, 1H), 8.77 (q, 1H), 11.00 (s, 1H); MS (ESI) m/z 348 and 350 (MH^+).

2-(2-Chloro-5-(trifluoromethyl)pyridin-4-ylamino)-5-fluoro-N-methoxybenzamide (2d). Yield 40%; δ_H (500 MHz, DMSO-d_6) 3.61 (s, 3H), 6.85 (s, 1H), 7.47 (m, 1H), 7.62 (m, 1H), 8.52 (s, 1H), 9.35 (bs, 1H), 11.85 (s, 1H); MS (ESI) m/z 364 and 366 (MH^+).

N-(1,3-Dimethyl-1h-pyrazol-4-yl)-4-iodo-5-(trifluoromethyl)pyridin-2-amine (3a). Sodium hydride 60% oil dispersion (3.9 g, 97.34 mmol) was added portionwise to aminopyrazole acetamide **8a** (14.2 g, 92.7 mmol) dissolved in THF (200 mL) at 35 °C under nitrogen. The resulting beige suspension was stirred for 15 min at 35 °C and then cooled to 5 °C. 2-Chloro-4-iodo-5-(trifluoromethyl)pyridine (**4**) (14.25 g, 46.35 mmol) was added, and the suspension was warmed to 50 °C and stirred for 2 h. The dark suspension was cooled to 5 °C, and water (200 mL) was added, followed by lithium hydroxide hydrate (7.78 g, 185.40 mmol). The resulting purple solution was stirred at room temperature for 2.5 h. The solution was diluted with water and extracted twice with ethyl acetate. The combined organic phases were washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (0–60% EtOAc/DCM). The solvent was evaporated to dryness to afford the title compound **3a** (12.2 g, 69%) as an off-white solid; d_H (500 MHz, DMSO-d_6) 2.08 (s, 3H), 3.75 (s, 3H), 7.40 (bs, 1H), 7.78 (bs, 1H), 8.27 (s, 1H), 8.85 (s, 1H); MS (ESI) m/z 382 (MH^+).

N-(1,3-Dimethyl-1H-pyrazol-5-yl)-4-iodo-5-(trifluoromethyl)pyridin-2-amine (3b). A solution of aminopyrazole acetamide **8b** (31.9 g, 208.2 mmol) in THF (100 mL) was added dropwise to a stirred suspension of sodium hydride 60% in oil dispersion (8.74 g, 218.6 mmol) in a mixture of THF (299 mL) and DMF (40 mL) over a period of 20 min under a nitrogen atmosphere at room temperature. The resulting suspension was stirred at 30 °C for 15 min,

2-chloro-4-iodo-5-(trifluoromethyl)pyridine (**4**) (32 g, 104.1 mmol) was added, and the reaction mixture was stirred at 70 °C overnight. The reaction mixture was allowed to cool to room temperature, and water (300 mL) was added, followed by lithium hydroxide hydrate (13.1 g, 312.26 mmol). The mixture was stirred at room temperature for 2.5 h and then extracted with EtOAc. The organic phases were combined, washed with water and brine, dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (0–100% EtOAc/DCM). The solvent was evaporated to dryness. The residue was triturated with PE (100 mL), collected by filtration, washed with PE (100 mL), and dried to give **3b** (28 g, 72%) as a pale purple solid; d_H (500 MHz, DMSO-d_6) 2.12 (s, 3H), 3.56 (s, 3H), 6.07 (s, 1H), 7.42 (s, 1H), 8.33 (s, 1H), 9.37 (s, 1H); MS (ESI) m/z 382 (MH^+).

Using CDI for the Synthesis of 6d–m

A suspension of CDI (1.2 eq.) and the appropriate 2-amino-benzoic acid (1 eq.) in THF (1 M) was stirred under a hydrogen atmosphere at room temperature overnight. A 1 N solution of methylamine in THF (2 eq.) was added dropwise. The resulting solution was stirred for 3 h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in EtOAc and washed with a saturated aqueous sodium bicarbonate solution, water, and brine. The organic phase was dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (30% EtOAc/DCM) to give the expected product **6**.

2-Amino-6-methoxy-N-methylbenzamide (6d). Yield 75%; δ_H (500 MHz, DMSO-d_6) 2.71 (d, 3H), 3.72 (s, 3H), 5.94 (bs, 2H), 6.17 (d, 1H), 6.28 (d, 1H), 6.98 (dd, 1H), 7.99 (q, 1H); MS (ESI) m/z 181 (MH^+).

2-Amino-4-fluoro-N-methylbenzamide (6e). Yield 62%; δ_H (500 MHz, DMSO-d_6) 2.69 (d, 3H), 6.28 (ddd, 1H), 6.42 (dd, 1H), 6.74 (bs, 2H), 7.48 (dd, 1H), 8.16 (q, 1H); MS (ESI) m/z 169 (MH^+).

2-Amino-4-chloro-N-methylbenzamide (6f). Yield 74%; δ_H (500 MHz, $CDCl_3$) 2.95 (d, 3H), 5.63 (bs, 2H), 5.98 (bs, 1H), 6.59 (dd, 1H), 6.67 (d, 1H), 7.20 (d, 1H); MS (ESI) m/z 183 and 185 [$(M-H)^-$].

2-Amino-4-methoxy-N-methylbenzamide (6g). Yield 33%; δ_H (500 MHz, DMSO-d_6) 2.67 (d, 3H), 3.67 (s, 3H), 6.07 (dd, 1H), 6.19 (d, 1H), 6.60 (bs, 2H), 7.39 (d, 1H), 7.97 (q, 1H); MS (ESI) m/z 181 (MH^+).

2-Amino-3-fluoro-N-methylbenzamide (6h). Yield 77%; δ_H (500 MHz, $CDCl_3$) 2.97 (d, 3H), 5.59 (bs, 2H), 6.07 (bs, 1H), 6.56 (dt, 1H), 7.04 (dd, 1H), 7.08 (d, 1H); MS (ESI) m/z 169 (MH^+).

2-Amino-5-chloro-N-methylbenzamide (6i). Yield 89%; δ_H (500 MHz, $CDCl_3$) 2.96 (d, 3H), 5.49 (bs, 2H), 6.03 (bs, 1H), 6.62 (d, 1H), 7.26 (d, 1H); MS (ESI) m/z 185 and 187 (MH^+).

2-Amino-5-methoxy-N-methylbenzamide (6j). Yield 61%; δ_H (500 MHz, DMSO-d_6) 2.71 (d, 3H), 3.66 (s, 3H), 5.95 (bs, 2H), 6.62 (d, 1H), 6.81 (dd, 1H), 7.01 (d, 1H), 8.18 (q, 1H); MS (ESI) m/z 181 (MH^+).

2-Amino-N-methyl-4-(methylsulfonyl)benzamide (6k). Yield 69%; δ_H (269.72 MHz, CD_3OH) 2.88 (s, 3H), 3.08 (s, 3H), 3.31 (s partially hidden by CD_2HOH, 3H), 7.06 (dd, 1H), 7.27 (d, 1H), 7.57 (d, 1H); MS (ESI) m/z 229 (MH^+).

2-Amino-N-methyl-5-(methylthio)benzamide (6l). Yield 51%; δ_H (500 MHz, $CDCl_3$) 2.40 (s, 3H), 2.96 (d, 3H), 33H), 5.55 (bs, 2H), 6.12 (bs, 1H), 6.63 (d, 1H), 7.25 (dd, 1H), 7.36 (d, 1H); MS (ESI) m/z 197 (MH^+).

Synthesis of 6a–c from the Ring Opening of 7

A 2 N solution of NaOH in water (3.1 eq.) was added to a 25% solution of O-methylhydroxylamine hydrochloride (3.2 eq.) at 5 °C, and then the appropriate 1H-benzo[d][1,3]oxazine-2,4-dione **7** (1 eq.) was added in several portions. The resulting suspension was stirred at 5 °C for 30 min allowed to warm to room temperature (bubbling occurred), and stirred for 3 h. The resulting solution was extracted twice with EtOAc, and the combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to afford the crude product **6** as an oil, which crystallized on standing.

2-Amino-N-methoxybenzamide (6a). Yield 63%; δ_H (500 MHz, DMSO-d_6) 3.66 (s, 3H), 6.29 (bs, 2H), 6.47 (dd, 1H), 6.69 (d, 1H), 7.14 (ddd, 1H), 7.29 (dd, 1H), 11.40 (bs, 1H); MS (ESI) m/z 167 (MH^+).

2-Amino-N,6-dimethoxybenzamide (6b). Yield 90%; δ_H (500 MHz, DMSO-d_6) 3.67 (s, 3H), 3.71 (s, 3H), 5.57 (bs, 2H), 6.19 (d, 1H), 6.31 (d, 1H), 7.02 (dd, 1H); 11.02 (bs, 1H); MS (ESI) m/z 197 (MH^+).

2-Amino-5-fluoro-N-methoxybenzamide (6c). Yield 97%; δ_H (500 MHz, DMSO-d_6) 3.82 (s, 3H), 6.20 (bs, 2H), 6.72 (dd, 1H), 7.09 (ddd, 1H), 7.15 (dd, 1H), 11.49 (bs, 1H); MS (ESI) m/z 183 [$(M\text{-}H)^-$].

Synthesis of 6d and 6m from the Ring Opening of 7

A 40% solution of methylamine in water (6 eq.) was added dropwise to a stirred suspension of **7** (1 eq.) in water (0.6 M) at 5 °C. The resulting suspension was stirred at room temperature for 2 h and concentrated to half of volume. The precipitate was collected by filtration, washed with water, and dried to give a first batch of the expected compound **6**. The aqueous filtrate was extracted twice with EtOAc, and the organic phases were combined, washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give a second batch of the expected compound **6**. The two batches were combined.

2-Amino-6-methoxy-N-methylbenzamide (6d). Yield 76% from **7b**.

2-Amino-N-methylbenzamide (6m). Yield 87% from **7a**; δ_H (500 MHz, DMSO-d_6) 2.72 (d, 3H), 6.39 (s, 2H), 6.49 (t, 1H), 6.66 (d, 1H), 7.11 (td, 1H), 7.44 (dd, 1H), 8.14 (bs, 1H); MS (ESI) m/z 151 (MH^+).

Synthesis of 7b and 7c

A 20% solution of phosgene in toluene (1.1 eq.) was dropwise added to a solution of the appropriate anthranilic acid (1 eq.) in a 1 N solution of NaOH in water (2.1 eq.) at 10 °C, and then the mixture was stirred for 30 min at room temperature. The resulting solid was collected by filtration, washed with water and a solution of 20% of MeCN in Et_2O, and dried to give the compound **7**.

5-Methoxy-1H-benzo[d][1,3]oxazine-2,4-dione (7b). Yield 88%; δ_H (500 MHz, DMSO-d_6) 3.88 (s, 3H), 6.69 (d, 1H), 6.83 (d, 1H), 7.64 (t, 1H), 11.59 (s, 1H); MS (ESI) m/z 192 [$(M\text{-}H)^-$].

6-Fluoro-1H-benzo[d][1,3]oxazine-2,4-dione (7c). Yield 88%; δ_H (500 MHz, DMSO-d_6) 3.33 (s, 3H), 6.64–7.70 (m, 3H), 11.79 (s, 1H); MS (ESI) m/z 180 [$(M\text{-}H)^-$].

N-(1,3-Dimethyl-1N-pyrazol-4-yl)acetamide (8a). Acetyl chloride (4.2 mL, 59.6 mmol) was added dropwise to a suspension of 11,3-dimethyl-1H-pyrazol-4-amine hydrochloride (**5a**) (8 g, 54.2 mmol) and triethylamine (18.9 mL, 135.5 mmol) in CH_2Cl_2 (120 mL) over a period of 15 min at 25 °C. The resulting suspension was stirred at 25 °C for 3 h and then concentrated *in vacuo*. The residue was taken into CH_2Cl_2 (10 mL), and the insolubles were removed by filtration. The filtrate was purified by flash chromatography on silica gel (2–7% MeOH/EtOAc). The solvent was evaporated to dryness to afford **8a** (6.8 g, 82%) as a pink oil, which crystallized on standing; d_H (500 MHz, DMSO-d_6) 1.98 (s, 3H), 2.10 (s, 3H), 3.67 (s, 3H), 7.79 (s, 1H), 9.29 (s, 1H); MS (ESI) m/z 154 (MH+).

N-(1,3-Dimethyl-1H-pyrazol-4-yl)acetamide (8b). A suspension of 1,3-dimethyl-1H-pyrazol-5-amine (**5b**) (42 g, 377.9 mmol), potassium acetate (41 g, 415.7 mmol), and acetic anhydride (42 ml, 377.9 mmol) in ethyl acetate (714 ml) was stirred at 25 °C overnight. Basic aluminium oxide 90 (200 g) was added, and stirring was carried on for 10 min. The solids were removed by filtration, and the filtrate was passed through a pad of basic aluminium oxide 90 (150 g) (5% MeOH/EtOAc). The filtrate was concentrated in vacuo to afford **8b** (81 g, 88%) as a red oil, which crystallized on standing; d_H (500 MHz, DMSO-d_6) 2.03 (s, 3H), 2.08 (s, 3H), 3.65 (s, 3H), 5.96 (s, 1H), 9.83 (s, 1H); MS (ESI) m/z 154 (MH^+).

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