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Regioselective halogenation of aminopyrimidinyl-pyrrole carboxylic acid derivatives

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ABSTRACT

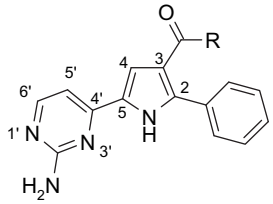
The regioselective synthesis of halogenated aminopyrimidinyl-pyrroles as useful scaffolds for the preparation of diversified selective kinase inhibitors is described. The chemistry is simple and mostly based on the use of *N*-halosuccinimides under mild reaction conditions but the regioselectivity observed is partially unexpected.

1. Introduction

Nitrogen containing heterocyclic scaffolds are the focus of many medicinal chemistry programs due to the great interest they arouse for a wide range of biological targets, for example, protein kinase inhibitors.[1] Regioselective derivatization of such scaffolds constitutes a common strategy for potency optimization against the desired biological target, but also for selectivity improvement vs a series of related targets whose inhibition might cause unwanted toxic effects.[2] To address and achieve such goals, the availability of suitably reactive precursors is of crucial importance.

During the development of our medicinal chemistry programs, novel heteroaryl-pyrrole scaffolds were shown to be useful tools to identify potent and selective kinase inhibitors.[3] In this respect, a procedure to prepare selectively halogenated heteroaryl-pyrroles would be extremely valuable, leading to intermediates that could be further derivatized by palladium-mediated C–C and C–N bond forming reactions under mild conditions.[4,5]

Our attention focused primarily on scaffold **1**, characterized by the aminopyrimidinyl-pyrrole nucleus, the halogenation of which is the main subject of the present work. The chemistry involved is straightforward and mostly based on the use of *N*-halosuccinimides under mild reaction conditions [6,7] but the investigation led to some interesting regioselectivity results that might be of relevance to others.



1a R = OEt
1b R = NH_2

2. Results and discussion

Scaffold **1** was prepared as shown in Scheme 1 from commercially available materials.[8]

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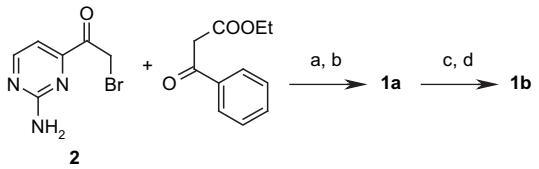
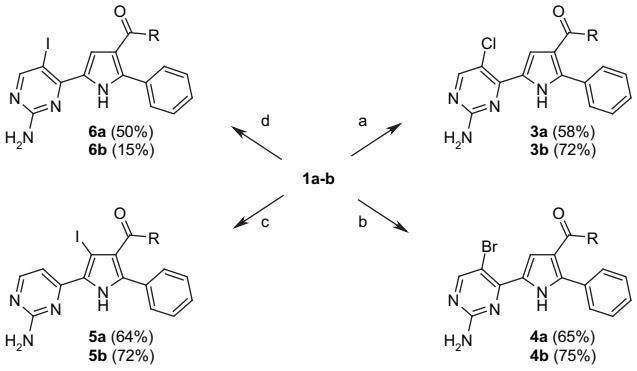


Scheme 1. (a) NaH, THF, DMF, 0 °C-rt; (b) NH_4OAc, EtOH, rt, (46% from **2**); (c) NaOH, EtOH, 100 °C; (d) HOBt·NH_3, DIPEA, EDCI·HCl, THF, rt, (43%).

The key step of the synthesis is based on the Hantzsch reaction that accesses the tri-substituted pyrrole frame. Bromoketone **2** was allowed to react with the sodium enolate of ethyl 3-oxo-3-phenylpropanoate in the presence of ammonium acetate, yielding ester **1a** that was transformed, via the carboxylic acid, into the primary amide **1b** by means of hydroxybenzotriazole ammonium salt in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl). As mentioned above, scaffold **1** is an interesting substrate for halogenations. When **1a** was exposed to halogenation with equimolar amounts of *N*-chlorosuccinimide or *N*-bromosuccinimide, analogues **3a** and **4a**, mono-halogenated at position 5′ of the pyrimidine ring, were respectively obtained (Scheme 2).

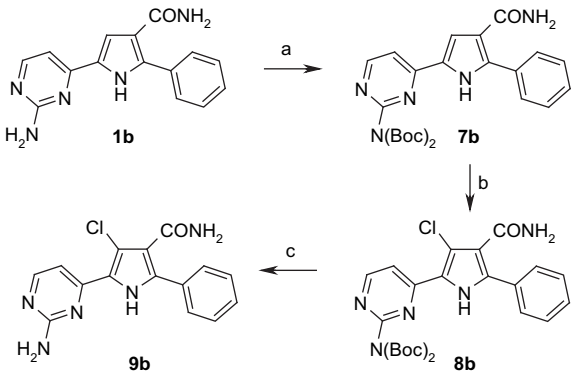


Scheme 2. (a) NCS (1 equiv), DMF, 60–80 °C; (b) NBS (1 equiv), DMF, rt; (c) NIS (1 equiv), DMF, rt; (d) CF_3COOAg, I_2, DMF, −40 °C, (**5a**–**b**+**6a**–**b**: chromatographic separation).

This transformation occurred in DMF, under heating in the first case or at room temperature in the second, reflecting the different reactivity of the two reagents imposed mainly by their different bond energies (N–Cl>N–Br). Moreover, halogenation of aromatic compounds with NXS in a polar solvent such as DMF is expected to proceed via aromatic electrophilic substitution with the electrophile attacking the most electron-rich and less sterically encumbered 2-amino-pyrimidine ring. In a similar fashion, we and others have already described the bromination at the C-5′ position of the 2-aminopyrimidine ring in systems such as 2-(2-aminopyrimidin-4-yl)-pyrazolo-pyridinones and 3-(2-aminopyrimidin-4-yl)-indoles by employing *N*-bromosuccinimide.[3a,9] Interestingly, halogenation could be oriented on the pyrrole nucleus by using equimolar *N*-iodosuccinimide that converted **1a** into iodopyrrole **5a** in DMF at room temperature. This rather unexpected result prompted us to carry out further investigations. Similarly, when the primary amide **1b** was treated with an equimolar amount of *N*-chlorosuccinimide or *N*-bromosuccinimide, analogues **3b** and **4b**, mono-halogenated at position 5′ of the pyrimidine ring, were obtained whereas an equimolar amount of *N*-iodosuccinimide produced the iodopyrrole **5b**,[10] thus confirming the selectivity pattern observed on the ester **1a**. The larger size and lower positive charge density of iodine, compared to both chlorine and bromine, seems to suggest that the observed regiochemistry is modulated by the nucleophilic carbon attack to the halogen, with the most reactive C-5′ pyrimidine position reacting with chlorine and bromine and the less reactive C-4 pyrrole one with iodine.

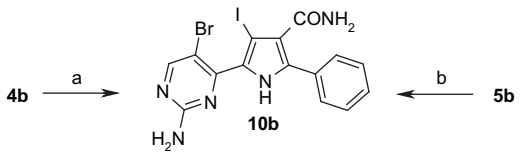
As iodoaromatics frequently show enhanced and uniquely high reactivity as compared to their bromo and chloro analogues, we were particularly interested in the preparation of 5′-iodopyrimidine derivatives.[11] Unfortunately, despite our efforts in trying both different sources of electrophilic iodine and reaction conditions, we were not able to find a gratifying solution. Generally speaking, we found, working on both **1** and related scaffolds, that, although formation of the iodopyrrole is usually favoured, iodination of the 5′-pyrimidine position is more likely to compete either when an alkyl substituent on the pyrrole nitrogen is present (i.e., methyl, ethyl, 2,2,2-trifluoro-ethyl, easily cleavable 2-(trimethylsilyl)ethoxymethyl) or by employing a strong source of positive iodine such as trifluoroacetyl hypoiodite in DMF at low temperatures. Further elucidation in order to better exploit the use of protecting groups on the pyrrole nitrogen (i.e., 2-(trimethylsilyl)ethoxymethyl) to re-orient the iodination reaction on the aminopyrimidine nucleus is still on-going. Direct iodination of **1b** by employing trifluoroacetyl hypoiodite generated in situ from iodine and silver trifluoroacetate in DMF at −40 °C gave poor results, generating a 1:1 mixture of **6b** and **5b** (Scheme 2). However, easy separation by flash chromatography under standard conditions of the reaction mixture was feasible and compound **6b** was isolated with 15% yield. Under the same conditions, better results were obtained when the ester **5a** was employed as in this case isolation yield of compound **6a** was higher (50%).

Halogenation of **1b** could also be re-oriented on the pyrrole nucleus by deactivation of the pyrimidine ring with electron-withdrawing protections at the amino group. When **1b** was protected at the aminopyrimidine nucleus as *N*,*N*-di-*tert*butoxycarbonyl derivative, it was transformed into chloropyrrole **9b** by treatment with *N*-chlorosuccinimide at 100 °C in DMF, followed by removal of the protection under acidic conditions (Scheme 3).



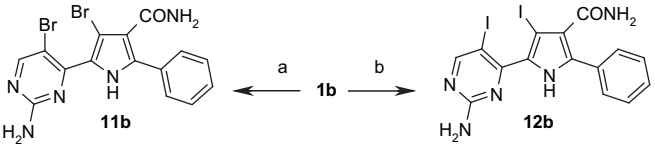
Scheme 3. (a) $(Boc)_2O$, THF, rt, chromatographic separation from mono- and tri-Boc derivatives, (14%); (b) NCS (1 equiv), DMF, 100 °C, (45%); (c) HCl in dioxane, 50 °C, (82%).

Furthermore, multiple halogenations take place on compound **1b**, both in a double-sequential and double-simultaneous mode. In fact, when bromopyrimidine **4b** was treated with equimolar *N*-iodosuccinimide compound **10b** was obtained. The same product was also formed upon treatment of iodopyrrole **5b** with equimolar amounts of *N*-bromosuccinimide (Scheme 4).



Scheme 4. (a) NIS (1 equiv), DMF, rt, (82%); (b) NBS (1 equiv), DMF, rt, (83%).

In this way, differential reactivity was achieved on the two rings, useful for directing further synthetic elaborations.[12] When the same approach was used to brominate **6b**, both at room temperature and at −20 °C, a complex mixture was obtained, where **4b** and **10b** were detected as major components and no trace could be found of the expected 5′-iodo-pyrimidinyl-4-bromopyrrole derivative.[13] On the other hand, compound **1b** was simultaneously dihalogenated to **11b** or **12b**, upon treatment with two equivalents of the proper *N*-halosuccinimide (Scheme 5).



Scheme 5. (a) NBS (2 equiv), DMF, rt, (90%); (b) NIS (2 equiv), DMF, rt, (46%).

These compounds, bearing multiple identical halogens, though appealing, are subjected to a not easily predictable regioselectivity rank, when subjected to cross-coupling reactions.[14]

The positions of the halogen atoms on the amino-pyrimidine or on the pyrrole ring were unambiguously determined by NMR spectroscopy. ^{1}H and ^{13}C NMR spectroscopic signals were assigned by means of literature data and 2D experiments (^{1}H–^{13}C HSQC and HMBC). The two aromatic protons of the aminopyrimidine ring give rise to two typical doublets with $^{3}J_{HH}$=5.2 Hz around 7.3 and 8.3 ppm and the hetero-aromatic proton of the pyrrole ring is a doublet with $^{4}J_{H\text{–}NH}$=2.7 Hz around 7.3–7.6 ppm. Halogenation on position 5′ of the aminopyrimidine ring is indicated by the disappearance of the two doublets and the appearance of a singlet above 8.3 ppm, while the halogenation on position 4 of the pyrrole ring is indicated by the disappearance of the doublet with $^{4}J_{H\text{–}NH}$=2.7 Hz around 7.3–7.6 ppm. In the case of two different halogens on the two heterocyclic rings, e.g., bromine on position 5′ of the aminopyrimidine and iodine on position 4 of the pyrrole ring, their relative positions were determined by comparing the ^{13}C chemical shift of the corresponding quaternary carbons (obtained by ^{1}H–^{13}C HMBC) with the data of the mono-halogenated products and with literature data.

3. Conclusion

The preparation of halogenated aminopyrimidinyl-pyrroles as useful intermediates for the synthesis of novel biologically active compounds is described. The chemistry allows a versatile diversification of two key positions of the molecule, i.e., 5′-pyrimidine and 4-pyrrole. Further decoration of the halogenated scaffolds by means of the wide array of metal-catalyzed cross-coupling reactions currently available will be described in due course.

4. Experimental

4.1. General

Purity was routinely measured by HPLC on a Waters X Terra RP 18 (4.6×50 mm, 3.5 μm) column using an SSP4000 (Thermo Separation Products) HPLC system equipped with an autosampler LC Pal (CTC Analytics) and UV6000LP diode array detector (UV detection 215–400 nm) and a Finnigan LCQ ion trap mass spectrometer equipped with an electrospray (ESI) ion source. Instrument control, data acquisition and processing were performed by using Xcalibur 1.2 software (Finnigan). HPLC chromatography was run at room temperature, and 1 mL/min flow rate. Mobile phase A was ammonium acetate 5 mM buffer (pH 5.5 with acetic acid): acetonitrile 90:10, and mobile phase B was ammonium acetate 5 mM buffer (pH 5.5 with acetic acid): acetonitrile 10:90; the gradient was from 0 to 100% B in 7 min then hold 100% B for 2 min before equilibration. ^{1}H and ^{13}C NMR spectra were acquired at 25 °C in DMSO-d_6 on a Varian Inova 500 spectrometer equipped with 5 mm 1H{13C,15N} *z*-axis-PFG Triple Resonance Cold Probe and on a Varian Inova 400 spectrometer equipped with 5 mm 1H{15N-31P} *z*-axis-PFG Indirect Detection probe. Residual not-deuterated solvent signal was used as reference (δ=2.50 ppm for ^{1}H and δ=39.5 for ^{13}C). Two-dimensional pulse sequences (T-Roesy, gradient-enhanced with adiabatic pulses HSQC and HMBC) provided by the standard Varian software Vnmrj 2.1B were used to assign carbons and regiochemistry. Low-resolution mass spectral (MS) data were determined on a Finnigan MAT LCQ ion trap instrument, equipped with ESI ion source and mass values are given as an *m*/*z* ratio. ESI(+) high-resolution mass spectra (HRMS) were obtained on a Waters Q-Tof Ultima directly connected with micro HPLC 1100 Agilent as previously described.[15] IR spectra of powders were recorded on a Thermo Scientific Nicoloet iS10 instrument equipped with an ATR SMART ENDURANCE (ν_{max} in cm^{-1}). Chromatographic purification was performed either under medium pressure on silica (Merck silica gel 40–63 μm) or on prepacked silica gel cartridges (Biotage) or on a Horizon system. Thin-layer chromatography was performed on Merck silica gel 60 plates coated with 0.25 mm layer with fluorescent indicator. Components were visualized by UV light (λ=254 and 366 nm) and iodine vapors. Melting points were determined in an open capillary and are uncorrected.

4.2. Synthesis

4.2.1. 5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxamide ***1b****. 4.2.1.1. Step 1.* To a solution of ethyl 3-oxo-3-phenylpropanoate (1.34 g, 7 mmol) in anhydrous THF (100 mL) at 0 °C, NaH (60% suspension in oil, 0.7 g, 17.5 mmol) was added under argon with stirring. After 5 min 1-(2-amino-pyrimidin-4-yl)-2-bromo-ethanone hydrobromide 2 (2.5 g, 8.4 mmol) was added and the mixture was stirred at room temperature for 3 h. Solvent was evaporated, the residue was dissolved in ethanol (65 mL), ammonium acetate (1.6 g, 21 mmol) was added and the solution was stirred at rt overnight. Solvent was evaporated to dryness and the residue was purified by flash chromatography (EtOAc/*n*-hexane 7:3), yielding ethyl 5-(2-amino-pyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxylate **1a** (990 mg, 46%) as a yellowish powder, mp 157–160 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.19 (t, *J*=7.1 Hz, 3H) 4.12 (q, *J*=7.1 Hz, 2H) 6.44 (s, 2H) 7.09 (d, *J*=5.2 Hz, 1H) 7.31 (d, *J*=2.4 Hz, 1H) 7.38–7.48 (m, 3H) 7.62 (dd, *J*=7.9, 1.6 Hz, 2H) 8.22 (d, *J*=5.2 Hz, 1H) 12.00 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 13.8, 59.2, 112.2, 116.0, 118.4, 126.2, 126.8 (2C), 127.5, 128.3 (2C), 130.8, 136.4, 157.8, 158.2, 163.5, 164.8; IR 1450, 1548, 1566, 1670, 1691, 3186, 3362 ν_{max} cm^{-1}; LCMS (ESI) *m*/*z* 309 $(M+H)^{+}$; HRMS (ESI) calcd for $C_{17}H_{16}N_4O_2+H^{+}$ 309.1346, found 309.135.

4.2.1.2. Step 2. To a suspension of ester **1a** (3.65 g, 11.8 mmol) in 95% EtOH (45 mL), 4 M aqueous NaOH (45 mL) was added and the mixture was refluxed for 5 h. Most solvent was evaporated and the residue, cooled in ice bath, was acidified to pH 5 with concentrated HCl. The precipitate was filtered, washed with little cold water, and dried. 5-(2-Amino-pyrimidin-4-yl)-2-phenyl-1*H*-pyrrole-3-carboxylic acid, obtained as a white solid (3.5 g), was used in the next step without further purifications.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.05 (br s, 2H) 7.22 (d, *J*=5.7 Hz, 1H) 7.37–7.48 (m, 4H) 7.63 (dd, *J*=7.9, 1.7 Hz, 2H) 8.24 (d, *J*=5.9 Hz, 1H) 11.99 (br s, 1H) 12.10 (br s, 1H); LCMS (ESI) *m*/*z* 279 $(M-H)^{-}$.

4.2.1.3. Step 3. To a suspension of the acid (4 g, 14.3 mmol) in anhydrous THF (80 mL), DIPEA (5.5 g, 42.9 mmol) and anhydrous DMF (8 mL), cooled in ice bath and under stirring, hydroxybenzotriazole ammonium salt (HOBT·NH_3, 3.26 g, 21.4 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 4.1 g, 21.4 mmol) were added. The reaction mixture was stirred at room temperature overnight then it was poured into a stirred 1:1 mixture of water and EtOAc. The organic phase was washed with water, the aqueous layer was extracted with EtOAc and the combined organic layers were washed with water, dried over anhydrous Na_2SO_4 and concentrated, affording the title compound as a precipitate that was filtered and washed with little cold MeOH. The mother liquor was purified by flash chromatography (DCM/MeOH/acetone 9:1:1), affording the desired amide. The two product batches were combined, yielding the title compound (1.71 g, 43%) as an orange powder, mp 225–228 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.36 (s, 2H) 6.82 (br s, 1H) 7.02 (d, J=5.2 Hz, 1H) 7.27 (d, J=2.6 Hz, 1H) 7.32 (br s, 1H) 7.32–7.37 (m, 1H) 7.37–7.44 (m, 2H) 7.64 (dd, J=8.3, 1.3 Hz, 2H) 8.20 (d, J=5.2 Hz, 1H) 11.63 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 106.2, 116.1, 118.4, 126.2, 126.7 (2C), 127.5, 128.2 (2C), 130.7, 136.5, 157.8, 158.2, 163.4, 167.8; IR 1456, 1480, 1557, 1643, 3117, 3317 ν_{max} cm^{-1}; LCMS (ESI) m/z 280 (M+H)$^+$; HRMS (ESI) calcd for $C_{15}H_{13}N_5O$+H$^+$ 280.1193, found 280.1189.

4.2.2. Ethyl 5-(2-amino-5-chloro-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylate ***3a****.* To ester **1a** (31 mg, 0.1 mmol) in dry DMF (0.5 mL), under argon atmosphere, *N*-chlorosuccinimide (13 mg, 0.1 mmol) was added and the mixture was stirred at 80 °C for 2 h. The reaction mixture was poured into stirred water, the precipitate was filtered, washed thoroughly and dried, yielding the title compound (20 mg, 58%) as an off white solid, mp 171–172 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (t, J=7.1 Hz, 3H) 4.14 (q, J=7.1 Hz, 2H) 6.65 (br s, 2H) 7.39–7.48 (m, 3H) 7.55 (d, J=2.7 Hz, 1H) 7.59–7.66 (m, 2H) 8.30 (s, 1H) 11.70 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 13.8, 59.2, 112.5, 113.2, 116.7, 116.9, 126.6, 127.5, 128.4 (2C), 129.7 (2C), 139.3, 151.6, 158.5, 161.5, 163.6; IR 1456, 1484, 1543, 1560, 1633, 1646, 1702, 3162, 3297, 3419 ν_{max} cm^{-1}; LCMS (ESI) m/z 343 (M+H)$^+$; HRMS (ESI) calcd for $C_{17}H_{15}ClN_4O_2$+H$^+$ 343.0956, found 343.0968.

4.2.3. Ethyl 5-(2-amino-5-bromo-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylate ***4a****.* To ester **1a** (31 mg, 0.1 mmol) in dry DMF (0.5 mL), under argon atmosphere, *N*-bromosuccinimide (18 mg, 0.1 mmol) was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into stirred water, the precipitate was filtered, washed thoroughly and dried. The title compound was obtained (25 mg, 65%) as a white solid, mp 169 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (t, J=7.1 Hz, 3H) 4.14 (q, J=7.1 Hz, 2H) 6.67 (br s, 2H) 7.39–7.48 (m, 3H) 7.59–7.64 (m, 2H) 7.66 (d, J=2.7 Hz, 1H) 8.38 (s, 1H) 11.69 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 13.8, 58.8, 101.0, 113.0, 116.1, 116.3, 127.3 (2C), 127.7, 128.1, 129.3 (2C), 139.4, 153.2, 160.4, 161.9, 163.4; IR 1457, 1481, 1540, 1556, 1635, 1712, 3145, 3293, 3427 ν_{max} cm^{-1}; LCMS (ESI) m/z 387 (M+H)$^+$; HRMS (ESI) calcd for $C_{17}H_{15}BrN_4O_2$+H$^+$ 387.0451, found 387.0457.

4.2.4. Ethyl 5-(2-amino-pyrimidin-4-yl)-4-iodo-2-phenyl-1H-pyrrole-3-carboxylate ***5a****.* To ester **1a** (31 mg, 0.1 mmol) in dry DMF (0.5 mL), under argon atmosphere, *N*-iodosuccinimide (18 mg, 0.08 mmol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was poured into stirred water, the precipitate was filtered, washed thoroughly and dried. The title compound was obtained (27 mg, 64%) as a yellowish solid, mp 136 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.07 (t, J=7.1 Hz, 3H) 4.10 (q, J=7.1 Hz, 2H) 6.56 (br s, 2H) 7.30 (d, J=5.2 Hz, 1H) 7.37–7.49 (m, 5H) 8.32 (d, J=5.2 Hz, 1H) 12.13 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 13.6, 59.5, 67.0, 107.0, 127.7 (2C), 125.9, 128.0, 128.7 (2C), 130.8, 131.1, 138.6, 157.1, 158.3, 163.4, 164.0; IR 1430, 1456, 1563, 1636, 1698, 3141, 3293 ν_{max} cm^{-1}; LCMS (ESI) m/z 435 (M+H)$^+$; HRMS (ESI) calcd for $C_{17}H_{15}IN_4O_2$+H$^+$ 435.0312, found 435.0308.

With similar procedures and starting from amide **1b**, the following compounds were obtained.

4.2.5. 5-(2-Amino-5-chloro-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxamide ***3b****.* 100 °C, 18 h, 72% yield, off white powder, mp 257–260 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 6.62 (br s, 2H), 6.88 (br s, 1H), 7.40 (br s, 1H), 7.33–7.39 (m, 1H), 7.39–7.47 (m, 2H), 7.58 (d, J=2.6 Hz, 1H), 7.63–7.69 (m, 2H), 8.27 (s, 1H), 11.27 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 112.5, 116.1, 118.5, 126.2, 127.8 (2C), 128.1, 129.2 (2C), 131.4, 136.5, 152.2, 158.5, 161.5, 166.2; IR 1442, 1452, 1538, 1557, 1585, 1620,1646, 3166, 3362, 3481 ν_{max} cm^{-1}; LCMS (ESI) m/z 314 (M+H)$^+$; HRMS (ESI) calcd for $C_{15}H_{12}ClN_5O$+H$^+$ 314.0803, found 314.0802.

4.2.6. 5-(2-Amino-5-bromo-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxamide ***4b****.* Room temperature, 18 h, 75% yield, pale yellow powder, mp 229–232 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 6.65 (br s, 2H) 6.89 (br s, 1H) 7.34–7.39 (m, 1H) 7.36 (br s, 1H) 7.39–7.46 (m, 2H) 7.64 (d, J=2.7 Hz, 1H) 7.65–7.69 (m, 2H) 8.35 (s, 1H) 11.27 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 100.5, 115.3, 118.2, 127.0, 127.7 (2C), 128.0, 128.9 (2C), 131.7, 136.1, 153.7, 159.8, 161.8, 166.3; IR 1437, 1455, 1537, 1549, 1600, 1650, 3190, 3309, 3407 ν_{max} cm^{-1}; LCMS (ESI) m/z 358 (M+H)$^+$; HRMS (ESI) calcd for $C_{15}H_{12}BrN_5O$+H$^+$ 358.0298, found 358.0302.

4.2.7. 5-(2-Amino-pyrimidin-4-yl)-4-iodo-2-phenyl-1H-pyrrole-3-carboxamide ***5b****.* Room temperature, 4 h, 72% yield, pale yellow powder, mp 244 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 6.49 (br s, 2H) 7.30 (d, J=5.2 Hz, 1H) 7.33 (t, J=7.4 Hz, 1H) 7.37 (br s, 1H) 7.42 (t, J=7.6 Hz, 2H) 7.54 (s, 1H) 7.64 (dd, J=8.4, 1.2 Hz, 2H) 8.30 (d, J=5.2 Hz, 1H) 11.70 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 66.3, 106.2, 126.2, 126.8 (2C), 127.5, 128.2 (2C), 129.6, 130.7, 132.2, 157.8, 158.2, 163.4, 167.9; IR 1451, 1556, 1570, 1617, 1658, 3174, 3366, 3415 ν_{max} cm^{-1}; LCMS (ESI) m/z 406 (M+H)$^+$; HRMS (ESI) calcd for $C_{15}H_{12}IN_5O$+H$^+$ 406.0159, found 406.0143.

4.2.8. Ethyl 5-(2-amino-5-iodo-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxylate ***6a****.* Ester **1a** (308 mg, 1 mmol) and iodine (279 mg, 1.1 mmol) in dry DMF (2 mL), under a nitrogen atmosphere, stirred at −40 °C were treated dropwise with silver trifluoroacetate (243 mg, 1.1 mmol) in DMF (4 mL). The mixture was stirred at −40 °C for 6 h and then filtered. The filtrate was diluted with EtOAc (150 mL), washed with 10% $Na_2S_2O_3$, dried over sodium sulfate, evaporated and purified by flash chromatography over silica gel (DCM/MeOH 95:5) to give the title compound (220 mg, 50%) as a pale yellow solid, mp 156 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (t, J=7.1 Hz, 3H) 4.14 (q, J=7.1 Hz, 2H) 6.65 (br s, 2H) 7.38–7.48 (m, 3H) 7.60–7.66 (m, 2H) 7.77 (d, 1H) 8.52 (s, 1H) 11.65 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 13.9, 60.0, 71.2, 113.1, 118.0, 127.7 (3C), 128.7 (2C), 128.8, 130.9, 135.5, 156.3, 161.9, 163.3, 166.6; IR 1456, 1480, 1532, 1548, 1636, 1670, 1711, 3158, 3288, 3423 ν_{max} cm^{-1}; LCMS (ESI) m/z 435 (M+H)$^+$; HRMS (ESI) calcd for $C_{17}H_{15}IN_4O_2$+H$^+$ 435.0313, found 435.0319.

4.2.9. 5-(2-Amino-5-iodo-pyrimidin-4-yl)-2-phenyl-1H-pyrrole-3-carboxamide ***6b****.* Amide **1b** (279 mg, 1 mmol) and iodine (267 mg,

1.05 mmol) in dry DMF (2 mL), under a nitrogen atmosphere, stirred at −40 °C (internal temperature) were treated dropwise with silver trifluoroacetate (232 mg, 1.05 mmol) in DMF (3 mL). The mixture was stirred at −40 °C for 24 h and then filtered over a short plug of Celite. The panel was washed with a small amount of DMF and the filtrate was collected in a flask containing 10% aqueous $Na_2S_2O_3$ (25 mL). Precipitation of a pale yellow solid occurred. The solid was filtered and washed with water. By HPLC-MS analysis the crude resulted a mixture of starting material (34%), **5b** (28%) and title compound (38%). Purification by flash chromatography over silica gel (DCM/MeOH 9:1) furnished the title compound (60 mg, 15%) as a pale yellow solid, mp 244 °C.

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 6.66 (br s, 2H) 6.93 (br s, 1H) 7.32 (br s, 1H) 7.34–7.39 (m, 1H) 7.39–7.45 (m, 2H) 7.67 (s, 1H) 7.63–7.69 (m, 2H) 8.51 (s, 1H) 11.30 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 71.8, 114.7, 118.0, 127.7 (3C), 128.7 (2C), 128.8, 131.3, 135.6, 156.3, 161.9, 166.3, 166.6; IR 1441, 1454, 1531, 1546, 1569, 1602, 1646, 3166, 3346, 3472 ν_{max} cm^{-1}; LCMS (ESI) *m*/*z* 406 (M+H)$^+$; HRMS (ESI) calcd for $C_{15}H_{12}IN_5O+H^+$ 406.0160, found 406.0170.

4.2.10. 5-(2-Amino-pyrimidin-4-yl)-4-chloro-2-phenyl-1H-pyrrole-3-carboxamide ***9b****. 4.2.10.1. Step 1.* A solution of amide **1b** (850 mg, 3 mmol), $(Boc)_2O$ (1.7 g, 8 mmol) and DMAP (50 mg, 0.41 mmol) in THF (20 mL) and DMF (1 mL) was stirred at room temperature for 48 h. The mixture was poured into water and the precipitate was filtered. It was dissolved in ethyl acetate, washed with water, dried (anhydrous Na_2SO_4) and concentrated. The residue, composed by a mixture of mono-, di- and tri-Boc derivatives, was purified by flash chromatography (EtOAc/*n*-hexane 9:1) affording the di-Boc derivative **7b** (14%). LCMS (ESI) *m*/*z* 480 (M+H$^+$).

4.2.10.2. Step 2. A solution of amide **7b** (165 mg, 0.34 mmol) and *N*-chlorosuccinimide (46 mg, 0.34 mmol) in DMF (1 mL) was stirred at 100 °C for 2 h. After cooling the mixture was poured into stirred water, extracted with ethyl acetate, washed with water, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography (EtOAc/*n*-hexane 5:1) affording **8b** (45%). LCMS (ESI) *m*/*z* 514 (M+H$^+$).

4.2.10.3. Step 3. To a solution of **8b** (80 mg, 0.15 mmol) in MeOH (1 mL), 4 N HCl in dioxane (3 mL) was added and the mixture was stirred at room temperature for 20 h and then at 50 °C for 1 h. After concentration diethyl ether was added under stirring and the mixture stirred for 30 min. The precipitate was filtered, washed with diethyl ether and dried and the title compound was obtained (38 mg, 82%) as a pale yellow powder, mp 252 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.47 (br s, 2H) 7.16 (d, *J*=5.2 Hz, 1H) 7.31–7.38 (m, 1H) 7.38–7.46 (m, 2H) 7.42 (br s, 1H) 7.60 (br s, 1H) 7.61–7.69 (m, 2H) 8.29 (d, *J*=5.4 Hz, 1H) 11.64 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 105.5, 111.2, 119.4, 124.3, 127.0 (2C), 127.5, 128.0 (2C), 130.9, 131.3, 155.5, 158.3, 163.0, 165.4; IR 1432, 1456, 1546, 1567, 1636, 1672, 3154, 3280, 3378 ν_{max} cm^{-1}; LCMS (ESI) *m*/*z* 314 (M+H)$^+$; HRMS (ESI) calcd for $C_{15}H_{12}ClN_5O+H^+$ 314.0803, found 314.0792.

4.2.11. 5-(2-Amino-5-bromo-pyrimidin-4-yl)-4-iodo-2-phenyl-1H-pyrrole-3-carboxamide ***10b****.* To amide **4b** (243 mg, 0.68 mmol) in DMF (1.5 mL), *N*-iodosuccinimide (160 mg, 0.71 mmol) was added and the mixture was stirred at 50 °C for 4 h, then overnight at rt. The reaction mixture was poured into stirred water, the precipitate was filtered, washed thoroughly and dried. The title compound was obtained as an orange solid (277 mg, 82%).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 6.96 (s, 2H) 7.27–7.32 (m, 1H) 7.33 (br s, 1H) 7.40 (t, *J*=7.8 Hz, 2H) 7.44 (br s, 1H) 7.56 (dd, *J*=8.3, 1.0 Hz, 2H) 8.45 (s, 1H) 12.03 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 67.0, 105.9, 122.8, 126.3 (2C), 127.3, 128.3 (2C), 130.4, 131.0, 131.9, 158.2, 160.0, 162.0, 167.9; IR 1446, 1463, 1539, 1557, 1592, 1634, 3178, 3313, 3399 ν_{max} cm^{-1}; LCMS (ESI) *m*/*z* 484 (M+H)$^+$; HRMS (ESI) calcd for $C_{15}H_{11}BrIN_5O+H^+$ 483.9264, found 483.9260.

4.2.12. 5-(2-Amino-5-bromo-pyrimidin-4-yl)-4-iodo-2-phenyl-1H-pyrrole-3-carboxamide ***10b****.* To amide **5b** (120 mg, 0.3 mmol) in DMF (1.5 mL), *N*-bromosuccinimide (60 mg, 0.34 mmol) was added and the mixture was stirred at room temperature for 15 h. The reaction mixture was poured into stirred water, the precipitate was filtered, washed thoroughly and dried. The title compound was obtained (120 mg, 83%) as a whitish solid, mp 277 °C.

4.2.13. 5-(2-Amino-5-bromo-pyrimidin-4-yl)-4-bromo-2-phenyl-1H-pyrrole-3-carboxamide ***11b****.* To amide **1b** (140 mg, 0.5 mmol) in DMF (1.5 mL), *N*-bromosuccinimide (180 mg, 1 mmol) was added and the mixture was stirred at room temperature for 15 h. The reaction mixture was poured into stirred water, the precipitate was filtered, washed thoroughly and dried. The title compound was obtained (197 mg, 90%) as a yellowish solid, mp 254 °C.

^{1}H NMR (400 MHz, DMSO-d_6): 6.96 (s, 2H) 7.28–7.34 (m, 1H) 7.35 (br s, 1H) 7.41 (t, *J*=7.6 Hz, 2H) 7.48 (br s, 1H) 7.56–7.63 (m, 2H) 8.46 (s, 1H) 12.01 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 96.6, 105.6, 119.4, 126.5, 126.7 (2C), 127.3, 128.3 (2C), 130.4, 130.7, 156.6, 160.3, 161.9, 166.3; IR 1459, 1539, 1556, 1594, 1625, 3174, 3321, 3399 ν_{max} cm^{-1}; LCMS (ESI) *m*/*z* 436 (M+H)$^+$; HRMS (ESI) calcd for $C_{15}H_{11}Br_2N_5O+H^+$ 435.9403, found 435.9396.

With a similar procedure the following compound was obtained.

4.2.14. 5-(2-Amino-5-iodo-pyrimidin-4-yl)-4-iodo-2-phenyl-1H-pyrrole-3-carboxamide ***12b****.* 55 °C, 8 h, 46% yield, white powder, mp 244 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.90 (s, 2H) 7.25–7.32 (m, 1H) 7.29 (br s, 1H) 7.34 (br s, 1H) 7.40 (t, *J*=7.7 Hz, 2H) 7.58 (dd, *J*=8.4, 1.2 Hz, 2H) 8.56 (s, 1H) 11.95 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 65.6, 79.0, 122.9, 126.4 (2C), 126.7, 128.3(2C), 130.3, 131.1, 133.0, 161.8, 162.3, 165.3, 167.5; IR 1437, 1460, 1533, 1550, 1593, 1634, 3178, 3309, 3395 ν_{max} cm^{-1}; LCMS (ESI) *m*/*z* 532 (M+H)$^+$; HRMS (ESI) calcd for $C_{15}H_{11}I_2N_5O+H^+$ 531.9126, found 531.9113.

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