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Tetrahedron 62 (2006) 2380–2387

Tetrahedron

Synthesis of analogs of the phenylamino-pyrimidine type protein kinase C inhibitor CGP 60474 utilizing a Negishi cross-coupling strategy

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Received 5 October 2005; revised 25 November 2005; accepted 28 November 2005

Available online 20 December 2005

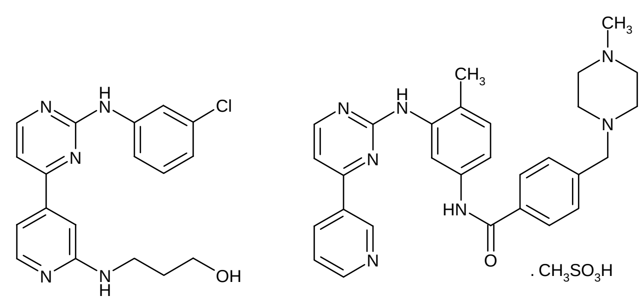
Abstract—Analogs of 3-{4-[2-(3-chlorophenylamino)-pyrimidin-4-yl]-pyridin-2-yl-amino}-propanol (CGP 60474) were synthesized as useful models for the evaluation of structure–activity relationships of phenylamino-pyrimidine-type protein kinase C inhibitors. The approach involved Pd-assisted cross-coupling as the key step. Negishi-type coupling was performed both with free amino functionalities and Boc-protected amines present and showed that the protection–cross-coupling–deprotection sequence leads to significantly higher yields.

1. Introduction

Protein kinase C (PKC) plays a crucial role in signal transductions, cellular proliferation, and differentiation.[1] PKC is the term for a whole family of cytosolic serine/threonine kinases. The individual PKC subtypes show differences in the mode of activation and in the specificity with respect to protein substrates.[2,3] It has already been shown in animal tumor models, that different inhibitors of PKC show cytostatic activity.[4,5] Therefore, the discovery and the development of specific protein kinase inhibitors will have the potential to define more clearly the respective functional roles of every protein kinase in cells.

Phenylamino-pyrimidines like 3-{4-[2-(3-chlorophenylamino)-pyrimidin-4-yl]-pyridin-2-yl-amino}-propanol (CGP 60474)[6] represent a promising class of inhibitors of PKC with a high degree of selectivity versus other serine/threonine and tyrosine kinases and show competitive kinetics relative to ATP. Imatinib (Glivec™),[7] a tyrosine kinase inhibitor with high activity against chronic myeloid leukemia (CML), was introduced as the first commercial product of this type to the pharmaceutical market recently by Novartis (Fig. 1).[8,9]

The preparation of the title compounds was based on a recently published strategy.[10] The scaffold of CGP 60474 and its isomer **I** were prepared in that course via Negishi cross-coupling from the organozinc **1a** as key intermediate (Scheme 1). This method was now extended to the preparation of a series of other analogs. With respect to CGP 60474 one or both of the present heterocycles (pyrimidine and pyridine) were substituted by other ring systems (phenyl or pyridine).



CGP 60474 *Imatinib*, Glivec™

Figure 1. Significant Phenylamino-pyrimidines.

2. Results and discussion

The envisioned target compounds are presented in Figure 2. From the original pyridinyl-pyrimidine motif in CGP 60474 variations of the pyrimidine and pyridine ring were undertaken. The target compounds contain therefore a pyridine–phenyl (**2**), a pyridine–pyridine (**3**), and a pyrimidine–phenyl (**4**) connection.

Keywords: Negishi cross-coupling; Protein kinase inhibitors; Nucleophilic displacement; Phenylamino-pyrimidines.
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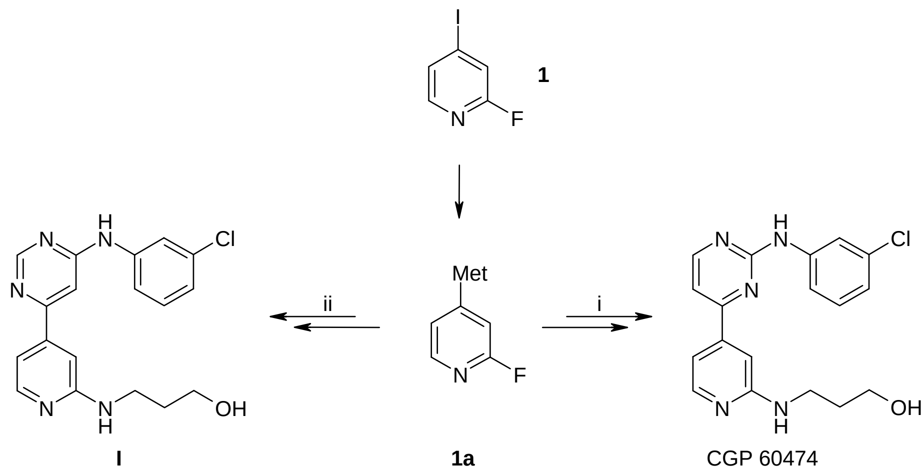
doi:10.1016/j.tet.2005.11.067



Scheme 1. (i) Three steps, 70% overall yield. (ii) three steps, 33% overall yield.

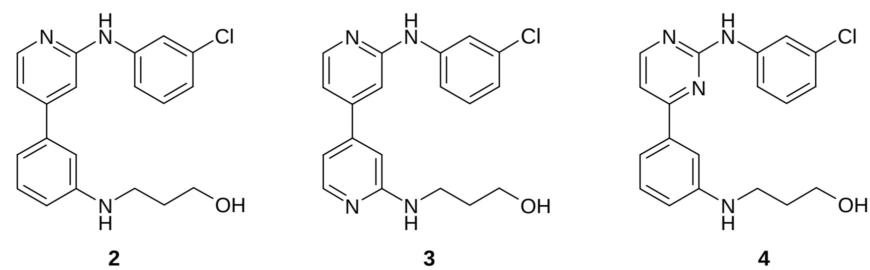
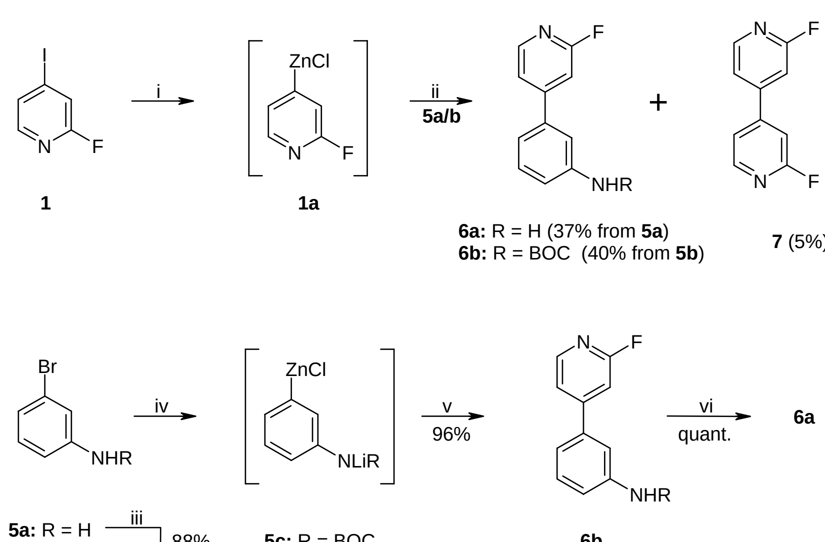


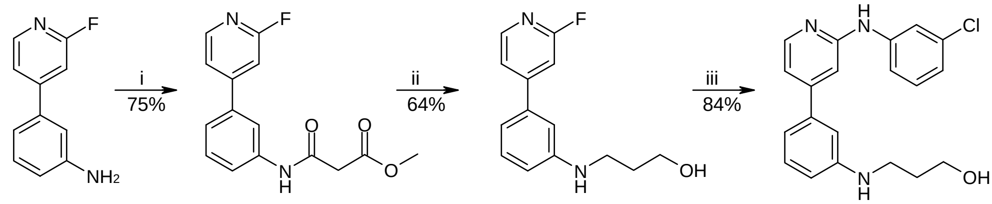
Figure 2. Target compounds **2**, **3**, and **4**.

Compounds **2** and **3** should again be prepared from key intermediate **1a** via a Negishi cross-coupling reaction.[11] For preparation of compound **2**, **1a** was initially reacted with 3-bromoaniline (**5a**) under $Pd(PPh_3)_4$ catalysis. Since in this reaction only 37% of the desired cross-coupling product **6a** were obtained (besides 5% of homo-coupling by-product **7**), suitable protection of the amine function was required. Substrate **5a** was Boc-protected via a standard method[12] in 88% yield to give **5b**. Cross-coupling reaction of this compound yielded again only 40% of the desired product. A possible hydrolysis of **1a** by the NH proton of carbamate **5b** was excluded by initial deprotonation with NaH at room temperature. This led to no improvement in the cross-coupling process but *N*-alkylation of the cross-coupling product by iodobutane was observed to some extent.

Consequently, the cross-coupling strategy was 'inverted' utilizing the organozinc species derived from the Boc-protected aniline **5b** (Scheme 2). The NH-proton of **5b** was removed with MeLi at 15 °C before the metal–halogen



Scheme 2. (i) *n*-BuLi, $ZnCl_2$, THF, −75 °C to rt; (ii) $Pd(PPh_3)_4$, **5a/b**, THF, reflux; (iii) $(Boc)_2O$, THF, reflux; (iv) MeLi, *t*-BuLi, $ZnCl_2$, THF; (v) $Pd(PPh_3)_4$, **1**, THF, reflux; (vi) TFA, CH_2Cl_2, rt.



Scheme 3. (i) $ClCOCH_2COOMe$, NEt_3, THF, 0 °C; (ii) BH_3–THF, THF, 0 °C; (iii) HCl, 3-chloroaniline, water/dioxane 4:1, reflux.

exchange was performed at −75 °C with *n*-BuLi. Subsequent addition of an excess of $ZnCl_2$ gave the desired organozinc derivative, which was then submitted to the cross-coupling reaction. Again, some *N*-alkylated coupling product was detected. This could be avoided by replacing *n*-BuLi with *t*-BuLi. With these modifications the yield of **6b** was optimized to 96%. Subsequent deprotection with TFA gave **6a** quantitatively.

The aminopropanol side chain was introduced via acylation of **6a** in the presence of NEt_3 with methyl chlorocarbonylacetate in dry THF to yield 75% of **8**. Subsequent reduction with BH_3–THF gave **9** in 64% yield (Scheme 3).

The nucleophilic displacement of the fluorine moiety was initially performed by heating **9** in an excess of 3-chloroaniline to 210–230 °C for 17 h to give **2** in 51% yield. Optimized yields were obtained performing the reaction with equimolar amounts of HCl under reflux in a water–dioxane (4/1) mixture for 48 h providing **2** in 84% yield.

2.1. Synthesis of target compound 3

In the case of the target bipyridinyl **3**, a different strategy had to be employed since an immediate cross-coupling reaction of intermediate **1a** with **1** would lead to the symmetric compound **7** with no selectivity for the nucleophilic displacements of the two fluoro atoms. Hence, one nucleophilic displacement had to be performed before the cross-coupling step. The challenge of this approach lies in the similar reactivity of positions 2 and 4 in the halogenated pyridine substrate. Indeed, when the reaction was carried out under standard reaction conditions[13] we did not observe selectivity between these two positions. Instead of the desired mono substituted **10**, di-substituted compound **11** was obtained as the major product only accompanied by starting material. Milder reaction conditions did not give any conversion. An option to overcome this problem is proton catalyzed activation of the pyridine system, which activates the 2-position.[14,15] In an optimization approach aqueous reaction conditions proved to be crucial and compound **10** was obtained in 66% yield only accompanied by small amounts of by-product **11** (9%).

The Negishi reaction was performed with coupling partner **10** and gave an optimized 37% of **13a** besides starting material **10**. Boc-protection of the amine (**12**, 80%) improved substantially the yield in the cross-coupling step giving **13b** in 73%. Cleavage of the Boc group via a standard protocol yielded **13a** quantitatively (Scheme 4).

The aminopropanol side chain was introduced by refluxing **13a** in 3-aminopropanol[10] to give 84% of **3**. We found that **3** can be accessed directly from **13b** under the conditions of the nucleophilic displacement in 92% yield due to the thermal instability of the Boc group.

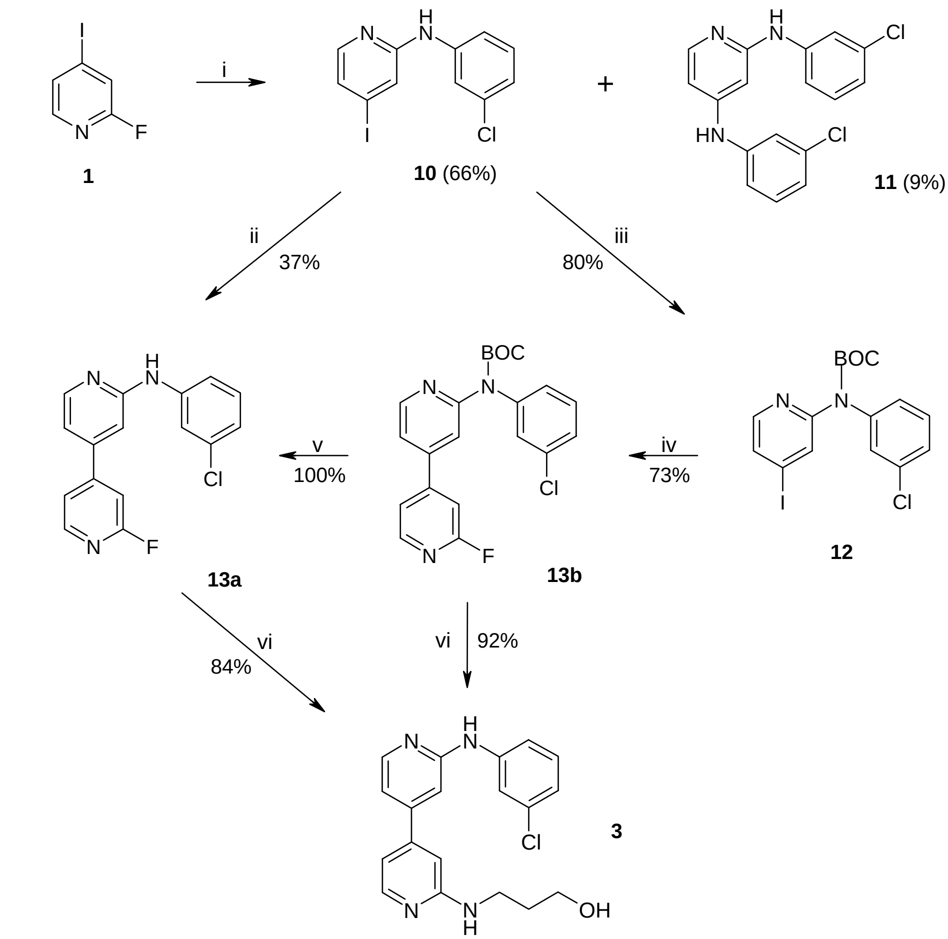
2.2. Synthesis of target compound 4

The synthesis of **4** is very similar to the route finally applied to the preparation of target compound **2**. In this case, 2,4-dichloropyrimidine was cross-coupled with **5c** under Negishi conditions to give 75% of desired product **14** and 9% of by-product **15**, which is formed in a follow-up reaction of **14**. In contrast to aromatic organozinc species,[16,17] aliphatic organozinc compounds can undergo a cross-coupling reaction in the 2-position of the pyrimidine system under thermal conditions. The formation of **15** can therefore be explained by a cross-coupling reaction of methylzinc chloride (from excess of MeLi and $ZnCl_2$) with **14**. The structure of **14** was confirmed via 2D NMR experiments (NOE, NOESY). Recently, we have demonstrated that the 2-position is accessible for cross-coupling also with aromatic organozincs under microwave conditions.[18]

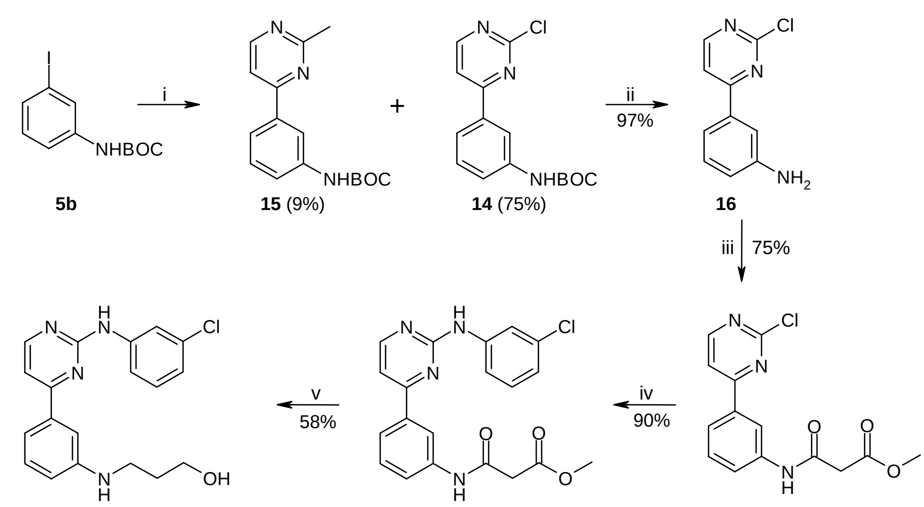
The Boc group was then cleaved to give **16** (97%), followed by introduction of the side chain as already described for the synthesis of **2**. Acylation of the amine function gave 75% of **17**. Reduction of **17** with BH_3–THF failed to give the desired compound even under very mild reaction conditions (ice cooling) only leading to decomposition of the heterocyclic system. In order to decrease the high reactivity of the 2-position in the pyrimidine part 3-chloroaniline was introduced prior to the reduction of the side chain in this series. The nucleophilic displacement was performed in dry dioxane under *p*-TSA-catalysis at reflux and yielded **18** in 90%. The reduction with BH_3–THF at this stage finally gave **4** in a satisfactory 58% yield (Scheme 5).

3. Conclusion

Based on the synthesis of CGP 60474 we developed suitable reaction sequences for the formation of all three target compounds (**2**, **3**, and **4**). Compound **2** was synthesized starting from 3-bromoaniline and 2-fluoro-4-iodopyridine (**1**, prepared from commercially available 2-fluoropyridine in two steps and improved 88% yield compared to the literature[19,20]) in six steps with 34% overall yield, compound **4** was obtained in five steps from



Scheme 4. (i) HCl, 3-chloroaniline, water/dioxane 4:1, reflux; (ii) (1) *n*-BuLi, $ZnCl_2$, THF, −75 °C to rt; than $Pd(PPh_3)_4$, **10**, THF, reflux; (iii) NaH, $(Boc)_2O$, THF, reflux; (iv) **1**, *n*-BuLi, $ZnCl_2$, THF, −75 °C to rt; (2) $Pd(PPh_3)_4$, **12**, THF, reflux; (v) TFA, CH_2Cl_2, rt; (vi) 3-aminopropanol, reflux.



Scheme 5. (i) (1) *n*-BuLi, $ZnCl_2$, THF, −75 °C to rt; (2) 2,4-dichloropyrimidine, $Pd(PPh_3)_4$, THF, reflux; (ii) TFA, CH_2Cl_2, rt; (iii) $ClCOCH_2COOMe$, NEt_3, THF, 0 °C; (iv) 3-chloroaniline, *p*-TSA·H_2O, dioxane, reflux; (v) BH_3–THF, THF, 0 °C.

3-bromoaniline and 2,4-dichloropyrimidine with 26% overall yield, and compound **3** was formed starting from **1** in four steps and 35% overall yield. The results of the biological screening of the title compounds showed no improved fungicidal activity compared to CGP 60474 and will be published elsewhere.

4. Experimental

4.1. General

Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected.

Combustion analysis was carried out in the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna. Flash column chromatography was performed on silica gel 60 from Merck 40–63 μm). NMR-spectra were recorded from $CDCl_3$ or d_6-DMSO solutions on a Bruker AC 200 (200 MHz) or Bruker Avance UltraShield 400 (400 MHz) spectrometer and chemical shifts are reported in ppm using TMS as internal standard.

4.1.1. 3-{3-[2-(3-Chlorophenylamino)-pyridin-4-yl]-phenylamino}-propanol (2). Substrate **9** (0.50 g, 2.03 mmol, 1 equiv), 1.6 N HCl (1.3 mL, 2.03 mmol, 1 equiv) and 3-chloroaniline (1.5 mL, 14.2 mmol, 7 equiv) were dissolved in 20 mL of a water–dioxane mixture (4/1) and refluxed for 48 h. The solution was poured onto water, adjusted to basic pH with saturated aqueous Na_2CO_3 solution, and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (LP/EtOAc 2:1→1:2) to give **2** as a brown oil (0.60 g, 1.70 mmol, 84%); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.79 (quin, $^3J=6.6$ Hz, 2H), 3.14 (m, 2H), 3.55 (m, 2H), 4.58 (br s, 1H), 5.73 (br s, 1H), 6.68 (d, $^3J=7.6$ Hz, 1H), 6.75–6.95 (m, 3H), 7.02 (d, $^3J=5.5$ Hz, 1H), 7.08 (s, 1H), 7.20 (t, $^3J=7.6$ Hz, 1H), 7.27 (t, $^3J=8.5$ Hz, 1H,), 7.56 (d, 1H), 8.09 (s, 1H), 8.24 (d, 1H), 9.37 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 32.0 (t), 40.0 (t), 58.8 (t), 108.3 (d), 109.6 (d), 112.9 (d), 113.2 (d), 113.8 (d), 116.2 (d), 117.0 (d), 119.7 (d), 129.7 (d), 130.1 (d), 133.2 (s), 138.6 (s), 143.4 (s), 147.7 (d), 149.7 (s, 2C), 156.1 (s).

4.1.2. 3-{[2′-(3-Chlorophenylamino)-[4,4′]-bipyridinyl-2-yl]-amino}-propanol (3). Substrate **13b** (0.50 g, 1.25 mmol) or **13a** (0.20 g, 0.67 mmol) were refluxed in an excess of 3-aminopropanol (20 mL) for 3 h. The mixture was cooled with ice and water was added (80 mL). The crude product, precipitated as sticky oil, was dissolved in ethyl acetate and subsequently washed with water (2×) and brine. The organic solution was dried over Na_2SO_4 and the solvent removed in vacuo to afford **3** as yellow crystals (0.41 g, 1.16 mmol, 92% in the case of starting material **13b**; 0.20 g, 0.56 mmol, 84% in the case of starting material **13a**); mp 138–140 °C (EtOAc); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.70 (quin, $^3J=6.6$ Hz, 2H), 3.35 (m, 2H), 3.50 (q, $^3J=6.6$ Hz, 1H), 4.53 (t, $^3J=6.6$ Hz, 1H), 6.63–6.80 (m, 3H), 6.91 (m, 1H), 7.02 (dd, $^3J=5.3$ Hz, $^4J=1.1$ Hz, 1H), 7.09 (s, 1H), 7.27 (t, $^3J=8.0$ Hz, 1H), 7.52 (m, 1H), 8.00–8.13 (m, 2H), 8.28 (d, $^3J=5.5$ Hz, 1H), 9.40 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 32.4 (t), 38.1 (t), 58.7 (t), 104.9 (d), 108.3 (d), 109.0 (d), 112.6 (d), 116.3 (d), 117.1 (d), 119.9 (d), 130.1 (d), 133.2 (s), 143.2 (s), 145.8 (s), 147.2 (s), 148.1 (d), 148.7 (d), 156.1 (s), 159.8 (s). Anal. Calcd for $C_{19}H_{19}ClN_4O$ (354.84): C, 64.31; H, 5.40; N, 15.79. Found: C, 64.18; H, 5.30; N, 15.53.

4.1.3. 3-{3-[2-(3-Chlorophenylamino)-pyrimidin-4-yl]-phenylamino}-propanol (4). BH_3–THF complex (23.5 mL, 1 M in THF, 23.5 mmol, 10.7 equiv) was cooled to 0 °C and **18** (1.00 g, 2.52 mmol, 1 equiv) in dry THF (20 mL) was added dropwise within 15 min. The mixture was stirred for 15 min at 0 °C and for 5 h at room temperature. 6 N HCl (20 mL) was added and the mixture was boiled for 5 min. After cooling to room temperature, water was added and the solution was adjusted to basic pH with saturated aqueous Na_2CO_3 solution. The mixture was extracted with ethyl acetate, the combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (LP/EtOAc 1:1→1:2) to give **4** as yellow crystals (0.52 g, 1.47 mmol, 58%); mp 100–102 °C (DIPE); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.78 (quin, $^3J=6.6$ Hz, 2H), 3.18 (m, 2H), 3.59 (t, $^3J=6.6$ Hz, 2H), 4.52 (br s, 1H), 5.73 (t, $^3J=6.6$ Hz, 1H), 6.78 (m, 1H), 6.99 (m, 1H), 7.15–7.45 (m, 5H), 7.78 (m, 1H), 8.11 (m, 1H), 8.56 (d, $^3J=5.6$ Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): $\delta=31.9$ (t), 40.0 (t), 58.7 (t), 108.6 (d), 109.2 (d), 114.3 (d), 115.3 (d), 117.0 (d), 117.8 (d), 120.6 (d), 129.2 (d), 130.0 (d), 133.0 (s), 137.2 (s), 142.7 (s), 149.5 (s), 158.7 (d), 159.8 (s), 164.6 (s). Anal. Calcd for $C_{19}H_{19}ClN_4O$ (354.84): C, 64.31; H, 5.40; N, 15.79. Found: C, 64.06; H, 5.60; N, 15.66.

4.1.4. *N*-(3-Bromophenyl)-carbamic acid 1,1-dimethylethyl ester (5b). 3-Bromoaniline (7.00 g, 40.7 mmol, 1 equiv) and $(Boc)_2O$ (9.16 g, 40.7 mmol, 1 equiv) were refluxed in dry THF (120 mL) for 65 h. The solvent was evaporated in vacuo and the crude product was washed twice with cold LP to afford **8** as colorless crystals (9.72 g, 35.7 mmol, 88%); mp 85–86 °C (LP); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.51 (s, 9H), 6.54 (br s, 1H), 7.06–7.26 (m, 3H), 7.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 28.2 (q), 80.9 (*s*), 116.9 (d), 121.3 (d), 122.6 (s), 125.8 (d), 130.1 (d), 139.7 (s), 152.4 (s).

4.1.5. 3-(2-Fluoropyridin-4-yl)-phenylamine (6a). *Method A*. Compound **6b** (6.17 g, 21.4 mmol, 1 equiv) was suspended in dry dichloromethane (80 mL) and trifluoroacetic acid (25 mL, 15.7 equiv) was added. The mixture was stirred for 2 h at room temperature. The solution was poured onto water, adjusted to basic pH with saturated aqueous Na_2CO_3 solution, and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford **6a** as yellow crystals (4.02 g, 21.4 mmol, 100%);

Method B. 2-Fluoro-4-iodo-pyridine **1** (0.97 g, 4.36 mmol, 1.5 equiv) was dissolved in dry THF (30 mL) and *n*-BuLi in hexane (2.1 mL, 2.29 M, 4.80 mmol, 1.65 equiv) was added at −75 °C. After stirring for 30 min, freshly dried $ZnCl_2$ (0.59 g, 4.36 mmol, 1.5 equiv) in dry THF (5 mL) was added. The mixture was allowed to warm to room temperature. $Pd(PPh_3)_4$ (0.03 g, 0.03 mmol, 0.01 equiv) and 3-bromoaniline (0.50 g, 2.91 mmol, 1 equiv) in dry THF (10 mL) were added and the mixture was refluxed for 4 h. The mixture was poured onto water, adjusted to basic pH with 2 N NaOH solution, and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography (LP/EtOAc 7:1) to afford **6a** as yellow crystals (0.20 g, 1.06 mmol, 37%); mp 110–112 °C (methanol); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 5.32 (br s, 2H), 6.68–6.75 (m, 1H), 6.88–6.93 (m, 1H), 6.98 (t, $^4J=1.8$ Hz, 1H), 7.17 (t, $^3J=8.0$ Hz, 1H), 7.32 (s, 1H), 7.47–7.52 (m, 1H), 8.25 (d, $^3J=5.6$ Hz 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 106.2 (d, $^2J_{CF}=38$ Hz), 112.0 (d), 114.5 (d), 115.5 (d), 119.4 (d, $^4J_{CF}=4$ Hz), 129.8 (d), 136.7 (s, $^4J_{CF}=3$ Hz), 147.9 (d, $^3J_{CF}=16$ Hz), 149.4 (s), 154.2 (s, $^3J_{CF}=8$ Hz), 164.0 (s, $^1J_{CF}=234$ Hz). Anal. Calcd for $C_{11}H_9FN_2$ (188.20): C, 70.20; H, 4.82; N, 14.88. Found: C, 69.91; H, 4.74; N, 14.81.

4.1.6. *N*-[3-(2-Fluoropyridin-4-yl)-phenyl]-carbamic acid 1,1-dimethylethyl ester (6b). Substrate **5b** (6.10 g, 22.4 mmol, 1 equiv) was dissolved in dry THF (200 mL) and MeLi in diethyl ether (17.1 mL, 1.44 M, 24.7 mmol, 1.1 equiv) was added at room temperature. After 30 min the mixture was cooled to −85 °C and *t*-BuLi in pentane (37.1 mL, 1.33 M, 49.3 mmol, 2.2 equiv) was added. The solution was stirred at −85 °C for 30 min. Then freshly dried $ZnCl_2$ (10.1 g, 74.0 mmol, 3.3 equiv) in dry THF (80 mL) was added. After 30 min the reaction mixture was allowed to warm to room temperature. $Pd(PPh_3)_4$ (0.25 g, 0.22 mmol) and **1** (5.00 g, 22.4 mmol, 1 equiv) in dry THF (25 mL) were added and the mixture was refluxed for 1 h. The cooled solution was poured onto a solution of EDTA (22 g) in water (300 mL), and adjusted to basic pH with saturated aqueous Na_2CO_3 solution. The mixture was extracted with diethyl ether, the combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure to give **9** as yellow crystals (6.18 g, 21.4 mmol, 96%); mp 181–184 °C (DIPE); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.52 (s, 9H), 7.30–7.65 (m, 3H), 7.48–7.65 (m, 2H), 7.92 (s, 1H), 8.30 (d, $^3J=5.3$ Hz, 1H), 9.52 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 28.1 (q), 79.3 (*s*), 106.4 (d, $^2J_{CF}=39$ Hz), 116.4 (d), 119.5 (d), 119.6 (d, $^4J_{CF}=4$ Hz), 120.7 (d), 129.6 (d), 136.5 (s, $^4J_{CF}=4$ Hz), 140.4 (s), 148.1 (d, $^3J_{CF}=16$ Hz), 152.8 (s), 153.4 (s, $^3J_{CF}=8$ Hz), 164.0 (s, $^1J_{CF}=235$ Hz). Anal. Calcd for $C_{16}H_{17}FN_2O_2$ (288.32): C, 66.65; H, 5.94; N, 9.72. Found: C, 66.52; H, 5.78; N, 9.56.

4.1.7. 2,2′-Difluoro-[4,4′]-bipyridinyl (7).[21] Compound **7** was formed as by-product during the formation of **6a** according to method B. Colorless crystals (20 mg, 0.10 mmol, 5%); R_f 0.60 (LP/EtOAc 2:1). Anal. Calcd for $C_{10}H_6F_2N_2$ (192.17): C, 62.50; H, 3.15; N, 14.58. Found: C, 62.21; H, 3.29; N, 14.33.

4.1.8. 3-{[3-(2-Fluoropyridin-4-yl)-phenyl]-amino}-3-oxopropanoic acid methyl ester (8). Substrate **6a** (2.00 g, 10.6 mmol, 1 equiv) and triethylamine (1.18 g, 11.7 mmol, 1.1 equiv) were dissolved in dry THF (30 mL) and cooled to 0 °C. 3-Chloro-3-oxopropanoic acid methyl ester (1.60 g, 11.7 mmol, 1.1 equiv) in dry THF (3 mL) was added dropwise within 10 min. After stirring for 2 h at 0 °C the mixture was poured onto water and extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by column chromatography (LP/EtOAc 1:1) to yield **8** as orange crystals (2.31 g, 8.01 mmol, 75%); mp 72–75 °C (EtOAc); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 3.55 (s, 2H), 3.68 (s, 3H), 7.40 (s, 1H), 7.47–7.56 (m, 2H), 7.56–7.63 (m, 1H), 7.64–7.72 (m, 1H), 8.03 (s, 1H), 8.32 (d, $^3J=5.1$ Hz, 1H), 10.4 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 43.5 (t), 52.0 (q), 106.6 (d, $^2J_{CF}=39$ Hz), 117.5 (d), 119.6 (d, $^4J_{CF}=4$ Hz), 120.5 (d), 122.3 (d), 129.8 (d), 136.7 (s, $^4J_{CF}=3$ Hz), 139.6 (s), 148.2 (d, $^3J_{CF}=16$ Hz), 153.1 (s, $^3J_{CF}=8$ Hz), 164.0 (s, $^1J_{CF}=235$ Hz), 164.4 (s), 168.1 (s). Anal. Calcd for $C_{15}H_{13}FN_2O_3$ (288.28): C, 62.50; H, 4.55; N, 9.72. Found: C, 62.27; H, 4.64; N, 9.64.

4.1.9. 3-[3-(2-Fluoropyridin-4-yl)-phenylamino]-propanol (9). BH_3–THF complex (25.5 mL, 1 M in THF, 25.5 mmol, 3.67 equiv) was cooled to 0 °C and **8** (2.00 g, 6.94 mmol, 1 equiv) in dry THF (30 mL) was added dropwise within 15 min. After additional stirring for 15 min at 0 °C, the mixture was refluxed for 2 h. After cooling to room temperature water was added and the mixture was stirred for 1 h. The solution was adjusted to basic pH with saturated aqueous Na_2CO_3 solution. The mixture was extracted with diethyl ether, the combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (LP/EtOAc 1:1 → 1:2) to give **9** as yellow crystals (1.10 g, 4.47 mmol, 64%); mp 88–90 °C (DIPE); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.75 (quin, $^3J=6.6$ Hz, 2H), 3.18 (q, $^3J=6.6$ Hz, 2H), 3.58 (q, $^3J=6.6$ Hz, 2H), 4.52 (t, $^3J=6.6$ Hz, 1H), 5.76 (t, $^3J=6.6$ Hz, 1H), 6.70 (d, $^3J=8.2$ Hz, 1H), 6.90–7.00 (m, 2H), 7.22 (t, $^3J=8.2$ Hz, 1H), 7.38 (s, 1H), 7.55–7.60 (m, $^3J=5.1$ Hz, $^5J=1.5$ Hz, 1H), 8.25 (d, $J=5.1$ Hz, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 32.0 (t), 39.8 (t), 58.7 (t), 106.3 (d, $^2J_{CF}=38$ Hz), 109.7 (d), 113.7 (d), 114.1 (d), 119.6 (d, $^4J_{CF}=4$ Hz), 129.7 (d), 136.8 (s, $^4J_{CF}=3$ Hz), 147.9 (d, $^3J_{CF}=16$ Hz), 149.8 (s), 154.3 (s, $^3J_{CF}=8.4$ Hz), 164.0 (s, $^1J_{CF}=234$ Hz). Anal. Calcd for $C_{14}H_{15}FN_2O$ (246.28): C, 68.28; H, 6.14; N, 11.37. Found: C, 68.08; H, 6.24; N, 11.26.

4.1.10. *N*-(3-Chlorophenyl)-4-iodo-2-pyridinamine (10). Substrate **1** (4.00 g, 17.9 mmol, 1.2 equiv), 3-chloroaniline (1.91 g, 14.9 mmol, 1 equiv) and 1.6 N HCl (9.3 mL, 14.9 mmol, 1 equiv) were dissolved in a water–dioxane mixture (9/1, 250 mL) and refluxed for 22 h. Dioxane (30 mL) was added and the mixture was refluxed for further 24 h. The solvents were evaporated and the residue was suspended in a saturated aqueous Na_2CO_3 solution (150 mL). After extraction with diethyl ether, the combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was triturated with LP–EtOAc (4/1) to give crystalline **10** (2.85 g), which was dried in vacuo. The mother liquor was concentrated and the residue was purified by column chromatography (LP/EtOAc 4:1 → 1:1) to obtain a second fraction of **10** (0.40 g). Total yield: 3.25 g (9.83 mmol, 66%) of **10** as colorless crystals; mp 127–129 °C (LP); R_f 0.40 (LP/EtOAc 4:1); ^{1}H NMR (d_6-DMSO, 400 MHz): δ 6.94 (ddd, $^3J=8.1$ Hz, $^4J=1.8$, 1.2 Hz, 1H), 7.16 (dd, $^3J=5.5$ Hz, $^4J=1.5$ Hz, 1H), 7.23–7.34 (m, 2H), 7.45 (ddd, $^3J=8.1$ Hz, $^4J=1.8$, 1.2 Hz, 1H), 7.91 (d, $J=5.5$ Hz, 1H), 7.96 (t, $J=1.8$ Hz, 1H), 9.32 (s, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 106.3 (s), 116.5 (d), 117.3 (d), 119.5 (d), 120.3 (d), 123.2 (d), 130.1 (d), 133.1 (s), 142.5 (s), 147.8 (d), 155.7 (s). Anal. Calcd for $C_{11}H_8ClIN_2$ (330.56): C, 39.97; H, 2.44; N, 8.47. Found: C, 40.25; H, 2.61; N, 8.31.

4.1.11. *N*2,*N*4-Bis-(3-chlorophenyl)-pyridine-2,4-diamine (11). Formed as by-product during the formation of **10**. 0.22 g (0.60 mmol, 9%); ^{1}H NMR (d_6-DMSO, 400 MHz): δ 6.43 (dd, 1H, $^3J=6.0$ Hz, $^4J=1.8$ Hz), 6.51 (d, $J=1.8$ Hz, 1H), 6.85 (ddd, 1H, $^3J=8.2$ Hz, $^4J=2.4$, 1.4 Hz), 7.03 (ddd, 1H, $^3J=8.2$ Hz, $^4J=2.4$, 1.4 Hz), 7.13–7.28 (m, 3H), 7.35 (t, 1H, $^3J=8.2$ Hz), 7.40–1.48 (m, 1H), 7.95 (d, $^3J=6.0$ Hz, 1H), 8.02 (t, $^4J=2.4$ Hz, 1H), 8.82 (s, 1H), 9.02 (s, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 94.3 (d), 104.5 (d), 116.0 (d), 116.9 (d), 117.8 (d), 118.8 (d), 119.2 (d), 119.9 (d), 129.8 (d), 130.7 (d), 133.1 (s), 133.7 (s), 142.6 (s), 143.6 (s), 147.9 (s), 150.3 (s), 156.6 (d). Anal. Calcd for $C_{17}H_{13}Cl_2N_3\cdot HCl$ (366.68): C, 55.69; H, 3.85; N, 11.46. Found: C, 55.83; H, 3.87; N, 11.17.

4.1.12. *N*-(3-Chlorophenyl)-*N*-(4-iodopyridin-2-yl)-carbamic acid 1,1-dimethylethyl ester (12). Substrate **10** (3.50 g, 10.6 mmol, 1 equiv) was dissolved in dry THF (50 mL), deprotonated with NaH (0.30 g, 12.7 mmol, 1.2 equiv) and treated with $(Boc)_2O$ (2.86 g, 12.7 mmol, 1.2 equiv) in dry THF (10 mL). The mixture was refluxed for 3 h, poured onto water, and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (LP/EtOAc 8:1) to give **12** as colorless crystals (3.65 g, 8.48 mmol, 80%); mp 91–94 °C (EtOAc); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.39 (s, 9H), 7.11–7.19 (m, 1H), 7.28–7.40 (m, 3H), 7.63 (dd, 1H, $^3J=5.1$ Hz, $^4J=1.3$ Hz), 8.01 (d, $^3J=5.1$ Hz, 1H), 8.08 (m, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 27.6 (q), 81.7 (*s*), 107.0 (s), 126.4 (d), 126.6 (d), 127.7 (d), 129.2 (d), 129.6 (d), 130.2 (d), 132.7 (s), 142.4 (s), 148.5 (d), 152.2 (s), 154.5 (s). Anal. Calcd for $C_{16}H_{16}ClIN_2O_2$ (430.67): C, 44.62; H, 3.74; N, 6.50. Found: C, 44.80; H, 3.79; N, 6.40.

4.1.13. *N*-(3-Chlorophenyl)-*N*-(2′-fluoro-[4,4′]-bipyridinyl-2-yl)amine (13a). *Method A*. Substrate **13b** (0.80 g, 2.00 mmol, 1 equiv) was suspended in dry dichloromethane (30 mL) and trifluoroacetic acid (1.5 mL, 2.02 mmol, 1.01 equiv) was added. The mixture was stirred at room temperature for 3 h, poured onto water, adjusted to basic pH with saturated aqueous Na_2CO_3 solution and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give **6** as yellow crystals (0.60 g, 100%).

Method B. *n*-BuLi in hexane (0.85 mL, 2.13 M, 1.81 mmol, 2 equiv) was added to **1** (0.40 g, 1.81 mmol, 2 equiv) in dry THF (100 mL) at −75 °C within 10 min. After 30 min freshly dried $ZnCl_2$ (0.25 g, 1.81 mmol, 2 equiv) in dry THF (5 mL) was added. The reaction mixture was warmed to room temperature and $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol, 0.055 equiv) and **10** (0.30 g, 0.91 mmol, 1 equiv) in dry THF (15 mL) were added. After refluxing for 3 h, the mixture was stirred another 48 h at room temperature. More $Pd(PPh_3)_4$ (0.05 g, 0.04 mmol, 0.05 equiv) was added and the solution was refluxed for 2 h. The mixture was poured onto water, adjusted to basic pH with saturated aqueous Na_2CO_3 solution, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography (LP/EtOAc 7:1) to afford **13a** as yellow crystals (0.10 g, 0.33 mmol, 37%); mp 158–160 °C (methanol); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 6.90–6.96 (m, 1H), 7.17 (s, 1H), 7.21 (dd, $^3J=5.5$ Hz, $^4J=1.4$ Hz, 1H), 7.28 (t, $^3J=8.2$ Hz, 1H), 7.47–7.57 (m, 2H), 7.67 (dt, $^3J=5.5$ Hz, $^4J=1.4$ Hz, 1H), 8.03 (t, $^4J=2.1$ Hz, 1H), 8.34 (d, $^3J=5.5$ Hz, 1H), 8.38 (d, $^3J=5.5$ Hz, 1H), 9.48 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 107.0 (d, $^2J_{CF}=39$ Hz), 108.8 (d), 112.6 (d), 116.4 (d), 117.2 (d), 119.6 (d, $^4J_{CF}=4$ Hz), 120.1 (d), 130.1 (d), 133.1 (s), 142.9 (s), 144.6 (s, $^4J_{CF}=3$ Hz), 148.4 (d), 148.5 (d, $^3J_{CF}=15$ Hz), 151.1 (s, $^3J_{CF}=8$ Hz), 156.2 (s), 164.0 (s, $^1J_{CF}=235$ Hz). Anal. Calcd for $C_{16}H_{11}ClFN_3$ (299.74): C, 64.12; H, 3.70; N, 14.02. Found: C, 63.97; H, 3.68; N, 13.84.

4.1.14. *N*-(3-Chlorophenyl)-*N*-(2′-fluoro-[4,4′]-bipyridinyl-2-yl)-carbamic acid 1,1-dimethylethyl ester (13b). *n*-BuLi in hexane (4.2 mL, 2.29 M, 9.54 mmol, 1.48 equiv) was added to 2-fluoro-4-iodo-pyridine (1.93 g, 8.67 mmol, 1.33 equiv) in dry THF (100 mL) at −75 °C within 10 min. After 30 min freshly dried $ZnCl_2$ (1.18 g, 9.54 mmol, 1.48 equiv) in dry THF (10 mL) was added. The reaction mixture was warmed to room temperature and $Pd(PPh_3)_4$ (0.04 g, 0.003 mmol, 0.0005 equiv) and **12** (2.80 g, 6.50 mmol, 1 equiv) in dry THF (15 mL) were added. After refluxing for 1.5 h the solution was poured onto water, adjusted to basic pH with saturated aqueous Na_2CO_3 solution, and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from EtOAc to afford **13b** as colorless crystals (1.90 g, 4.75 mmol, 73%); mp 172–175 °C (EtOAc); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.40 (s, 9H), 7.19 (dt, $^3J=8.2$ Hz, $^4J=2.0$ Hz, 1H), 7.26–7.42 (m, 3H), 7.68 (s, 1H), 7.72 (dd, $^3J=5.2$ Hz, $^4J=1.5$ Hz, 1H), 7.77–7.83 (m, 1H), 8.07 (s, 1H), 8.41 (d, $^3J=5.2$ Hz, 1H), 8.49 (d, $^3J=5.2$ Hz, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 27.8 (q), 81.7 (s), 107.4 (d, $^2J_{CF}=39$ Hz), 119.1 (d), 119.3 (d), 119.9 (d, $^4J_{CF}=4$ Hz), 126.3 (d), 126.4 (d), 127.4 (d), 130.3 (d), 132.8 (s), 142.8 (s), 145.3 (s), 148.8 (d, $^3J_{CF}=16$ Hz), 149.4 (d), 150.1 (s, $^3J_{CF}=8$ Hz), 152.5 (s), 155.5 (s), 164.0 (s, $^1J_{CF}=239$ Hz). Anal. Calcd for $C_{21}H_{19}ClFN_3O_2$ (399.85): C, 63.08; H, 4.79; N, 10.51. Found: C, 62.82; H, 4.78; N, 10.41.

4.1.15. *N*-[3-(2-Chloropyrimidin-4-yl)-phenyl]-carbamic acid 1,1-dimethylethyl ester (14). Substrate **5b** (4.57 g, 16.8 mmol, 1 equiv) was dissolved in dry THF (120 mL) and MeLi in diethyl ether (12.8 mL, 1.44 M, 18.5 mmol, 1.1 equiv) was added dropwise at +15 °C. After stirring for 30 min, the mixture was cooled to −85 °C and *t*-BuLi in pentane (27.6 mL, 1.34 M, 37.0 mmol, 2.2 equiv) was added dropwise. The solution was stirred for 30 min at −75 °C and freshly dried $ZnCl_2$ (7.55 g, 55.4 mmol, 3.3 equiv) in dry THF (80 mL) was added. The mixture was stirred for further 30 min and then allowed to warm to room temperature. $Pd(PPh_3)_4$ (0.19 g, 0.16 mmol, 0.01 equiv) and 2,4-dichloropyrimidine (2.50 g, 16.8 mmol, 1 equiv) in dry THF (15 mL) were added, and the mixture was refluxed for 1 h. The solution was poured onto a solution of EDTA (17 g) in water (200 mL), which was adjusted to basic pH with saturated aqueous Na_2CO_3 solution, and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (LP/EtOAc 3:1 → 1:1) to give **14** as yellow crystals (3.87 g, 12.7 mmol, 75%); mp 155–157 °C (DIPE); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.24 (s, 9H), 7.19 (t, $^3J=8.5$ Hz, 1H), 7.38 (d, $^3J=8.5$ Hz, 1H), 7.50 (d, $^3J=8.5$ Hz, 1H), 7.75 (d, $^3J=5.5$ Hz, 1H), 8.10 (s, 1H), 8.54 (d, $^3J=5.5$ Hz, 1H), 9.32 (s, 1H); ^{13}C

NMR (d_6-DMSO, 50 MHz): δ 28.1 (q), 79.4 (*s*), 116.1 (d), 116.6 (d), 121.2 (d), 121.7 (d), 129.5 (d), 135.1 (s), 140.5 (s), 152.8 (s), 160.5 (s), 161.2 (d), 166.3 (s). Anal. Calcd for $C_{15}H_{16}ClN_3O_2$ (305.76): C, 58.92; H, 5.27; N, 13.74. Found: C, 58.71; H, 5.38; N, 13.53.

4.1.16. *N*-[3-(2-Methylpyrimidin-4-yl)-phenyl]-carbamic acid 1,1-dimethylethyl ester (15). The title compound formed as by-product during the formation of **14**. (LP/EtOAc 3:1). Yellow crystals (0.42 g, 1.47 mmol, 9%); mp 156–159 °C (EtOAc); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 1.49 (s, 9H), 2.67 (s, 3H), 7.40 (t, ^3J=8.4 Hz, 1H), 7.60 (d, ^3J=8.5 Hz, 1H), 7.65–7.85 (m, 2H), 8.34 (s, 1H), 8.73 (d, ^3J=5.5 Hz, 1H), 9.51 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 25.9 (q), 28.1 (q), 79.2 (*s*), 114.0 (d), 116.5 (d), 120.7 (d), 120.8 (d), 129.2 (d), 136.8 (s), 140.2 (s), 152.8 (s), 158.1 (d), 162.8 (s), 167.4 (s). Anal. Calcd for $C_{16}H_{19}N_3O_2$ (285.34): C, 67.35; H, 6.71; N, 14.73. Found: C, 67.10; H, 6.75; N, 14.52.

4.1.17. 2-Chloro-4-(3-aminophenyl)-pyrimidine (16). Substrate **14** (4.43 g, 14.5 mmol, 1 equiv) was suspended in dry dichloromethane (20 mL) and treated with trifluoroacetic acid (10 mL, 135 mmol, 9.3 equiv). The mixture was stirred at room temperature for 3 h, poured onto water, adjusted to basic pH with saturated aqueous Na_2CO_3 solution and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to yield **16** as yellow crystals (2.93 g, 14.2 mmol, 98%); mp 137–138 °C (MeOH); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 5.40 (br s, 2H), 6.79 (dt, ^3J=8.0 Hz, ^4J=2.3 Hz, 1H), 7.19 (dd, ^3J=8.0 Hz, 1H), 7.28 (d, J=8.0 Hz, 1H), 7.42 (t, ^4J=2.3 Hz, 1H), 7.93 (d, ^3J=5.3 Hz, 1H), 8.74 (d, J=5.3 Hz, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 112.1 (d), 114.9 (d), 115.8 (d), 117.6 (d), 129.7 (d), 135.1 (s), 149.4 (s), 160.5 (s), 160.7 (d), 167.0 (s). Anal. Calcd for $C_{10}H_8ClN_3$ (205.65): C, 58.41; H, 3.92; N, 20.43. Found: C, 58.25; H, 4.19; N, 20.14.

4.1.18. 3-{[3-(2-Chloropyrimidin-4-yl)-phenyl]-amino}-3-oxopropanoic acid methyl ester (17). Substrate **16** (2.50 g, 12.2 mmol, 1 equiv) and triethylamine (1.35 g, 13.4 mmol, 1.1 equiv) were dissolved in dry THF (50 mL) and cooled to 0 °C. 3-Chloro-3-oxopropanoic acid methyl ester (1.83 g, 13.4 mmol, 1.1 equiv) in dry THF (5 mL) was added dropwise within 10 min. After stirring for 2 h at 0 °C the mixture was poured onto water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by column chromatography (LP/EtOAc 1:1) to yield **17** as colorless crystals (2.80 g, 9.16 mmol, 75%); mp 117–119 °C (DIPE); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 3.52 (s, 2H), 3.67 (s, 3H), 7.52 (t, ^3J=8.3 Hz, 1H), 7.84–7.93 (m, 2H), 8.07 (d, ^3J=5.5 Hz, 1H), 8.38 (t, ^4J=2.2 Hz, 1H), 8.82 (d, ^3J=5.5 Hz, 1H), 10.48 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 43.5 (t), 52.0 (q), 116.0 (d), 117.5 (d), 122.4 (d), 122.5 (d), 129.7 (d), 135.0 (s), 139.6 (s), 160.5 (s), 161.2 (d), 164.3 (s), 165.8 (s), 168.0 (s). Anal. Calcd for $C_{14}H_{12}ClN_3O_3$ (305.72): C, 55.00; H, 3.96; N, 13.74. Found: C, 54.74; H, 4.12; N, 13.48.

4.1.19. 3-{[3-[2-(3-Chlorophenylamino)-pyrimidin-4-yl]-phenyl]-amino}-3-oxopropanoic acid methyl ester (18). Substrate **17** (2.00 g, 6.54 mmol, 1 equiv), 3-chloroaniline (1.25 g, 9.81 mmol, 1.5 equiv), and *p*-TSA·H_2O (1.06 g, 5.56 mmol, 0.85 equiv) were dissolved in dry dioxane (40 mL) and refluxed for 4 h. The solvent was removed in vacuo and the residue was suspended in water. The suspension was adjusted to basic pH with saturated aqueous Na_2CO_3 solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by column chromatography ((LP/EtOAc 1:1 → 1:3) to yield **18** as yellow crystals (2.34 g, 5.90 mmol, 90%); mp 173–176 °C (EtOAc); ^{1}H NMR (d_6-DMSO, 200 MHz): δ 3.54 (s, 2H), 3.68 (s, 3H), 7.00 (d, ^3J=8.2 Hz, 1H), 7.28–7.43 (m, 2H), 7.50 (t, ^3J=7.6 Hz, 1H), 7.68 (d, ^3J=8.2 Hz, 1H), 7.80–7.95 (m, 2H), 7.99 (t, ^4J=2.2 Hz, 1H), 8.48 (s, 1H), 8.62 (d, ^3J=5.5 Hz, 1H), 9.92 (s, 1H), 10.39 (s, 1H); ^{13}C NMR (d_6-DMSO, 50 MHz): δ 43.5 (t), 52.0 (q), 108.6 (d), 117.1 (d), 117.8 (d), 118.0 (d), 120.8 (d), 121.6 (d), 122.2 (d), 129.4 (d), 130.3 (d), 133.0 (s), 137.3 (s), 139.4 (s), 142.2 (s), 159.1 (d), 159.9 (s), 163.7 (s), 164.3 (s), 168.1 (s). Anal. Calcd for $C_{20}H_{17}ClN_4O_3$ (396.83): C, 60.53; H, 4.32; N, 14.12. Found: C, 60.59; H, 4.60; N, 13.96.

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