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Synthesis of aminopyrimidylindoles structurally related to meridianins

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Abstract—The synthesis of new meridianin derivatives substituted at the C-5′ position of the 2-aminopyrimidine ring by various aryl groups and substituted or not by a methyl group on the indole nitrogen is described. The 2-aminopyrimidine ring was obtained via a Bredereck synthesis. Aryl groups were introduced by Suzuki cross-coupling after bromination of the 2-aminopyrimidine ring at the C-5′ position.

1. Introduction

Many kinase inhibitors from natural origin are sources of inspiration for the discovery of new biologically active compounds. A large number of nitrogen aromatic heterocycles containing an indole or a carbazole framework exhibit kinase inhibitory properties. Granulatimide and isogranulatimide, carbazoles isolated from the ascidian *Didemnum granulatum*, and structurally related analogs are Checkpoint kinase 1 (Chk1) inhibitors (Fig. 1).[1,2] Purine derivatives like roscovitine and olomoucine, two compounds isolated from starfish oocytes, are potent cyclin-dependent kinase inhibitors.[3] Indirubin, the active ingredient of the Chinese preparation Danggui Longhui Wan used to treat chronic diseases, indirubin derivatives,[4,5] as well as indolocarbazole bacterial metabolites staurosporine,[6,7] UCN-01,[8] and K252-c[9] are also described as potent kinase inhibitors. Synthetic compounds such as bisindolylmaleimides[10] and 4-aryl-3-indolylmaleimides[11,12] are known kinase inhibitors (Fig. 1).

Meridianin alkaloids, which were isolated and characterized from the south atlantic tunicate *Aplidium meridianum*,[13] are indole derivatives substituted at the C-3 position by a 2-aminopyrimidine ring. Meridianins A–G[13–15] (Fig. 1) were described as potent kinase inhibitors[15] and some derivatives displayed antitumor activity.[16]

In the course of the synthesis of new kinase inhibitors, we were interested in meridianin derivatives substituted at the C-5′ position of the 2-aminopyrimidine ring. Various 3-(2-aminopyrimidin-4-yl)-indoles substituted at the C-5′ and C-6′ positions and/or on the amino group of the 2-aminopyrimidine ring have been described in the literature.[16–37] Compounds substituted at C-5′ position by cyano, carbohydrazonamido, carboxy, and methyl groups or by a chlorine or a fluorine atom have previously been reported (Fig. 1).[16,17,19] These recent publications prompted us to report our own results. Substituent at the C-5′ position appeared to be important in terms of biological activity. Indeed, we observed a dramatic increase of kinase inhibitory properties when the C-5′ position of meridianin G was substituted by a bromine atom (Scheme 1 and Table 1). The kinase activities of compounds **3** (meridianin G) and **5** toward eight protein kinases were evaluated by Upstate's kinase profiler screening service (Dundee, Scotland). Both compounds were tested at a compound concentration of 10 μM under standard conditions determined by Upstate[38–40] for each selected kinase (MKK1, ERK2, RSK2, PKC-α, GSK3-β, CDK2/A, CK2, and MST2—Table 1). Compound **5** exhibited a significantly higher inhibitory activity than meridianin G (compound **3**) against all the kinases tested. Indeed, compound **5** inhibits all the kinases tested with percentages of inhibition over 80%, and is particularly potent toward MKK1 and MST2 (percentage of inhibition higher than 95%), whereas the inhibitory properties of compound **3** were found to be much lower, with percentages of inhibition from 9% (RSK2) to 66% (MKK1). These results encouraged us to synthesize meridianin derivatives bearing other substituents at the C-5′ position. Since the late 1980s[11,12] and recently,[41] it was reported that aryl groups at the C-4 position of 3-indolylmaleimides led to compounds exhibiting interesting kinase inhibitory properties. Therefore, we decided to introduce aryl rings at the C-5′ position of the pyrimidine ring of meridianin G. Compounds bearing an aryl group at the C-6′ position were reported,[22,25] but to our knowledge,

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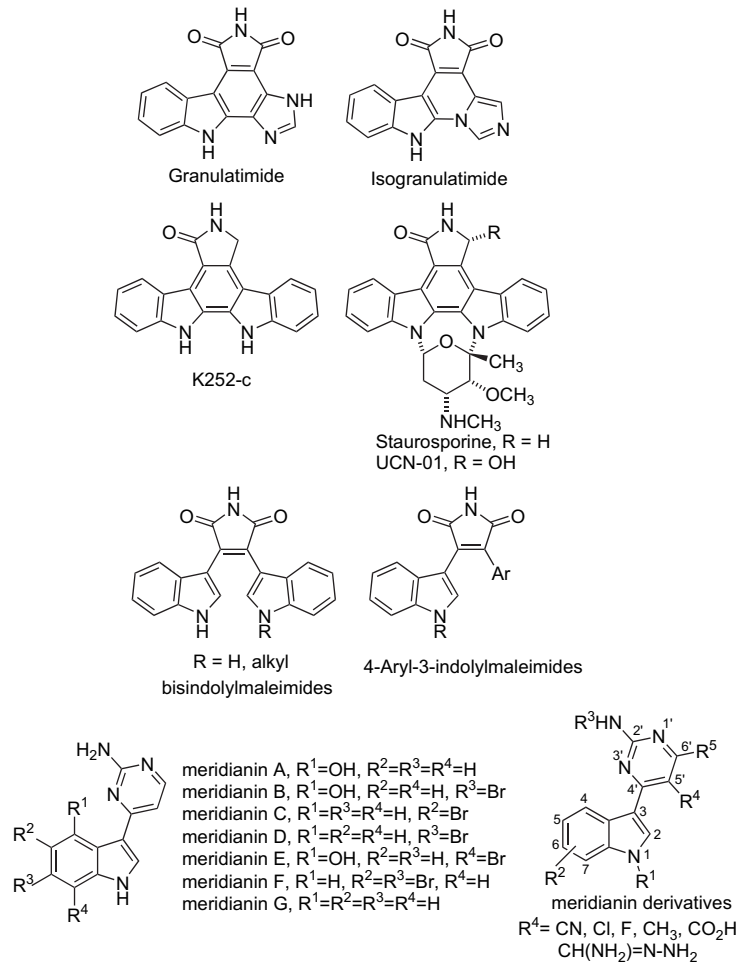
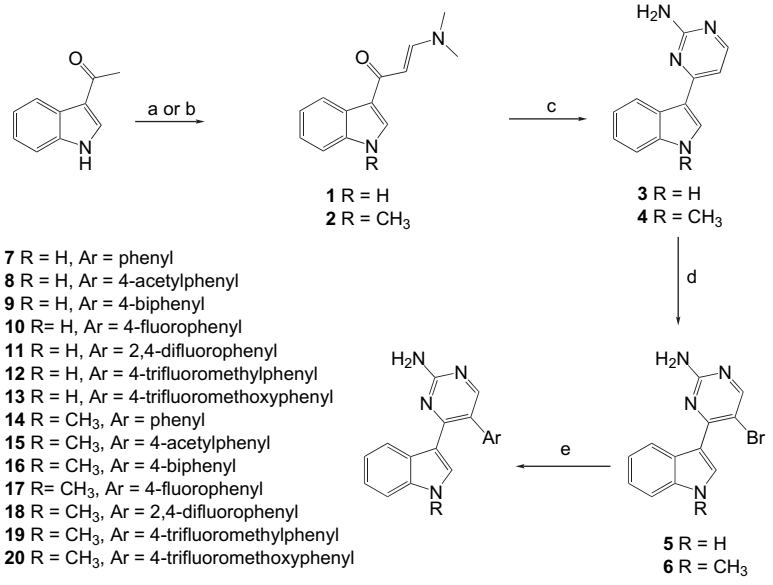


Figure 1. Kinase inhibitors and meridianin derivatives described in the literature.

meridianin derivatives with an aryl group at the C-5′ position have never been described. The replacement of the maleimide ring of 4-aryl-3-indolylmaleimides previously mentioned by the 2-aminopyrimidine ring could reinforce the interaction inside the ATP-binding pocket of the target kinase. To get an insight into the importance of the NH of the indole moiety, we also prepared derivatives substituted on the indole nitrogen with a methyl group. The introduction



Scheme 1. Synthesis of meridianin derivatives. (a) DMF/DMF-di-*tert*-butylacetal, reflux, R=H; (b) DMF/DMF-DMA, reflux, R=CH_3; (c) *iso*-propanol, guanidine, NaOMe, reflux; (d) NBS, THF, 0 °C; (e) $ArB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, EtOH/H_2O/toluene, reflux.

Table 1. Percentage of inhibition of various kinases at a compound concentration of 10 μM, for compounds **3** and **5**

Compound	MKK1	ERK2	RSK2	PKC-α	GSK3-β	CDK2/A	CK2	MST2
3	66	36	9	56	43	54	38	31
5	98	92	85	91	87	85	93	96

MKK1, Mitogen-activated Kinase Kinase 1; ERK2, Extracellular signal-Regulated Kinase 2; RSK2, p90 ribosomal S6 kinase 2; PKC-α, Protein Kinase C-α; GSK3-β, Glycogen Synthase 3-β; CDK2/A, Cyclin-Dependent Kinase 2/cyclin A; CK2, Casein Kinase 2; MST2, Mammalian STE20-like kinase 2.

of an alkyl group at this position could be relevant for biological activity, as it was shown in bisindolylmaleimide series.[10,42]

2. Chemistry

Meridianins have previously been synthesized from indole derivatives. The first of the three reported approaches consisted in a Suzuki cross-coupling with indole-3-boronic acid derivatives.[43] A Bredereck synthesis was also described from β-enaminones, which were, in turn, obtained from 3-acetylindole derivatives.[16,44,45] More recently, meridianins were obtained from trimethylsilylynones indole derivatives.[46] Commercially available 3-acetylindole was the starting point of our synthesis, which gave access to the meridianin analogs **5** and **6** in a straightforward three-step synthesis following the Bredereck approach (Scheme 1).[16,44,45,47] While the reported Bredereck routes started from *N*-tosylated 3-acetylindole, our synthesis was initiated with non-protected 3-acetylindole. This allowed us to obtain both meridianins **5** and **6** with the indole nitrogen methylated or simply protonated without the need for protection–deprotection steps. When 3-acetylindole was treated with DMF/dimethylformamide-dimethylacetal (DMF-DMA),[48] *N*-methylated compound **2** was obtained in 85% yield. Using DMF/dimethylformamide-di-*tert*-butylacetal instead of DMF/DMF-DMA led to compound **1** in 71% yield. When refluxing in toluene/DMF-DMA, compound **1** was obtained in only 24% yield but no *N*-methylated compound **2** was observed. Increasing the reflux temperature by replacement of toluene by xylene led to compound **2** in a poor yield.

The *E* configuration of the enaminone double bond in **1** and **2** was determined by NMR spectrometry. From the coupling constant between the two ethylenic protons (J=12.5 Hz), configuration could not be unambiguously determined. Therefore, a 2D-NOESY NMR experiment was performed on compound **1** (Fig. 2). The similar NOE effects between each two ethylenic protons at 5.77 ppm and 7.53 ppm and the CH_3 groups showed that compound **1** has an *E* configuration. We confirmed the *E* configuration by the measurement of the $^3J(^1H, ^{13}C{=}O)$ coupling constant existing between the ethylenic proton at the β-position relative to the carbonyl group and the ^{13}C of the ketone function. Indeed, the configuration of the double bond of α,β-unsaturated carbonyl compounds can be determined on the basis of this long range heteronuclear coupling constant. The ^3J(H, C) between ^1H and $^{13}C{=}O$ nuclei with a *Z* orientation around the double bond are usually smaller (2–6 Hz) than those with an *E* orientation (8–12 Hz).[49,50] Thus, in our case, the measured ^3J(H, C) value of 4 Hz indicated the *E* configuration for

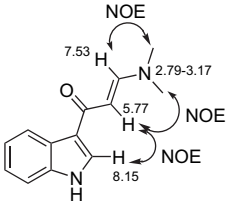


Figure 2. Determination of the configuration of the β-enaminone double bond of compound **1** by 2D-NOESY NMR experiment.

β-enaminone double bond of compound **1**. Surprisingly, in the ^1H NMR spectra of enaminones **1** and **2** in DMSO-d_6 or in $CDCl_3$, the two methyl groups of the β-enaminone moiety appeared as a broad signal between 2.79 ppm and 3.17 ppm for **1** and between 2.85 ppm and 3.09 ppm for **2**. The ^1H and ^{13}C NMR spectra of structurally related compounds[16,45] reported in the literature showed two independent peaks for each methyl of the $N(CH_3)_2$ group (Fig. 3). This suggests that the rotation energy barrier around the ═C–N bond is sufficient to make the *N*-methyl groups magnetically non-equivalent. This high rotation energy could be explained by the partial π character of the C–N bond, part of the conjugated β-enaminone system. In the case of compounds **3** and **4**, the absence of electron-withdrawing protecting group potentially decreases the π character of the C–N bond. This would lower the rotation energy barrier and provoke coalescence of the two CH_3 peaks. Consequently, the two methyl groups of the β-enaminone moiety were not visible on the 1D ^{13}C NMR in DMSO-d_6 or in $CDCl_3$. Nevertheless, ^1H–^{13}C HSQC experiment showed the correlation between these ^1H broad signal and two carbons.

Compounds **1** and **2** were treated with guanidine in *iso*-propanol in the presence of sodium methoxide to give compounds **3** and **4** in 74% and 44% yield, respectively. Meridianins **3** and **4** were then brominated with *N*-bromosuccinimide (NBS) in THF. Compounds **5** and **6** were obtained in 95% and 94% yield, respectively. The electrophilic substitution by the bromine atom was clearly directed to the 5-position of the pyrimidine ring.[51] The position of the bromine atom was unambiguously determined by NMR. ^1H and ^{13}C NMR signals were assigned from 1D and 2D (COSY ^1H–^1H, HSQC ^1H–^{13}C, and HMBC ^1H–^{13}C) experiments. The two aromatic protons of the pyrimidine ring of compound **4** correspond to two doublets at 6.94 ppm for H-5′ and at 8.10 ppm for H-6′. After bromination of **3**, only one singlet corresponding to H-6′ was observed at 8.31 ppm. The ^{13}C NMR spectra of compounds **4** and **6** also show the low field methine carbon corresponding to C-6′ at 157.1 ppm and 159.5 ppm, respectively.

Suzuki cross-couplings were then performed between brominated compound **5** or **6** and substituted phenylboronic

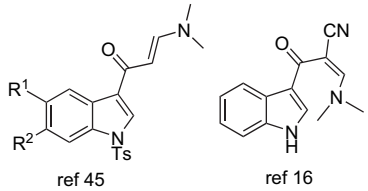


Figure 3. Examples of the literature in which the two methyl groups of $N(CH_3)_2$ appeared as distinct signals in the ^1H NMR spectra.

acids. Phenyl group of boronic acids was variously substituted by either halogen atoms (compounds **10**, **11**, **17**, and **18**), aryl (**9** and **16**), acetyl (**8** and **15**), trifluoromethyl (**12** and **19**), and trifluoromethoxy (**13** and **20**) groups. Couplings were carried out using palladium tetrakis(triphenylphosphine) in a 1:1:1 toluene/EtOH/H_2O mixture in the presence of sodium carbonate,[52] leading to compounds **7**–**20** in 21–60% isolated yields.

3. Conclusion

Encouraging preliminary biological evaluation of brominated derivative **5** led us to synthesize new meridianin derivatives. The synthetic approach described here allowed the substitution at the C-5′ position of the pyrimidine moiety by diversely substituted phenyl rings (compounds **7**–**20**). Moreover, since in bisindolylmaleimide series substitution of the indole nitrogen with an alkyl group led to potent kinase inhibitors, compounds **14**–**20**, substituted on the indole nitrogen by a methyl group, were also prepared. The biological evaluation of compounds **7**–**20** is currently in progress.

4. Experimental

4.1. General

IR spectra were recorded on a Perkin–Elmer Paragon 500 spectrometer ($\overline{\nu}_{max}$ in cm^{-1}). NMR spectra were recorded on a Bruker AVANCE 400 (^1H: 400 MHz, ^{13}C: 100 MHz) or AVANCE 500 (^1H: 500 MHz, ^{13}C: 125 MHz); chemical shifts δ are noted in parts per million and the following abbreviations are used: singlet (s), doublet (d), triplet (t), quadruplet (q), doubled doublet (dd), doublet of doublet of doublet (ddd), doubled triplet (dt), multiplet (m), broad signal (br s). Mass spectra (ESI^+) were recorded on a high resolution Waters Micro Q-Toff apparatus. Chromatographic purifications were performed on flash silica gel Geduran SI 60 (Merck) 0.040–0.063 mm column chromatography. TLC were performed on fluorescent silica gel plates (60 F254 from Merck).

4.2. Synthesis

4.2.1. 3-(3-*N*,*N*-Dimethylamino-1-oxoprop-2-enyl)-1*H*-indole 1. Dimethylformamide-di-*tert*-butylacetal (2.4 mL, 10.0 mmol) was added to a solution of 3-acetylindole (318 mg, 2.0 mmol) in DMF (6 mL) and the solution was refluxed for 48 h. Brine (10 mL) was added to the reaction mixture. After extraction with CH_2Cl_2 (3×10 mL), the combined organic fractions were dried over $MgSO_4$ and concentrated under vacuum. The residue was dissolved in EtOAc (5 mL) and precipitated with cyclohexane (15 mL). The precipitate was collected by filtration and washed with Et_2O (3×10 mL) to give **1** (303 mg, 1.41 mmol, 71% yield) as a pale yellow powder.

Mp 219–221 °C. IR (KBr) 3448, 1630, 1508, 1446, 1416, 1376, 1304, 1284, 1164, 1114, 1095, 1011. MS *m*/*z* (EI) 214 (M^+). ^1H NMR (400 MHz, DMSO-d_6): 2.79–3.17 (6H, br s, CH_3), 5.77 (1H, d, *J*=12.5 Hz), 7.06–7.16 (2H, m), 7.40 (1H, d, *J*=7.5 Hz), 7.53 (1H, d, *J*=12.5 Hz), 8.15 (1H, s), 8.28 (1H, d, *J*=7.5 Hz), 11.53–11.65 (1H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 93.3, 111.6, 120.5, 121.8 (2C), 130.1, 151.0 (CH), 118.0, 126.1, 136.5 (C), 183.5 (C═O).

4.2.2. 1-Methyl-3-(3-*N*,*N*-dimethylamino-1-oxoprop-2-enyl)-1*H*-indole 2. Dimethylformamide-dimethylacetal (45.0 mL, 339 mmol) was added to a solution of 3-acetylindole (5.00 g, 31.4 mmol) in DMF (63 mL) and the solution was refluxed for 24 h. Brine (100 mL) was added to the reaction mixture. After extraction with CH_2Cl_2 (3×100 mL), the combined organic fractions were dried over $MgSO_4$ and concentrated under vacuum. The residue was dissolved in EtOAc (50 mL) and precipitated with cyclohexane (350 mL). The precipitate was collected by filtration and washed with Et_2O (3×20 mL) to give **2** (6.11 g, 26.8 mmol, 85% yield) as a pale yellow powder.

Mp 157–158 °C. IR (KBr) 3448, 1642, 1631, 1552, 1523, 1466, 1368, 1083. MS *m*/*z* (EI) 228 (M^+). ^1H NMR (400 MHz, DMSO-d_6): 2.85–3.09 (6H, br s, CH_3), 3.83 (3H, s, CH_3), 5.71 (1H, d, *J*=12.5 Hz), 7.14 (1H, t, *J*=7.5 Hz), 7.20 (1H, t, *J*=7.0 Hz), 7.46 (1H, d, *J*=8.0 Hz), 7.53 (1H, d, *J*=12.5 Hz), 8.15 (1H, s), 8.28 (1H, d, *J*=8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 32.8 (CH_3), 93.2, 110.0, 120.8, 121.9 (2C), 134.1, 151.0 (CH), 116.9, 126.5, 137.1 (C), 183.0 (C═O).

4.2.3. 3-(2-Aminopyrimidin-4-yl)-1*H*-indole 3. Sodium methoxide (1.48 g, 27.4 mmol) and guanidine hydrochloride (788 mg, 8.25 mmol) were added to a solution of **1** (1.15 g, 5.37 mmol) in *iso*-propanol (6 mL) and the mixture was refluxed for 48 h. Water (25 mL) was added to the reaction mixture. After extraction with EtOAc (3×15 mL), the organic fractions were dried over $MgSO_4$ and concentrated under vacuum. The residue was dissolved in EtOAc (5 mL) and precipitated with cyclohexane (25 mL). The precipitate was collected by filtration and washed with CH_2Cl_2 (3×5 mL) to give **3** (831 mg, 3.95 mmol, 74% yield) as a beige powder.

Spectral data are in agreement with literature data.[16]

4.2.4. 3-(2-Amino-5-bromopyrimidin-4-yl)-1-methyl-1*H*-indole 4. Sodium methoxide (5.79 g, 107 mmol) and guanidine hydrochloride (3.84 g, 40.2 mmol) were added to a solution of **2** (6.11 g, 26.8 mmol) in *iso*-propanol (135 mL) and the mixture was refluxed for 48 h. Water (250 mL) was added to the reaction mixture. After extraction with EtOAc (3×150 mL), the organic fractions were dried over $MgSO_4$ and concentrated under vacuum. The residue was dissolved in EtOAc (20 mL) and precipitated with cyclohexane (250 mL). The precipitate was collected by filtration and washed with CH_2Cl_2 (3×20 mL) to give **4** (2.64 g, 11.8 mmol, 44% yield) as a beige powder.

Mp 191–193 °C. IR (KBr) 3454, 1624, 1576, 1534, 1458, 1219. HRMS (ESI^+) calcd for $C_{13}H_{13}N_4$ $(M+H)^+$ 225.1140, found 225.1130. ^1H NMR (400 MHz, DMSO-d_6): 3.85 (3H, s), 6.37–6.45 (2H, br s, NH_2), 6.94 (1H, d, *J*=5.5 Hz), 7.17 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.24 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.5 Hz), 7.49 (1H, d, *J*=8.0 Hz), 8.10 (1H, d, *J*=5.5 Hz), 8.17 (1H, s), 8.59 (1H, d, *J*=8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 33.0

(CH_3), 105.2, 110.2, 120.6, 122.1, 122.5, 132.2, 157.1 (CH), 112.7, 125.7, 137.5, 162.3, 163.5 (C).

4.2.5. 3-(2-Amino-5-bromopyrimidin-4-yl)-1*H*-indole 5. NBS (372 mg, 2.09 mmol) was added to a solution of **3** (440 mg, 2.09 mmol) in THF (18 mL) and the reaction mixture was stirred at 0 °C for 1.5 h. After evaporation of the solvent, water was added to the reaction mixture and the solid was filtered and washed with water to give **5** (573 mg, 1.98 mmol, 95% yield) as a red powder.

Mp 183–185 °C. IR (KBr) 3483, 1654, 1648, 1638, 1559, 1542, 1520, 1460, 1435. HRMS (ESI^+) calcd for $C_{12}H_{10}{}^{79}BrN_4$ $(M+H)^+$ 289.0089, found 289.0097. ^1H NMR (400 MHz, DMSO-d_6): 6.70–6.80 (2H, br s, NH_2), 7.13 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.20 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.47 (1H, d, J=8.0 Hz), 8.31 (1H, s), 8.48 (1H, d, J=3.0 Hz), 8.54 (1H, d, J=8.0 Hz), 11.72–11.81 (1H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 111.7, 120.4, 122.2, 123.0, 130.1, 160.0 (CH), 102.1, 111.8, 126.3, 136.0, 159.2, 161.8 (C).

4.2.6. 3-(2-Amino-5-bromopyrimidin-4-yl)-1-methyl-1*H*-indole 6. NBS (1.15 g, 6.46 mmol) was added to a solution of **4** (1.45 g, 6.46 mmol) in THF (65 mL) and the reaction mixture was stirred at 0 °C for 2 h. Diethylether (100 mL) was added to the reaction mixture and the resulting precipitate was collected by filtration and washed with Et_2O to give **6** (1.84 g, 6.07 mmol, 94% yield) as a brown powder.

Mp 211–213 °C. IR (KBr) 3479, 1630, 1561, 1531, 1513, 1450, 1370. HRMS (ESI^+) calcd for $C_{13}H_{12}{}^{79}BrN_4$ $(M+H)^+$ 303.0245, found 303.0228. ^1H NMR (400 MHz, DMSO-d_6): 3.90 (3H, s, N–CH_3), 6.68–6.92 (2H, br s, NH_2), 7.18 (1H, t, J=7.5 Hz), 7.27 (1H, t, J=7.5 Hz), 7.52 (1H, d, J=8.0 Hz), 8.31 (1H, s), 8.53 (1H, s), 8.59 (1H, d, J=8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 32.8 (N–CH_3), 109.8, 120.5, 122.1, 123.0, 133.9, 159.5 (CH), 101.6, 110.5, 126.5, 136.3, 158.7, 161.4 (C).

4.2.7. General procedure for the preparation of compounds 7–20. A solution of Na_2CO_3 (2.5 equiv) in H_2O (2 mL/mmol) was added to a suspension of **6**, the required boronic acid (1.1 equiv) and $Pd(PPh_3)_4$ (5 mol%) in EtOH (2 mL/mmol), and toluene (2 mL/mmol). The resulting mixture was refluxed for 12 h under argon. The reaction mixture was extracted with $CHCl_3$ (3×20 mL) and the combined organic layers were washed with H_2O (10 mL), 0.5 N aqueous NaOH (10 mL), H_2O (10 mL), and brine (10 mL), and then dried over $MgSO_4$ and concentrated under vacuum.

4.2.8. 3-(2-Amino-5-phenylpyrimidin-4-yl)-1*H*-indole 7. Compound **7** was prepared according to the above general procedure, starting from **5** (289 mg, 1.00 mmol). The residue was dissolved in Et_2O (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was collected by filtration and further purified by flash chromatography (EtOAc/cyclohexane 8:2). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was filtered to give **7** (59 mg, 21% yield) as a beige powder.

Mp 226–228 °C. IR (KBr) 3420, 3316, 1648, 1576, 1528, 1474. HRMS (ESI^+) calcd for $C_{18}H_{15}N_4$ $(M+H)^+$ 287.1297, found 287.1299. ^1H NMR (400 MHz, DMSO-d_6): 6.54–6.59 (2H, br s, NH_2), 6.60 (1H, d, J=3.0 Hz), 7.06 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.12 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.5 Hz), 7.27–7.31 (2H, m), 7.32–7.43 (4H, m), 8.00 (1H, s), 8.45 (1H, d, J=8.0 Hz), 11.24–11.30 (1H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 111.4, 120.0, 121.9, 122.8, 127.1, 128.8 (3C), 129.5 (2C), 157.9 (CH), 112.8, 121.0, 126.2, 135.8, 139.0, 159.9, 162.5 (C).

4.2.9. 3-(2-Amino-5-(4-acetylphenyl)pyrimidin-4-yl)-1*H*-indole 8. Compound **8** was prepared according to the above general procedure, starting from **5** (289 mg, 1.00 mmol). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was collected by filtration and further purified by flash chromatography (EtOAc/cyclohexane 8:2). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was filtered to give **8** (90 mg, 27% yield) as a pale yellow powder.

Mp 221–222 °C. IR (KBr) 3502, 3313, 1676, 1627, 1603, 1584, 1529, 1508, 1458, 1269, 1242. HRMS (ESI^+) calcd for $C_{20}H_{17}N_4O$ $(M+H)^+$ 329.1402, found 329.1403. ^1H NMR (400 MHz, DMSO-d_6): 2.59 (3H, s, CH_3), 6.67–6.74 (2H, br s, NH_2), 6.74 (1H, d, J=3.0 Hz), 7.05 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.13 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.5 Hz), 7.35 (1H, d, J=8.0 Hz), 7.44 (2H, d, J=8.5 Hz), 7.96 (2H, d, J=8.5 Hz), 8.07 (1H, s), 8.33 (1H, d, J=8.0 Hz), 11.26–11.34 (1H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 26.7 (CH_3), 111.5, 120.1, 122.0, 122.5, 128.6 (2C), 128.9, 129.6 (2C), 158.1 (CH), 112.6, 120.1, 126.0, 128.9, 135.2, 135.9, 144.1, 159.9, 162.7 (C), 197.5 (C=O).

4.2.10. 3-(2-Amino-5-(4-biphenyl)pyrimidin-4-yl)-1*H*-indole 9. Compound **9** was prepared according to the above general procedure, starting from **5** (289 mg, 1.00 mmol). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The solid was collected by filtration and further purified by flash chromatography (EtOAc/cyclohexane 8:2). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was filtered to give **9** (178 mg, 49% yield) as a beige powder.

Mp 240–242 °C. IR (KBr) 3474, 3406, 1630, 1576, 1528, 1457. HRMS (ESI^+) calcd for $C_{24}H_{19}N_4$ $(M+H)^+$ 363.1610, found 363.1606. ^1H NMR (400 MHz, DMSO-d_6): 6.58–6.64 (2H, br s, NH_2), 6.75 (1H, d, J=3.0 Hz), 7.07 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1,0 Hz), 7.13 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1,5 Hz), 7.35 (d, 1H, J=8.0 Hz), 7.36–7.40 (3H, m), 7.48 (2H, t, J=7.5 Hz), 7.70–7.75 (4H, m), 8.06 (1H, s), 8.47 (1H, d, J=8.0 Hz), 11.27–11.33 (1H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 111.5, 120.0, 121.9, 122.8, 126.5 (2C), 126.9 (2C), 127.5, 128.9, 129.0 (2C), 130.0 (2C), 158.0 (CH), 112.8, 120.6, 126.2, 135.8, 138.1, 138.6, 139.5, 160.0, 162.6 (C).

4.2.11. 3-(2-Amino-5-(4-fluorophenyl)pyrimidin-4-yl)-1*H*-indole 10. Compound **10** was prepared according to the above general procedure, starting from **5** (289 mg,

1.00 mmol). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was collected by filtration and further purified by flash chromatography (EtOAc/cyclohexane 8:2). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was filtered to give **10** (141 mg, 46% yield) as a pale yellow powder.

Mp 232–234 °C. IR (KBr) 3410, 1585, 1526, 1458, 1426, 1209. HRMS (ESI$^+$) calcd for $C_{18}H_{14}FN_4$ (M+H)$^+$ 305.1202, found 305.1204. ^{1}H NMR (400 MHz, DMSO-d_6): 6.56–6.62 (2H, br s, NH_2), 6.65 (1H, d, J=3.0 Hz), 7.05 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.12 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.5 Hz), 7.19–7.26 (2H, m), 7.29–7.37 (3H, m), 8.01 (1H, s), 8.40 (1H, d, J=8.0 Hz), 11.25–11.34 (1H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 111.5, 115.7 (d, J_{CF}=21 Hz), 120.1, 122.0, 122.7, 128.8, 131.5 (d, J_{CF}=8 Hz), 158.1 (CH), 112.8, 120.0, 126.2, 135.2 (d, J_{CF}=3 Hz), 135.8, 160.1, 161.5 (d, J_{CF}=243 Hz), 162.6 (C).

4.2.12. 3-(2-Amino-5-(2,4-difluorophenyl)pyrimidin-4-yl)-1*H*-indole 11. Compound **11** was prepared according to the above general procedure, starting from **5** (289 mg, 1.00 mmol). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was collected by filtration and further purified by flash chromatography (EtOAc/cyclohexane 8:2). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was filtered to give **11** (110 mg, 34% yield) as a beige powder.

Mp 222–224 °C. IR (KBr) 3509, 3409, 1607, 1587, 1530, 1458, 1423, 1138. HRMS (ESI$^+$) calcd for $C_{18}H_{13}F_2N_4$ (M+H)$^+$ 323.1108, found 323.1104. ^{1}H NMR (400 MHz, DMSO-d_6): 6.64 (1H, d, J=3.0 Hz), 6.67–6.73 (2H, br s, NH_2), 7.09 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.14 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.5 Hz), 7.20 (1H, dt, $J_{1,\ CH+CF}$=8.5 Hz, J_2=2.5 Hz), 7.31 (1H, dt, $J_{1,\ CF}$=9.5 Hz, J_2=2.5 Hz), 7.36 (1H, d, J=8.0 Hz), 7.45 (1H, dt, J_1=8.5 Hz, $J_{2,\ CF}$=7.0 Hz), 8.01 (1H, s), 8.52 (1H, d, J=8.0 Hz), 11.24–11.36 (1H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 104.5 (t, J=26 Hz), 111.5, 112.2 (dd, J_{CF1}=21 Hz, J_{CF2}=4 Hz), 120.1, 122.1, 122.9, 127.6, 133.2 (dd, J_{CF1}=10 Hz, J_{CF2}=4 Hz), 158.5 (CH), 112.9, 113.3, 122.8 (dd, J_{CF1}=17 Hz, J_{CF2}=4 Hz), 126.1, 135.9, 159.6 (dd, J_{CF1}=246 Hz, J_{CF2}=12 Hz), 160.7, 162.0 (dd, J_{CF1}=247 Hz, J_{CF2}=12 Hz), 163.0 (C).

4.2.13. 3-(2-Amino-5-(4-trifluoromethylphenyl)pyrimidin-4-yl)-1*H*-indole 12. Compound **12** was prepared according to the above general procedure, starting from **5** (289 mg, 1.00 mmol). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was collected by filtration and further purified by flash chromatography (EtOAc/cyclohexane 8:2). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was filtered to give **12** (106 mg, 30% yield) as a pale yellow powder.

Mp 125–127 °C. IR (KBr) 3484, 3365, 1636, 1615, 1585, 1528, 1464, 1439, 1323, 1172, 1107, 1068. HRMS (ESI$^+$) calcd for $C_{19}H_{14}F_3N_4$ (M+H)$^+$ 355.1171, found 355.1168. ^{1}H NMR (400 MHz, DMSO-d_6): 6.68–6.75 (2H, br s, NH_2), 6.72 (1H, d, J=3.0 Hz), 7.05 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.13 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.5 Hz), 7.35 (1H, dt, J_1=8.0 Hz, J_2=1.0 Hz), 7.52 (2H, d, J=8.0 Hz), 7.72 (2H, d, J=8.0 Hz), 8.09 (1H, s), 8.29 (1H, d, J=8.0 Hz), 11.30–11.37 (1H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 111.5, 120.0, 122.0, 122.4, 125.5 (2C, q, J_{CF}=4 Hz), 128.9, 130.2 (2C), 158.3 (CH), 112.5, 119.7, 124.4 (q, J_{CF}=272 Hz), 126.0, 127.3 (q, J_{CF}=32 Hz), 135.9, 143.3, 159.9, 162.8 (C).

4.2.14. 3-(2-Amino-5-(4-trifluoromethoxyphenyl)pyrimidin-4-yl)-1*H*-indole 13. Compound **12** was prepared according to the above general procedure, starting from **5** (289 mg, 1.00 mmol). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was collected by filtration and further purified by flash chromatography (EtOAc/cyclohexane 8:2). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was filtered to give **13** (106 mg, 29% yield) as a pale yellow powder.

Mp 104–106 °C. IR (KBr) 3485, 3372, 1627, 1583, 1535, 1464, 1254, 1161. HRMS (ESI$^+$) calcd for $C_{19}H_{14}F_3N_4O$ (M+H)$^+$ 371.1120, found 371.1105. ^{1}H NMR (400 MHz, DMSO-d_6): 6.63–6.67 (2H, br s, NH_2), 6.70 (1H, d, J=3.0 Hz), 7.04 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.12 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.5 Hz), 7.33–7.43 (5H, m), 8.06 (1H, s), 8.31 (1H, d, J=8.0 Hz), 11.32–11.39 (1H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 111.5, 120.0, 121.3 (2C), 121.9, 122.5, 128.7, 131.3 (2C), 158.1 (CH), 112.7, 119.7, 120.1 (q, J_{CF}=256 Hz), 126.0, 135.9, 138.3, 147.4 (q, J_{CF}=2 Hz), 159.9, 162.7 (C).

4.2.15. 3-(2-Amino-5-phenylpyrimidin-4-yl)-1-methyl-1*H*-indole 14. Compound **14** was prepared according to the above general procedure, starting from **6** (306 mg, 1.01 mmol). The residue was dissolved in EtOAc (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was collected by filtration and washed with Et_2O (3×2 mL) to give **14** (133 mg, 0.443 mmol, 44% yield) as a pale yellow powder.

Mp 210–212 °C. IR (KBr) 3489, 1625, 1583, 1528, 1459, 1370. HRMS (ESI$^+$) calcd for $C_{19}H_{17}N_4$ (M+H)$^+$ 301.1453, found 301.1438. ^{1}H NMR (400 MHz, DMSO-d_6): 3.58 (3H, s, CH_3–N), 6.56–6.60 (2H, br s, NH_2), 6.63 (1H, d, J=3.0 Hz), 7.07 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.18 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.26–7.30 (2H, m), 7.35–7.42 (4H, m), 8.02 (1H, s), 8.32 (1H, d, J=8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 32.8 (CH_3–N), 109.8, 120.2, 121.9, 122.8, 127.1, 128.8 (2C), 129.3 (2C), 132.6, 158.1 (CH), 112.1, 121.0, 126.5, 136.4, 138.7, 159.5, 162.5 (C).

4.2.16. 3-(2-Amino-5-(4-acetylphenyl)pyrimidin-4-yl)-1-methyl-1*H*-indole 15. Compound **15** was prepared according to the above general procedure, starting from **6** (289 mg, 0.95 mmol). The residue was dissolved in EtOAc (2 mL) and Et_2O (25 mL) was added. The resulting precipitate was collected by filtration and washed with Et_2O (3×2 mL) to give **15** (192 mg, 0.56 mmol, 59% yield) as an orange powder.

Mp 201–203 °C. IR (KBr) 3402, 1654, 1578, 1528, 1508, 1478, 1459, 1364. HRMS (ESI^+) calcd for $C_{21}H_{19}N_4O$ $(M+H)^+$ 343.1559, found 343.1566. ^1H NMR (400 MHz, DMSO-d_6): 2.59 (3H, s, CH_3), 3.63 (3H, s, N–CH_3), 6.68–6.74 (2H, br s, NH_2), 6.85 (1H, s), 7.05 (1H, t, J=7.5 Hz), 7.18 (1H, t, J=7.5 Hz), 7.41 (1H, d, J=8.5 Hz), 7.44 (2H, d, J=8.0 Hz), 7.94 (2H, d, J=8.0 Hz), 8.09 (1H, s), 8.16 (1H, d, J=8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 26.7 (CH_3), 32.8 (CH_3–N), 109.9, 120.2, 122.0, 122.4, 128.6 (2C), 129.3 (2C), 132.7, 158.4 (CH), 111.9, 120.0, 126.3, 135.1, 136.5, 143.7, 159.4, 162.7 (C), 197.5 (C═O).

4.2.17. 3-(2-Amino-5-(4-biphenyl)pyrimidin-4-yl)-1-methyl-1*H*-indole 16. Compound **16** was prepared according to the above general procedure, starting from **6** (289 mg, 0.95 mmol). The residue was dissolved in EtOAc (2 mL) and Et_2O (25 mL) was added. The resulting precipitate was collected by filtration and washed with Et_2O (3×2 mL) to give **16** (168 mg, 0.45 mmol, 47% yield) as an orange powder.

Mp 210–212 °C. IR (KBr) 3490, 1624, 1578, 1528, 1478, 1459, 1364. HRMS (ESI^+) calcd $C_{25}H_{21}N_4$ $(M+H)^+$ 377.1766, found 377.1747. ^1H NMR (400 MHz, DMSO-d_6): 3.60 (3H, s, N–CH_3), 6.60–6.65 (2H, br s, NH_2), 6.82 (1H, s), 7.07 (1H, t, J=7.5 Hz), 7.18 (1H, t, J=7.5 Hz), 7.35–7.42 (4H, m), 7.48 (2H, t, J=7.5 Hz), 7.68–7.74 (4H, m), 8.09 (1H, s), 8.31 (1H, d, J=8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 32.8 (N–CH_3), 109.9, 120.2, 121.9, 122.8, 126.5 (2C), 126.9 (2C), 127.5, 129.0 (2C), 129.8 (2C), 132.7, 158.3 (CH), 112.1, 120.5, 126.5, 136.5, 137.8, 138.6, 139.6, 159.5, 162.5 (C).

4.2.18. 3-(2-Amino-5-(4-fluorophenyl)pyrimidin-4-yl)-1-methyl-1*H*-indole 17. Compound **17** was prepared according to the above general procedure, starting from **6** (289 mg, 0.95 mmol). The residue was dissolved in EtOAc (2 mL) and Et_2O (25 mL) was added. The resulting precipitate was collected by filtration and washed with Et_2O (3×2 mL) to give **17** (156 mg, 0.49 mmol, 52% yield) as a pale brown powder.

Mp 222–224 °C; IR (KBr) 3489, 1629, 1581, 1535, 1478, 1460. HRMS (ESI^+) calcd for $C_{19}H_{16}FN_4$ $(M+H)^+$ 319.1359, found 319.1359. ^1H NMR (400 MHz, DMSO-d_6): 3.63 (3H, s, N–CH_3), 6.58–6.64 (2H, br s, NH_2), 6.72 (1H, s), 7.07 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.16–7.24 (3H, m), 7.28–7.33 (2H, m), 7.40 (1H, d, J=8.0 Hz), 8.03 (1H, s), 8.28 (1H, d, J=8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 32.8 (N–CH_3), 109.9, 115.7 (d, J_{CF}=21 Hz), 120.2, 122.0, 122.7, 131.3 (d, J_{CF}=8 Hz), 132.6, 158.3 (CH), 112.0, 120.0, 126.4, 134.9 (d, J_{CF}=3 Hz), 136.5, 159.6, 161.4 (d, J_{CF}=244 Hz), 162.6 (C).

4.2.19. 3-(2-Amino-5-(2,4-difluorophenyl)pyrimidin-4-yl)-1-methyl-1*H*-indole 18. Compound **18** was prepared according to the above general procedure, starting from **6** (289 mg, 0.95 mmol). The residue was dissolved in EtOAc (2 mL) and Et_2O (25 mL) was added. The resulting precipitate was collected by filtration and washed with Et_2O (3×2 mL) to give **18** (68 mg, 0.202 mmol, 21% yield) as a pale yellow powder.

Mp >235 °C. IR (KBr) 3490, 1629, 1583, 1542, 1534, 1478, 1459. HRMS (ESI^+) calcd for $C_{19}H_{15}F_2N_4$ $(M+H)^+$ 337.1265, found 337.1258. ^1H NMR (500 MHz, DMSO-d_6): 3.63 (3H, s, N–CH_3), 6.67 (1H, s), 6.69–6.75 (2H, br s, NH_2), 7.12 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.17–7.23 (2H, m), 7.29 (1H, dt, $J_{1,CF}$=9.5 Hz, J_2=2.5 Hz), 7.41 (1H, d, J=8.0 Hz), 7.44 (1H, dt, J_1=8.5 Hz, $J_{2,CF}$=7.0 Hz), 8.01 (1H, s), 8.45 (1H, d, J=8.0 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): 32.8 (N–CH_3), 104.5 (t, J_{CF}=26 Hz), 109.9, 112.2 (dd, J_{CF1}=21 Hz, J_{CF2}=3 Hz), 120.4, 122.1, 122.9, 131.5, 133.1 (dd, J_{CF1}=10 Hz, J_{CF2}=4 Hz), 158.8 (CH), 112.2, 113.4, 122.6 (dd, J_{CF1}=16 Hz, J_{CF2}=4 Hz), 126.4, 136.5, 159.5 (dd, J_{CF1}=246 Hz, J_{CF2}=12 Hz), 160.3, 162.0 (dd, J_{CF1}=246 Hz, J_{CF2}=12 Hz), 163.0 (C).

4.2.20. 3-(2-Amino-5-(4-trifluoromethylphenyl)pyrimidin-4-yl)-1-methyl-1*H*-indole 19. Compound **19** was prepared according to the above general procedure, starting from **6** (289 mg, 0.95 mmol). The residue was dissolved in Et_2O (2 mL) and cyclohexane (25 mL) was added. The resulting precipitate was collected by filtration and washed with cyclohexane (3×2 mL) to give **19** (105 mg, 0.285 mmol, 30% yield) as a pale orange powder.

Mp 185–187 °C. IR (KBr) 3449, 1637, 1582, 1542, 1528, 1478, 1466, 1323, 1107. HRMS (ESI^+) calcd for $C_{20}H_{16}N_4F_3$ $(M+H)^+$ 369.1327, found 369.1317. ^1H NMR (400 MHz, DMSO-d_6): 3.64 (3H, s, N–CH_3), 6.68–6.76 (2H, br s, NH_2), 6.87 (1H, s), 7.04 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.17 (1H, ddd, J_1=8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.41 (1H, d, J=8.0 Hz), 7.51 (2H, d, J=8.0 Hz), 7.69 (2H, d, J=8.0 Hz), 8.07 (1H, d, J=8.0 Hz), 8.12 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6): 32.8 (CH_3–N), 110.0, 120.2, 122.0, 122.3, 125.5 (2C, q, J_{CF}=4 Hz), 129.9 (2C), 132.7, 158.6 (CH), 111.9, 119.7, 124.4 (q, J_{CF}=272 Hz), 126.2, 127.3 (q, J_{CF}=32 Hz), 136.6, 143.1, 159.5, 162.7 (C).

4.2.21. 3-(2-Amino-5-(4-trifluoromethoxyphenyl)pyrimidin-4-yl)-1-methyl-1*H*-indole 20. Compound **20** was prepared according to the above general procedure, starting from **6** (289 mg, 0.95 mmol). The residue was dissolved in EtOAc (2 mL) and Et_2O (25 mL) was added. The resulting precipitate was collected by filtration and washed with Et_2O (3×2 mL) to give **20** (218 mg, 0.57 mmol, 60% yield) as a brown powder.

Mp 183–185 °C. IR (KBr) 3487, 1624, 1526, 1476, 1456, 1258, 1217, 1195, 1178. HRMS (ESI^+) calcd for $C_{20}H_{16}F_3N_4O$ $(M+H)^+$ 385.1276, found 385.1273. ^1H NMR (400 MHz, DMSO-d_6): 3.63 (3H, s, N–CH_3), 6.62–6.68 (2H, br s, NH_2), 6.75 (1H, s), 7.04 (1H, t, J=7.5 Hz), 7.18 (1H, t, J=7.5 Hz), 7.34–7.42 (5H, m), 8.09 (1H, s), 8.13 (1H, d, J=8.0 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 32.7 (N–CH_3), 109.9, 120.2, 121.4 (2C), 121.9, 122.4, 131.2 (2C), 132.6, 158.3 (CH), 112.0, 119.6, 120.1 (q, J=256 Hz), 126.2, 136.5, 138.1, 147.4 (q, J_{CF}=2 Hz), 159.5, 162.6 (C).

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