Palladium-Catalyzed Cross-Couplings of Lithium Arylzincates with Aromatic Halides: Synthesis of Analogues of Isomeridianin G and Evaluation as GSK-3β Inhibitors

Anne Seggio,[a,b] Ghislaine Priem,[b] Floris Chevallier,[a] Florence Mongin*[a]

[a] Chimie et Photonique Moléculaires, UMR CNRS 6510, Université de Rennes 1, Bâtiment 10A, Case 1003, Campus Scientifique de Beaulieu, 35042 Rennes Cedex, France
Fax +33(2)23236955; E-mail: florence.mongin@univ-rennes1.fr

[b] GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow CM19 5AW, UK

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Abstract: Several analogues of isomeridianin G have been synthesized using palladium-catalyzed cross-coupling reactions of lithium triorganozincates as a key step. The latter have been prepared by deprotonative lithiation followed by transmetalation using $ZnCl_2$·TMEDA (0.33 equiv).

Key words: cross-coupling, heterocycles, palladium, zinc, lithium

The importance of heterobiaryls in compounds of biological interest have stimulated tremendous efforts for the development of synthetic methods in the area of aryl–aryl bond formation.[1] Like the Suzuki–Miyaura[2] and Stille[3] reactions, the Negishi[4] cross-couplings between organozincs and aryl halides are known to tolerate numerous functional groups. When compared with the first reactions, the latter become attractive when heteroaryl boronic acids cannot be prepared; furthermore they do not require highly toxic starting materials.

The organozincs are often prepared by reacting the corresponding lithium or magnesium compounds with zinc halides.[5] A drawback of the Negishi coupling procedure lies in the fact that anhydrous zinc chloride or zinc bromide is required.

Miller and Farrell reported the use of a catalytic amount of zinc chloride to perform nickel- or palladium-catalyzed couplings of aryl Grignard reagents with aryl halides.[6] Other studies avoided the use of a zinc salt by generating lithium zincates either by iodine–metal exchange[7] or by deprotonation.[8] In 2002, Gauthier and co-workers documented an approach through lithium zincates using only one third equivalent of zinc chloride for the synthesis of 5-aryl-2-furaldehydes from 5-lithio-2-furaldehyde diethyl acetal.[9] In addition, Mutule and Suma described in 2005 a one-pot Grignard formation–transmetalation–Negishi reactions using the less hygroscopic TMEDA-chelated zinc chloride.[10]

We have recently published palladium-catalyzed Negishi reactions[11] for which the lithium triarylzincates were generated by transmetalation of the corresponding lithio compounds using $ZnCl_2$·TMEDA.[12] Herein, we report the whole study, as well as the use of the deprotonation–transmetalation–coupling sequence as a key step for the synthesis of molecules of biological interest.

For this present study, numerous lithioaromatics obtained by deprotonation were transmetalated using 0.33 equivalent of $ZnCl_2$·TMEDA. The lithium triarylzincates generated were then involved in cross-coupling reactions with aromatic halides using catalytic amounts of palladium(II) chloride and 1,1′-bis(diphenylphosphino)ferrocene (dppf) (2 mol% each).[13]

Diverse 4-substituted bromobenzenes[14] were used (Table 1). Thiophene was lithiated using butyllithium in tetrahydrofuran (THF) at –75 °C,[15] before the transmetalation step to generate lithium tri(2-thienyl)zincate. The subsequent palladium-catalyzed cross-coupling was performed with 4-bromoanisole, 4-bromonitrobenzene, methyl 4-bromobenzoate, and 4-bromobenzonitrile at 55 °C to afford the corresponding derivatives **1a–d** in yields ranging from 10%[16] to 79% (entries 1–4). It was noticed that reactions performed with the corresponding chlorobenzenes, which have higher carbon–halogen bond dissociation energies,[17] failed. *N*-Boc-indole was deprotonated upon treatment with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF at –90 °C,[18,19] and then treated similarly to provide the expected substituted *N*-Boc-2-phenylindoles **2a–c** (entries 5–7). These conditions also proved suitable for the functionalization of 5-fluoro and 5-bromo *N*-Boc-indoles (compounds **3**, **4a**,**b**, entries 8–10).

Activated heteroaryl chlorides[20] were also used to prepare bis(heterocycles) (Table 2). The 2-lithiobenzo[*b*]furan derivative was prepared using butyllithium in THF at –15 °C,[21] and converted to the corresponding lithium arylzincate. Subsequent cross-coupling with 2,4-dichloropyrimidine and 2-chloropyridine provided the expected bis(heterocycles) **5a**,**b** in satisfying yields (entries 1,2).[22,23] The furylpyrimidine **6** was prepared similarly (entry 3).[24] Benzo[*b*]thiophene, thiophene, and 2-chlorothiophene were deprotonated using butyllithium at –75 °C,[15] and the lithio derivatives gave the corresponding coupled products **7a**,**b**, **1e**, and **8** (entries 4–7). *N*-Boc-pyrrole was deprotonated upon treatment with LiTMP in THF at –75 °C[25] to give the pyrimidyl and pyridyl derivatives **9a**,**b** after subsequent transmetalation-coupling reactions (entries 8,9). The syntheses of the 2-indolylpyridine **2e**

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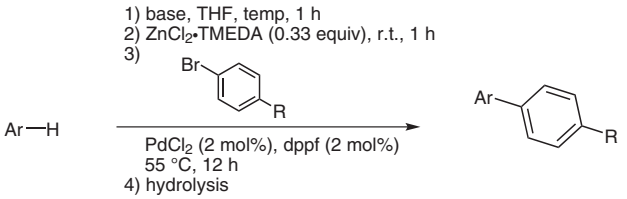
and -pyrimidines **2d**,**10**–**13** were performed from different 2-lithiated *N*-Boc-indoles generated by deprotonation using LiTMP at –90 °C (entries 10–15). Anisole was similarly *ortho*-functionalized after direct lithiation at 25 °C[26] to afford the 2-pyridyl derivative **14** (entry 16). The reaction also proved convenient for the functionalization of a π-deficient substrate, 2-fluoropyridine, which was converted into the unsymmetrical bipyridine **15** (entry 10) after lithiation using LiTMP in THF at –75 °C,[27] followed by transmetalation and cross-coupling steps.

Table 1 Coupling Reactions of Lithium Triarylzincates with Substituted Phenyl Bromides



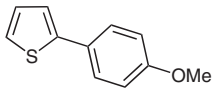
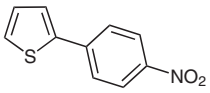
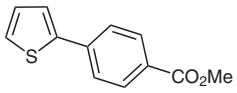
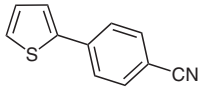
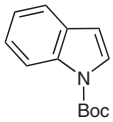
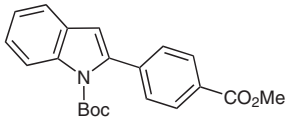
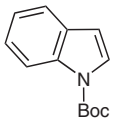
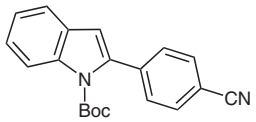
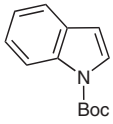
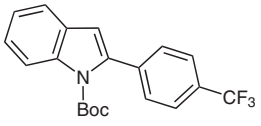
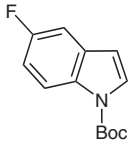
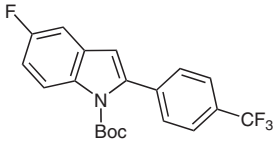
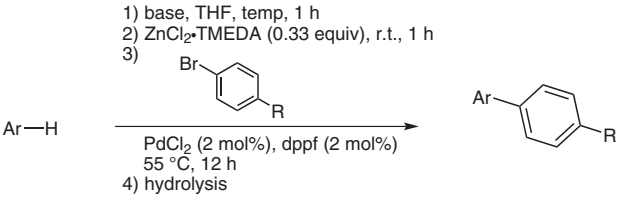
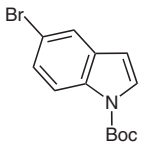
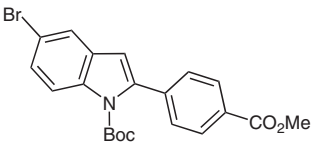
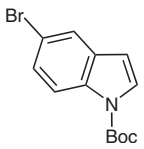
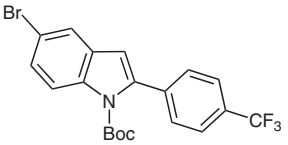
Entry	Substrate	Base, Temp (°C)	Product	Yield (%)
1		BuLi, –75	 **1a**	10
2		BuLi, –75	 **1b**	38 76[a]
3		BuLi, –75	 **1c**	41
4		BuLi, –75	 **1d**	79
5		LiTMP, –90	 **2a**	48
6		LiTMP, –90	 **2b**	61
7		LiTMP, –90	 **2c**	60
8		LiTMP, –90	 **3**	36

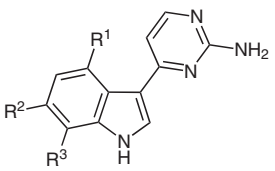
Table 1 Coupling Reactions of Lithium Triarylzincates with Substituted Phenyl Bromides (continued)



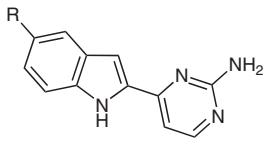
Entry	Substrate	Base, Temp (°C)	Product	Yield (%)
9		LiTMP, –90	 **4a**	66
10		LiTMP, –90	 **4b**	31

[a] Coupling step performed in the presence of DME (5 equiv).[14g]

Meridianins are a family of compounds isolated and characterized from the south atlantic tunicate *Aplidium meridianum*.[28] Some of them proved to inhibit GSK-3 (Glycogen Synthase Kinase),[29] a kinase involved in the abnormal phosphorylation of tau protein and the production of β-amyloid – two processes implicated in Alzheimer's disease[30] (Figure 1).



meridianin B (R^1 = OH, R^2 = Br, R^3 = H): 0.5 μM
meridianin E (R^1 = OH, R^2 = H, R^3 = Br): 2.5 μM

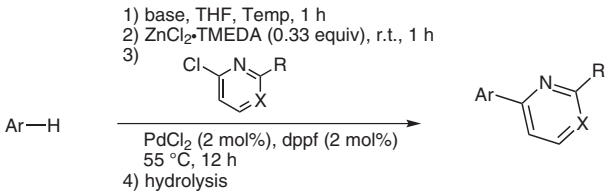


isomeridianin C (R = Br): >1000 μM
isomeridianin G (R = H): 420 μM

Figure 1 Inhibition Activities (IC_{50}) at GSK-3β of meridianins B and E, and isomeridianins C and G.

The method we developed proved suitable to prepare isomeridianin G as well as different analogues.[31] The replacement of the indole ring by other five-membered aromatic heterocycles was first considered. To this purpose, the chloro group of 2-chloropyrimidyl compounds **2d**, **9a**, **5a**, **6**, **7a**, and **1e** was substituted with allylamine to afford the derivatives **16**–**21** after subsequent cleavage of the allyl group under classical conditions[32] (Table 3).

Table 2 Coupling Reactions of Lithium Triarylzincates with Heteroaryl Chlorides



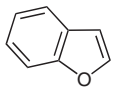
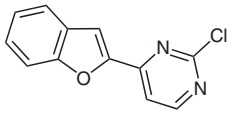
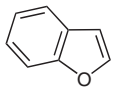
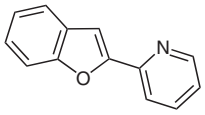
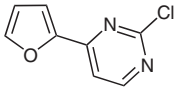
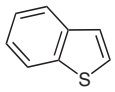
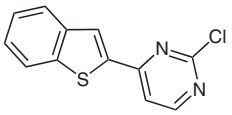
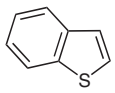
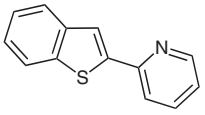
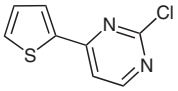
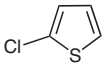
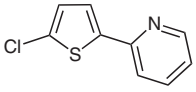
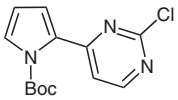
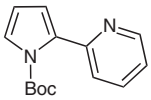
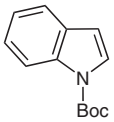
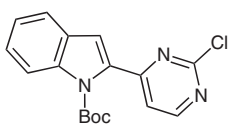
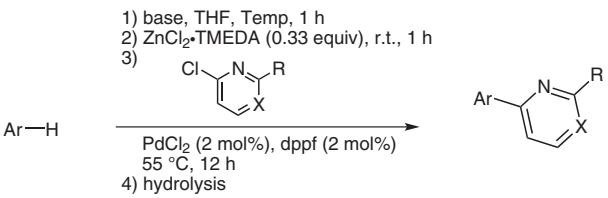
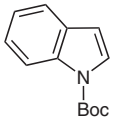
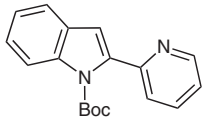
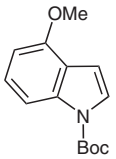
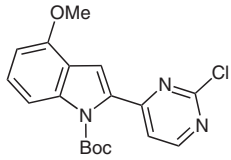
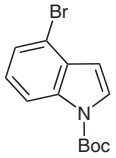
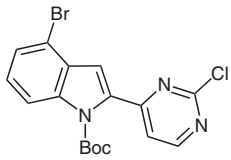
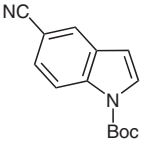
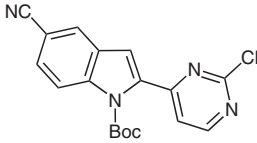
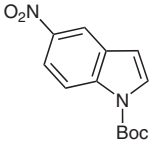
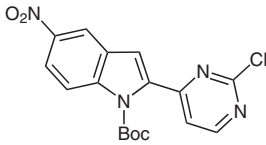
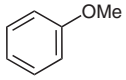
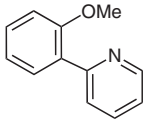
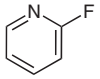
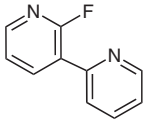
Entry	Substrate	Base, Temp (°C)	Product	Yield (%)
1		BuLi, –15	 **5a**	56
2		BuLi, –15	 **5b**	61 76[a]
3		BuLi, –15	 **6**	61
4		BuLi, –75	 **7a**	29[b]
5		BuLi, –75	 **7b**	81
6		BuLi, –75	 **1e**	56
7		BuLi, –75	 **8**	85
8		LiTMP, –75	 **9a**	25[b]
9		LiTMP, –75	 **9b**	61
10		LiTMP, –90	 **2d**	25[b]

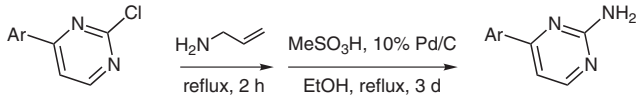
Table 2 Coupling Reactions of Lithium Triarylzincates with Heteroaryl Chlorides (continued)



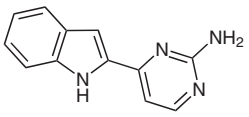
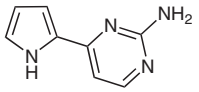
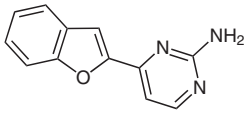
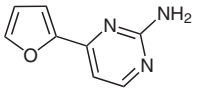
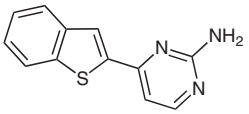
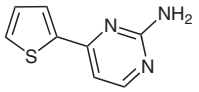
Entry	Substrate	Base, Temp (°C)	Product	Yield (%)
11		LiTMP, –90	 **2e**	27
12		LiTMP, –90	 **10**	18[b]
13		LiTMP, –90	 **11**	17[b]
14		LiTMP, –90	 **12**	21[b]
15		LiTMP, –90	 **13**	20[b]
16		BuLi, 25[c]	 **14**	64
17		LiTMP, –75	 **15**	62

[a] Coupling step performed in presence of DME (5 equiv).[14g]
[b] Since 2,4-dichloropyrimidine rapidly reacts with damp air, lower yields can be partly attributed to the presence of pyrimidinone in the starting heteroaryl chloride.
[c] Reaction time: 2 h instead of 1 h.

Table 3 Synthesis of Isomeridianin G and Pyrimidine Analogues

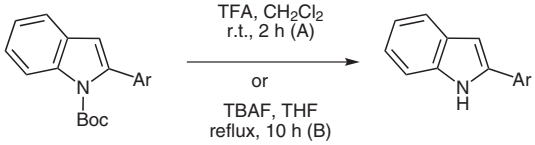


2d, **9a**, **5a**, **6**, **7a**, **1e** **16–21**

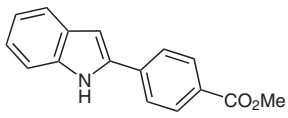
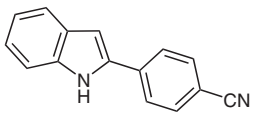
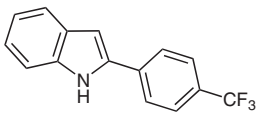
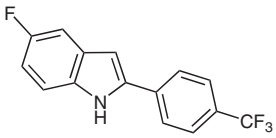
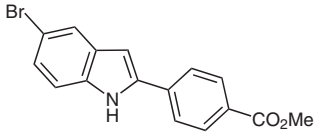
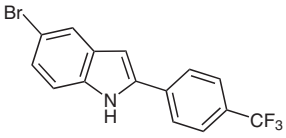
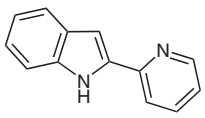
Entry	Substrate	Product	Yield (%) (2 steps)
1	**2d**	 **16** (isomeridianin G)	48[a]
2	**9a**	 **17**	70[a]
3	**5a**	 **18**	55
4	**6**	 **19**	26
5	**7a**	 **20**	58
6	**1e**	 **21**	29

[a] Cleavage of the Boc protection occurred during the first step.

Table 4 Synthesis of Indole Analogues



2a–c,**e**, **3**, **4a**, **b** **22–28**

Entry	Substrate	Method	Product	Yield (%)
1	**2a**	A	 **22**	52
2	**2b**	A	 **23**	46
3	**2c**	B	 **24**	55
4	**3**	A	 **25**	46
5	**4a**	A	 **26**	31
6	**4b**	A	 **27**	30
7	**2e**	B	 **28**	67

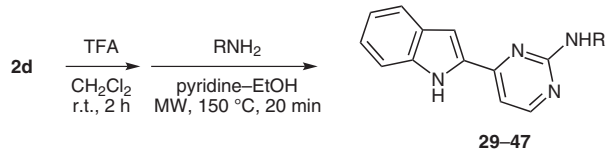
The replacement of the pyrimidine group by other six-membered ring aromatics was then considered. This was achieved by cleavage of the Boc protective group of coupled compounds using either trifluoroacetic acid (TFA) in dichloromethane at room temperature[33] or tetrabutylammonium fluoride (TBAF) under reflux of THF[34] to provide the indole analogues **22–28** (Table 4).

Finally, analogues containing both indole and pyrimidine rings with diverse amino groups on the 2-position of the pyrimidyl ring were synthesized from the chloro compound **2d**. The substitution of the chloro group was performed using a large range of amines under microwave irradiation[35] after initial Boc cleavage using TFA.

The GSK-3β inhibition activity (IC_{50} values) of the isomeridianin G analogues **16–47** was evaluated. While most of the compounds showed a weak activity (IC_{50} >27 μM), analogues **29**, **31**, **33**, **44**, and **46** were, however, found to inhibit GSK-3β in the 5–25 μM range (Table 5).

In conclusion, several analogues of isomeridianin G have been synthesized and evaluated as GSK-3β inhibitors. The key step of their synthesis is a palladium-catalyzed cross-coupling between an aromatic halide and a lithium triorganozincate which has been prepared by deprotolithiation followed by transmetalation using $ZnCl_2$·TMEDA (1/3 equiv). As compared with isomeridianin G (IC_{50} = 420 μM), the inhibition activity at GSK-3β has been greatly improved, with an IC_{50} value of 4.9 μM for the best compound **44**. It would be interesting to make further analogues of compound **44** containing an hydroxy group at the 4-position or/and a bromo group at the 6- or 7-position, such as meridianin templates.

Table 5 Synthesis of both Pyrimidine and Indole Analogues of Isomeridianin G, and Inhibition Activities at GSK-3β



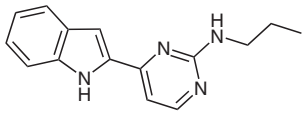
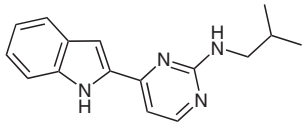
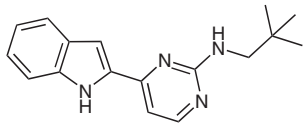
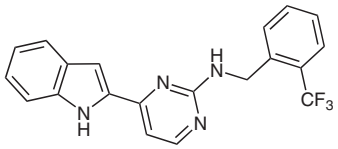
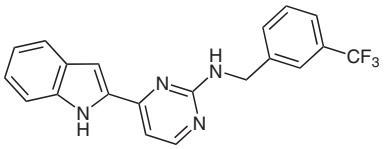
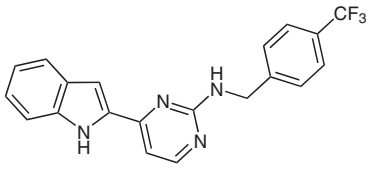
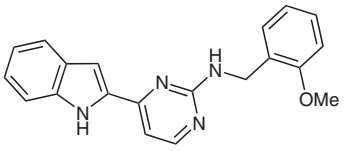
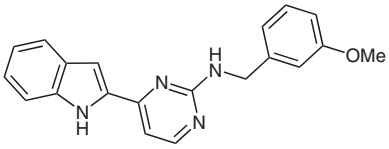
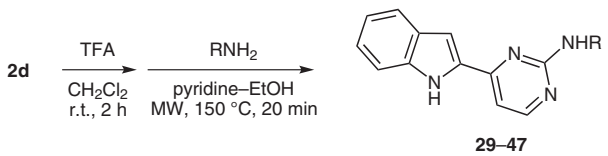
Entry	Product	Yield (%) (2 steps)	IC_{50} (mM)
1	 **29**	44	20.4
2	 **30**	48	>27
3	 **31**	59	11.5
4	 **32**	45	>27
5	 **33**	33	24.5
6	 **34**	49	>27
7	 **35**	50	>27
8	 **36**	43	>27

Table 5 Synthesis of both Pyrimidine and Indole Analogues of Isomeridianin G, and Inhibition Activities at GSK-3β (continued)



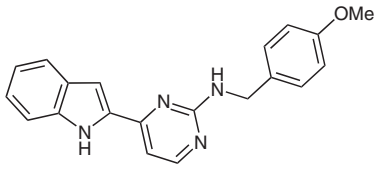
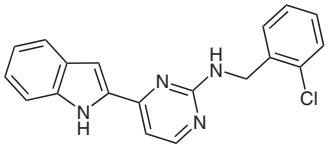
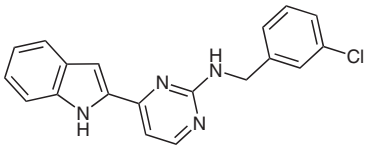
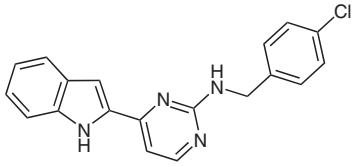
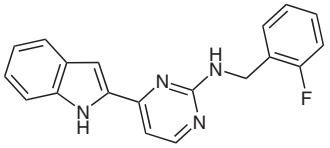
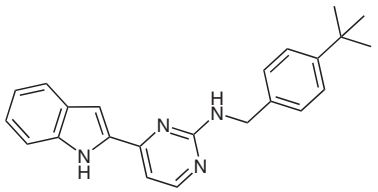
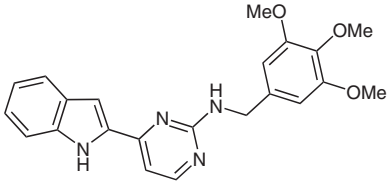
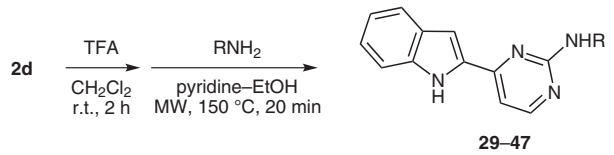
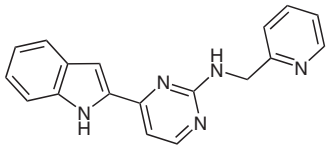
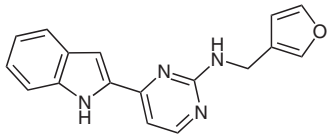
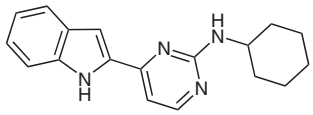
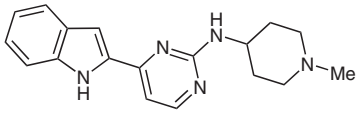
Entry	Product	Yield (%) (2 steps)	IC_{50} (mM)
9	 **37**	42	>27
10	 **38**	36	>27
11	 **39**	10	>27
12	 **40**	12	>27
13	 **41**	41	>27
14	 **42**	43	>27
15	 **43**	37	>27

Table 5 Synthesis of both Pyrimidine and Indole Analogues of Isomeridianin G, and Inhibition Activities at GSK-3β (continued)



29–47

Entry	Product	Yield (%) (2 steps)	IC_{50} (mM)
16	 **44**	73	4.9
17	 **45**	65	>27
18	 **46**	70	13.8
19	 **47**	50	>27

Metalation reactions were performed under argon atmosphere. THF was distilled over sodium/benzophenone. LiTMP was prepared in situ in THF at 0 °C from 2,2,6,6-tetramethylpiperidine and BuLi (1.6 M solution in hexanes). $ZnCl_2$·TMEDA was prepared as described previously.[36] Column chromatography separations were achieved on silica gel (40–63 μm). Mass-Directed AutoPreparative HPLC (MDAP) analyses were performed using a Waters ZQ instrument with H_2O–MeCN as gradient. Melting points were measured on a Kofler apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-200 spectrometer at 200 and 50 MHz, respectively, on a Bruker Avance III spectrometer at 300 and 75 MHz, respectively, or on a Bruker AC-400 spectrometer at 400 and 100 MHz, respectively. ^1H chemical shifts (δ) are given in ppm relative to the solvent residual peak, and ^{13}C chemical shifts relative to the central peak of the solvent signal.[37] Low-resolution mass spectra measurements were performed using a Waters ZQ instrument in ElectroSpray Chemical Ionization (ESCI) mode. High-Resolution Mass Spectra (HRMS) measurements and elemental analyses were performed at the CRMPO (Centre Régional de Mesures Physiques de l'Ouest) of Rennes using a Micromass MS/MS ZABSpec TOF instrument in EI mode and a Thermo-Finnigan Flash EA 1112 CHNS analyzer, respectively. The reactions under microwave irradiation were performed in a Biotage Initiator instrument. Kinase inhibition activity at GSK-3β of isomeridianin G and analogues was measured at GlaxoSmithKline R & D Harlow from an in vitro assay, following an in-house procedure.

N-Boc-Protected Indoles; General Procedure[19]

To a stirred solution of the required indole (35 mmol) in CH_2Cl_2 (70 mL) were successively added pyridine (3.7 mL, 45 mmol), Boc_2O (9.9 g, 45 mmol), and DMAP (0.43 g, 3.5 mmol). The mixture was stirred for 24 h at r.t. before addition of sat. aq NH_4Cl (50 mL) and extraction with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (the eluent is given in the product description).

N-Boc-indole

Eluent: heptane–CH_2Cl_2 (50:50); yield: 5.1 g (67%); colorless oil.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.67 (s, 9 H), 6.56 (d, *J* = 3.5 Hz, 1 H), 7.17–7.40 (m, 2 H), 7.56 (m, 1 H), 7.60 (d, *J* = 3.5 Hz, 1 H), 8.19 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.3 (3 C), 83.7, 107.4, 115.3, 121.1, 122.8, 124.3, 126.0, 130.7, 135.3, 149.9.

The spectral data were identical to those of a commercial sample.

N-Boc-5-nitroindole[38]

Eluent: hexane–CH_2Cl_2 (95:5 to 50:50); yield: 9.0 g (99%); white powder; mp 115 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.65 (s, 9 H), 6.71 (d, *J* = 4.0 Hz, 1 H), 7.73 (d, *J* = 4.0 Hz, 1 H), 8.19 (dd, *J* = 9.2, 2.4 Hz, 1 H), 8.26 (d, *J* = 9.2 Hz, 1 H), 8.48 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3 (3 C), 85.4, 108.1, 115.5, 117.5, 119.7, 129.1, 130.5, 138.5, 143.9, 149.2.

ESCI MS: *m*/*z* = 206.77, 262.81 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{14}N_2O_4$ (262.26): C, 59.54; H, 5.38; N, 10.68. Found: C, 59.53; H, 5.33; N, 10.44.

N-Boc-5-cyanoindole

Eluent: hexane–CH_2Cl_2 (95:5 to 50:50); yield: 8.2 g (97%); white powder, mp 128 °C (Lit.[39] mp 128–129 °C).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.68 (s, 9 H), 6.62 (dd, *J* = 3.9, 0.9 Hz, 1 H), 7.56 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.70 (d, *J* = 3.9 Hz, 1 H), 7.89 (dd, *J* = 1.7, 0.9 Hz, 1 H), 8.25 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3 (3 C), 85.2, 106.3, 107.2, 116.2, 120.1, 126.0, 127.6, 128.3, 130.7, 137.3, 149.3.

ESCI MS: *m*/*z* = 186.90, 242.92 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{14}N_2O_2$ (242.27): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.38; H, 5.79; N, 11.58.

The spectral data were identical to those previously described.[39]

N-Boc-4-methoxyindole

Eluent: hexane–CH_2Cl_2 (95:5 to 50:50); yield: 7.5 g (88%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 9 H), 3.94 (s, 3 H), 6.67 (d, *J* = 7.9 Hz 1 H), 6.69 (dd, *J* = 3.9, 0.9 Hz, 1 H), 7.23 (dd, *J* = 8.3, 7.9 Hz, 1 H), 7.50 (d, *J* = 3.9 Hz, 1 H), 7.75 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 (3 C), 55.6, 83.9, 103.2, 104.5, 108.5, 121.0, 124.6, 125.3, 136.7, 150.1, 153.1.

Anal. Calcd for $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found: C, 67.99; H, 6.87; N, 5.64.

N-Boc-4-bromoindole

Eluent: hexane–CH_2Cl_2 (100:0 to 50:50); yield: 9.4 g (91%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 9 H), 6.64 (d, *J* = 3.9 Hz, 1 H), 7.16 (dd, *J* = 8.3, 7.9 Hz, 1 H), 7.39 (dd, *J* = 7.9, 0.9 Hz, 1 H), 7.64 (d, *J* = 3.9 Hz, 1 H), 8.11 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3 (3C), 84.5, 107.3, 114.4, 114.9, 125.3, 125.7, 126.7, 131.3, 135.8, 149.7.

Anal. Calcd for $C_{13}H_{14}BrNO_2$ (296.16): C, 52.72; H, 4.76; N, 4.73. Found: C, 52.70; H, 4.66; N, 4.72.

***N*-Boc-5-fluoroindole**
Eluent: heptane–CH_2Cl_2 (60:40); yield: 5.7 g (70%); colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.67 (s, 9 H), 6.52 (d, *J* = 3.7 Hz, 1 H), 7.03 (ddd, *J* = 9.2, 9.0, 2.5 Hz, 1 H), 7.21 (dd, *J* = 9.2, 2.5 Hz, 1 H), 7.63 (d, *J* = 3.7 Hz, 1 H), 8.09 (dd, *J* = 9.0, 4.5 Hz, 1 H).

These data were identical to those previously described.[40]

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.4 (3 C), 84.1, 106.5 (d, *J* = 23 Hz), 107.1 (d, *J* = 3.9 Hz), 112.2 (d, *J* = 25 Hz), 116.2 (d, *J* = 9.3 Hz), 127.6 (2 C), 131.6 (d, *J* = 10 Hz), 149.7, 159.4 (d, *J* = 239 Hz).

***N*-Boc-5-bromoindole**
Eluent: heptane–CH_2Cl_2 (60:40); yield: 10 g (97%); brown-purple powder; mp 56 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.67 (s, 9 H), 6.51 (d, *J* = 3.5 Hz, 1 H), 7.39 (dd, *J* = 9.1, 2.0 Hz, 1 H), 7.59 (d, *J* = 3.5 Hz, 1 H), 7.68 (d, *J* = 2.0 Hz, 1 H), 8.02 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.3 (3 C), 84.3, 106.7, 116.2, 116.8, 123.7 (2 C), 127.2, 132.4, 134.1, 149.6.

These data were identical to those previously described.[41]

Deprotonation–Cross-Coupling Sequence; General Procedure
To a stirred and cooled solution (temperature given in the product description) of the appropriate reagent (4.0 mmol) in anhyd THF (5 mL) under argon were added the required base (4.0 mmol) and, 1 h later, $ZnCl_2$·TMEDA[35] (0.33 g, 1.3 mmol). The mixture was slowly warmed to r.t. (1 h) before addition of the appropriate aromatic halide (4.0 mmol), $PdCl_2$ (14 mg, 80 μmol), and dppf (44 mg, 80 μmol), and heated at 55 °C for 12 h. The mixture was cooled before addition of H_2O (0.5 mL). Extraction with EtOAc (2 × 25 mL), drying (Na_2SO_4), and removal of the solvents under reduced pressure afforded a crude compound, which was purified by chromatography on silica gel (the eluent is given in the product description) (Tables 1 and 2).

2-(4-Methoxyphenyl)thiophene (1a)
Prepared from thiophene (0.32 mL) using BuLi at –75 °C and 4-bromoanisole (0.50 mL); eluent: heptane–CH_2Cl_2 (100:0 to 95:5); yield: 67 mg (10%); beige powder; mp 104 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 7.05 (dd, *J* = 5.0, 3.5 Hz, 1 H), 7.21 (m, 2 H), 7.55 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.3, 114.2 (2 C), 122.0, 123.8, 127.2 (2 C), 127.4, 127.9, 144.3, 159.1.

The spectral data were identical to those previously described.[42]

Methyl 4-(2-Thienyl)benzoate (1c)
Prepared from thiophene (0.32 mL) using BuLi at –75 °C and methyl 4-bromobenzoate (0.86 g); eluent: heptane–CH_2Cl_2 (100:0 to 80:20); yield: 0.36 g (41%); white powder; mp 134 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.94 (s, 3 H), 7.12 (dd, *J* = 4.9, 3.6 Hz, 1 H), 7.36 (dd, *J* = 5.1, 1.1 Hz, 1 H), 7.42 (dd, *J* = 3.6, 1.3 Hz, 1 H), 7.67 (d, *J* = 8.8 Hz, 2 H), 8.04 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.8, 124.4, 125.5 (2 C), 126.2, 128.4, 129.1, 130.2 (2 C), 138.5, 143.1, 166.7.

The spectral data were identical to those previously described.[43]

2-(4-Cyanophenyl)thiophene (1d)
Prepared from thiophene (0.32 mL) using BuLi at –75 °C and 4-bromobenzonitrile (0.73 g); eluent: heptane–CH_2Cl_2 (100:0 to 80:20); yield: 0.54 g (79%); white powder; mp 88 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.13 (dd, *J* = 4.9, 3.7 Hz, 1 H), 7.40 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.43 (dd, *J* = 3.7, 1.2 Hz, 1 H), 7.66 (d, *J* = 8.8 Hz, 2 H), 7.70 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 110.3, 118.7, 125.0, 125.9, 127.0, 128.4 (2 C), 132.6 (2 C), 138.5, 141.9.

The spectral data were identical to those previously described.[44]

***N*-Boc-2-(4-methoxycarbonylphenyl)indole (2a)[45]**
Prepared from *N*-Boc-indole (0.81 mL) using LiTMP at –90 °C and methyl 4-bromobenzoate (0.86 g); eluent: heptane–CH_2Cl_2 (70:30); yield: 0.68 g (48%); white powder; mp 190 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ = 1.29 (s, 9 H), 3.92 (s, 3 H), 6.68 (s, 1 H), 7.16–7.41 (m, 2 H), 7.49–7.62 (m, 3 H), 8.08 (m, 2 H), 8.26 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 28.6 (3 C), 53.3, 85.3, 112.5, 116.8, 122.6, 124.8, 126.4, 130.5 (2 C), 130.7 (2 C), 130.9 (2 C), 139.5, 141.0, 141.1, 151.4, 167.8.

Anal. Calcd for $C_{21}H_{21}NO_4$ (351.40): C, 71.78; H, 6.02; N, 3.99. Found: C, 71.96; H, 6.14; N, 4.13.

***N*-Boc-2-(4-cyanophenyl)indole (2b)**
Prepared from *N*-Boc-indole (0.81 mL) using LiTMP at –90 °C and 4-bromobenzonitrile (0.73 g); eluent: heptane–CH_2Cl_2 (70–30); yield: 0.78 g (61%); white powder; mp 121 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ = 1.35 (s, 9 H), 6.80 (s, 1 H), 7.22–7.44 (m, 2 H), 7.64 (dd, *J* = 7.5, 1.1 Hz, 1 H), 7.72 (m, 2 H), 7.88 (m, 2 H), 8.22 (d, *J* = 8.5 Hz, 1 H).

These data were identical to those previously described.[46]

^{13}C NMR (75 MHz, acetone-d_6): δ = 28.7 (3 C), 85.8, 112.8, 113.1, 117.0, 117.6, 122.8, 125.1, 126.8, 131.0, 131.4 (2 C), 133.6 (2 C), 139.6, 140.5, 141.3, 151.5.

HRMS: *m/z* calcd for $C_{20}H_{18}N_2O_2$ (M^+): 318.1368; found: 318.1391.

Anal. Calcd for $C_{20}H_{18}N_2O_2$ (318.37): C, 75.45; H, 5.70; N, 8.80. Found: C, 75.46; H, 5.80; N, 8.72.

***N*-Boc-2-(4-trifluoromethylphenyl)indole (2c)**
Prepared from *N*-Boc-indole (0.81 mL) using LiTMP at –90 °C and 1-bromo-4-(trifluoromethyl)benzene (0.55 mL); eluent: heptane–toluene (80:20 to 40:60); yield: 0.86 g (60%); white powder; mp 104 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ = 1.34 (s, 9 H), 6.62 (s, 1 H), 7.29 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.37 (ddd, *J* = 8.3, 7.5, 1.5 Hz, 1 H), 7.51–7.61 (m, 3 H), 7.67 (d, *J* = 8.3 Hz, 2 H), 8.21 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 27.6 (3 C), 83.9, 111.0, 115.3, 120.7, 123.2, 124.2 (q, *J* = 272 Hz), 124.7, 124.8 (2 C), 128.9 (2 C), 129.0, 129.6 (q, *J* = 32 Hz), 137.5, 138.5, 138.8, 149.9.

These data were identical to those previously described.[47]

***N*-Boc-5-fluoro-2-(4-trifluoromethylphenyl)indole (3)**
Prepared from *N*-Boc-5-fluoroindole (0.59 g) using LiTMP at –90 °C and 1-bromo-4-(trifluoromethyl)benzene (0.34 mL); eluent: heptane–CH_2Cl_2 (100:0 to 70:30); yield: 0.34 g (36%); yellow powder; mp 117 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ = 1.32 (s, 9 H), 6.75 (s, 1 H), 7.16 (ddd, *J* = 9.0, 8.3, 3.0 Hz, 1 H), 7.35 (dd, *J* = 8.3, 3.0 Hz, 1 H),

7.72 (d, *J* = 8.3 Hz, 2 H), 7.82 (d, *J* = 8.3 Hz, 2 H), 8.22 (dd, *J* = 9.0, 3.0 Hz, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 28.6 (3 C), 85.9, 107.9 (d, *J* = 24 Hz), 112.2 (d, *J* = 4.4 Hz), 114.1 (d, *J* = 25 Hz), 118.3 (d, *J* = 9.9 Hz), 126.6 (2 C), 128.1 (q, *J* = 214 Hz), 131.1 (q, *J* = 31 Hz), 131.3 (2 C), 131.9 (d, *J* = 11 Hz), 135.9, 140.5, 142.4, 151.3, 161.2 (d, *J* = 238 Hz).

HRMS: *m*/*z* calcd for $C_{20}H_{17}F_4NO_2$ (M^+): 379.1195; found: 379.1183.

_N_-Boc-5-bromo-2-(4-methoxycarbonylphenyl)indole (4a)
Prepared from *N*-Boc-5-bromoindole (1.2 g) using LiTMP at –90 °C and methyl 4-bromobenzoate (0.86 g); eluent: heptane–CH_2Cl_2 (50:50 to 40:60); yield: 1.1 g (66%); beige powder; mp 154 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ = 1.31 (s, 9 H), 3.92 (s, 3 H), 6.74 (s, 1 H), 7.49 (dd, *J* = 8.5, 2.0 Hz, 1 H), 7.65 (d, *J* = 8.6 Hz, 2 H), 7.81 (d, *J* = 2.0 Hz, 1 H), 8.10 (d, *J* = 8.6 Hz, 2 H), 8.15 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 28.6 (3 C), 53.4, 86.1, 111.5, 117.6, 118.7, 125.1, 129.1, 130.7 (2 C), 130.9, 131.4 (2 C), 132.8, 138.3, 140.7, 142.5, 151.2, 167.9.

HRMS: *m*/*z* calcd for $C_{21}H_{20}{}^{79}BrNO_4$ (M^+): 429.0576; found: 429.0543.

Anal. Calcd for $C_{21}H_{20}BrNO_4$ (430.29): C, 58.62; H, 4.69; N, 3.26. Found: C, 58.59; H, 4.89; N, 3.29.

_N_-Boc-5-bromo-2-(4-trifluoromethylphenyl)indole (4b)
Prepared from *N*-Boc-5-bromoindole (1.2 g) using LiTMP at –90 °C and 1-bromo-4-(trifluoromethyl)benzene (0.54 mL); eluent: heptane–CH_2Cl_2 (100:0 to 60:40); yield: 0.54 g (31%); white powder; mp 104 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ = 1.31 (s, 9 H), 6.70 (s, 1 H), 7.46 (dd, *J* = 9.1, 2.0 Hz, 1 H), 7.59–7.85 (m, 5 H), 8.15 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 28.5 (3 C), 86.0, 111.6, 117.7, 118.7, 125.1, 125.8 (q, *J* = 271 Hz), 126.6 (q, *J* = 3.9 Hz, 2 C), 129.1, 130.6 (q, *J* = 32 Hz), 131.3 (2 C), 132.7, 138.1, 140.1 (q, *J* = 1.6 Hz), 141.9, 151.1.

HRMS: *m*/*z* calcd for $C_{20}H_{17}{}^{79}BrF_3NO_2$ (M^+): 439.0394; found: 439.0401.

4-(2-Benzo[*b*]furyl)-2-chloropyrimidine (5a)
Prepared from benzo[*b*]furan (0.44 mL) using BuLi at –15 °C and 2,4-dichloropyrimidine (0.60 g); eluent: CH_2Cl_2–MeOH (100:0 to 80:20); yield: 0.52 g (56%); pale yellow powder; mp 186 °C.

^{1}H NMR (200 MHz, acetone-d_6): δ = 7.37 (t, *J* = 7.8 Hz, 1 H), 7.51 (t, *J* = 7.8 Hz, 1 H), 7.69 (d, *J* = 7.8 Hz, 1 H), 7.82 (d, *J* = 7.8 Hz, 1 H), 7.90 (s, 1 H), 7.97 (d, *J* = 5.2 Hz, 1 H), 8.86 (d, *J* = 5.2 Hz, 1 H).

The ^{1}H NMR spectrum was identical to that previously described.[23]

^{13}C NMR (50 MHz, acetone-d_6): δ = 110.9, 112.4, 114.5, 123.5, 124.7, 127.8, 128.5, 152.2, 156.5, 158.6, 161.8, 162.1.

HRMS: *m*/*z* calcd for $C_{12}H_7{}^{35}ClN_2O$ (M^+): 230.0247; found: 230.0238.

Anal. Calcd for $C_{12}H_7ClN_2O$ (230.65): C, 62.49; H, 3.06; N, 12.15. Found: C, 62.75; H, 3.13; N, 12.35.

2-Chloro-4-(2-furyl)pyrimidine (6)
Prepared from furan (0.29 mL) using BuLi at –15 °C and 2,4-dichloropyrimidine (0.60 g); eluent: heptane–EtOAc (100:0 to 80:20); yield: 0.45 g (61%); white powder; mp 88 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.60 (dd, *J* = 3.5, 1.5 Hz, 1 H), 7.38 (dd, *J* = 3.5, 1.0 Hz, 1 H), 7.51 (d, *J* = 5.2 Hz, 1 H), 7.63 (m, 1 H), 8.57 (d, *J* = 5.2 Hz, 1 H).

The ^{1}H NMR spectrum was identical to that previously described.[23]

^{13}C NMR (50 MHz, $CDCl_3$): δ = 113.1, 113.1, 114.5, 146.2, 150.4, 158.1, 159.9, 161.7.

4-(2-Benzo[*b*]thienyl)-2-chloropyrimidine (7a)
Prepared from benzo[*b*]thiophene (0.54 g) using BuLi at –75 °C and 2,4-dichloropyrimidine (0.60 g); eluent: heptane–EtOAc (100:0 to 70:30); yield: 0.29 g (29%); pale yellow powder; mp 198 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38–7.46 (m, 2 H), 7.59 (d, *J* = 5.5 Hz, 1 H), 7.82–7.92 (m, 2 H), 8.12 (s, 1 H), 8.60 (d, *J* = 5.5 Hz, 1 H).

The ^{1}H NMR spectrum was identical to that previously described.[23]

^{13}C NMR (50 MHz, $CDCl_3$): δ = 114.5, 122.9, 125.2, 125.3, 126.3, 126.9, 139.8, 140.1, 141.8, 159.7, 161.9, 162.3.

2-(2-Benzo[*b*]thienyl)pyridine (7b)
Prepared from benzo[*b*]thiophene (0.54 g) using BuLi at –75 °C and 2-chloropyridine (0.38 mL); eluent: heptane–CH_2Cl_2 (50:50 to 30:70); yield: 0.69 g (81%); white powder; mp 126 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.21 (m, 1 H), 7.36 (m, 2 H), 7.73 (dt, *J* = 8.0, 1.6 Hz, 1 H), 7.81 (m, 4 H), 8.64 (d, *J* = 5.0 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 119.6, 121.1, 122.6 (2 C), 124.1, 124.5, 125.0, 136.6, 140.5, 140.6, 144.8, 149.7, 152.5.

The spectral data were identical to those of a commercial sample.

HRMS: *m*/*z* calcd for $C_{13}H_9NS$ (M^+): 211.0456; found: 211.0461.

2-Chloro-4-(2-thienyl)pyrimidine (1e)
Prepared from thiophene (0.32 mL) using BuLi at –75 °C and 2,4-dichloropyrimidine (0.60 g); eluent: heptane–EtOAc (100:0 to 80:20); yield: 0.44 g (56%); white powder; mp 124 °C.

The physical data were identical to those previously described.[48]

^{1}H NMR (200 MHz, acetone-d_6): δ = 7.17 (dd, *J* = 7.5, 5.7 Hz, 1 H), 7.46 (d, *J* = 7.8 Hz, 1 H), 7.59 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.82 (dd, *J* = 5.7, 1.5 Hz, 1 H), 8.53 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (50 MHz, acetone-d_6): δ = 113.7, 128.8, 129.2, 131.8, 140.5, 159.5, 161.7, 162.0.

2-(5-Chlorothienyl)pyridine (8)
Prepared from 2-chlorothiophene (0.37 mL) using BuLi at –75 °C and 2-chloropyridine (0.38 mL); eluent: heptane–EtOAc (100:0 to 80:20); yield: 0.67 g (85%); pale yellow powder; mp 67 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.91 (d, *J* = 3.8 Hz, 1 H), 7.15 (ddd, *J* = 7.1, 4.9, 1.5 Hz, 1 H), 7.33 (d, *J* = 3.8 Hz, 1 H), 7.56 (dt, *J* = 8.1, 1.0 Hz, 1 H), 7.66 (ddd, *J* = 9.1, 7.6, 2.0 Hz, 1 H), 8.53 (dq, *J* = 4.9, 1.0 Hz 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 117.2, 121.5, 122.9 (CH), 126.7, 131.4, 135.9, 143.0, 148.7, 150.8.

The spectral data were identical to those previously described.[49]

***N*-Boc-2-(2-chloro-4-pyrimidyl)indole (9a)**
Prepared from *N*-Boc-indole (0.82 mL) using LiTMP at –75 °C and 2,4-dichloropyrimidine (0.60 g); eluent: hexane–CH_2Cl_2 (70:30 to 30:70; yield: 0.33 g (25%); beige powder; mp 114 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 7.02 (d, *J* = 0.9 Hz, 1 H), 7.28 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1 H), 7.43 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.45 (d, *J* = 5.3 Hz, 1 H), 7.62 (ddd, *J* = 7.9, 1.3, 0.9 Hz 1 H), 8.17 (dd, *J* = 8.3, 0.9 Hz, 1 H), 8.64 (d, *J* = 5.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9 (3 C), 84.9, 115.1, 115.4, 117.9, 122.0, 123.7, 126.9, 128.4, 135.6, 138.9, 149.7, 159.4, 161.1, 163.0.

Anal. Calcd for $C_{17}H_{16}ClN_3O_2$ (329.78): C, 61.91; H, 4.89; N, 12.74. Found: C, 61.90; H, 4.86; N, 12.69.

***N*-Boc-2-(2-pyridyl)pyrrole (9b)**
Prepared from *N*-Boc-pyrrole (0.67 mL) using LiTMP at –75 °C and 2-chloropyridine (0.38 mL);

eluent: heptane–CH_2Cl_2 (70:30 to 0:100); yield: 0.60 g (61%); yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.31 (s, 9 H), 6.18 (t, *J* = 3.2 Hz, 1 H), 6.36 (dd, *J* = 3.5, 1.5 Hz, 1 H), 7.07–7.19 (m, 1 H), 7.29–7.39 (m, 2 H), 7.61 (ddd, *J* = 9.6, 7.5, 1.5 Hz, 1 H), 8.56 (d, *J* = 4.5 Hz, 1 H).

The spectral data were identical to those previously described.[50]

***N*-Boc-2-(2-chloro-4-pyrimidyl)pyrrole (2d)**
Prepared from *N*-Boc-pyrrole (0.67 mL) using LiTMP at –90 °C and 2,4-dichloropyrimidine (0.60 g); eluent: heptane–CH_2Cl_2 (50:50 to 0:100); yield: 0.26 g (25%); beige powder; mp 102 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 6.25 (t, *J* = 3.5 Hz, 1 H), 6.69 (dd, *J* = 3.5, 2.0 Hz, 1 H), 7.31 (d, *J* = 5.5 Hz, 1 H), 7.41 (dd, *J* = 3.5, 2.0 Hz, 1 H), 8.51 (d, *J* = 5.5 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.7 (3 C), 85.1, 111.4, 117.6, 120.0, 127.1, 130.5, 148.8, 158.9, 160.7, 161.9.

HRMS: *m*/*z* calcd for $C_{13}H_{14}{}^{35}ClN_3O_2$ (M^+): 279.0774; found: 279.0787.

***N*-Boc-2-(2-pyridyl)indole (2e)[51]**
Prepared from *N*-Boc-indole (0.81 mL) using LiTMP at –90 °C and 2-chloropyridine (0.38 mL); eluent: heptane–CH_2Cl_2 (60:40 to 0:100); yield: 0.32 g (27%); brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 9 H), 6.77 (s, 1 H), 7.22–7.29 (m, 2 H), 7.36 (ddd, *J* = 8.3, 6.8, 1.5 Hz, 1 H), 7.51 (dt, *J* = 7.5, 1.5 Hz, 1 H), 7.59 (d, *J* = 8.3 Hz, 1 H), 7.74 (ddd, *J* = 8.3, 7.5, 1.5 Hz, 1 H), 8.19 (d, *J* = 7.5 Hz, 1 H), 8.67 (d, *J* = 6.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.6 (3 C), 83.4, 111.0, 115.0, 120.9, 122.2, 122.9, 123.3, 124.9, 128.8, 136.0, 137.7, 139.3, 148.9, 150.0, 153.3.

HRMS: *m*/*z* calcd for $C_{18}H_{18}N_2O_2$ (M^+): 294.1368; found: 294.1352.

Anal. Calcd for $C_{18}H_{18}N_2O_2$ (294.35): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.14; H, 6.05; N, 9.30.

***N*-Boc-2-(2-chloro-4-pyrimidyl)-4-methoxyindole (10)**
Prepared from *N*-Boc-4-methoxyindole (1.0 g) using LiTMP at –90 °C and 2,4-dichloropyrimidine (0.60 g); eluent: hexane–CH_2Cl_2 (40:60 to 0:100); yield: 0.26 g (18%); yellow powder; mp 148 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 3.95 (s, 3 H), 6.69 (d, *J* = 7.9 Hz, 1 H), 7.16 (s, 1 H), 7.34 (dd, *J* = 8.3, 7.9 Hz, 1 H), 7.44 (d, *J* = 5.3 Hz, 1 H), 7.74 (d, *J* = 8.3 Hz, 1 H), 8.61 (d, *J* = 5.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9 (3 C), 55.7, 84.8, 103.5, 108.1, 112.5, 117.6, 119.2, 128.0, 134.1, 140.3, 149.8, 153.9, 159.3, 161.1, 162.9.

ESCI MS: *m*/*z* = 259.80, 261.73 $[M + H - Boc]^+$, 303.79, 305.74 $[M + H - t\text{-Bu}]^+$.

***N*-Boc-4-bromo-2-(2-chloro-4-pyrimidyl)indole (11)**
Prepared from *N*-Boc-4-bromoindole (1.2 g) using LiTMP at –90 °C and 2,4-dichloropyrimidine (0.60 g); eluent: hexane–CH_2Cl_2 (40:60 to 0:100); yield: 0.28 g (17%); beige powder; mp 125–126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 7.06 (d, *J* = 0.9 Hz, 1 H), 7.29 (dd, *J* = 8.3, 7.9 Hz, 1 H), 7.45 (dd, *J* = 7.9, 0.9 Hz, 1 H), 7.50 (d, *J* = 4.8 Hz, 1 H), 8.12 (ddd, *J* = 8.3, 1.2, 0.9 Hz, 1 H), 8.68 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.8 (3 C), 85.4, 114.3, 114.5, 115.7, 118.0, 126.5, 127.6, 129.2, 136.0, 139.0, 149.3, 159.7, 161.2, 162.6.

ESCI MS: *m*/*z* = 307.85, 309.82 $[M + H - Boc]^+$, 353.76, 355.79 $[M + H - t\text{-Bu}]^+$.

***N*-Boc-2-(2-chloro-4-pyrimidyl)-5-cyanoindole (12)**
Prepared from *N*-Boc-5-cyanoindole (0.97 g) using LiTMP at –90 °C and 2,4-dichloropyrimidine (0.60 g); eluent: hexane–CH_2Cl_2 (50:50 to 0:100); yield: 0.29 g (21%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 6.98 (s, 1 H), 7.50 (d, *J* = 4.8 Hz, 1 H), 7.60 (dd, *J* = 8.7, 1.7 Hz, 1 H), 7.91 (dd, *J* = 1.7, 0.9 Hz, 1 H), 8.21 (d, *J* = 8.7 Hz, 1 H), 8.69 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6 (3 C), 85.9, 106.9, 113.3, 116.2, 118.0, 119.4, 126.7, 128.1, 129.2, 137.4, 140.0, 148.6, 159.9, 161.0, 162.0.

ESCI MS: *m*/*z* = 254.87, 256.86 $[M + H - Boc]^+$, 298.88, 300.88 $[M + H - t\text{-Bu}]^+$.

***N*-Boc-2-(2-chloro-4-pyrimidyl)-5-nitroindole (13)**
Prepared from *N*-Boc-5-nitroindole (1.05 g) using LiTMP at –90 °C and 2,4-dichloropyrimidine (0.60 g); eluent: hexane–CH_2Cl_2 (50:50 to 0:100); yield: 0.30 g (20%); yellow powder; mp >260 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 7.09 (s, 1 H), 7.51 (d, *J* = 5.3 Hz, 1 H), 8.29–8.31 (m, 2 H), 8.56 (dd, *J* = 1.7, 0.9 Hz, 1 H), 8.73 (d, *J* = 5.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.8 (3 C), 86.4, 114.2, 115.8, 118.1, 118.3, 121.7, 128.0, 138.5, 141.1, 144.4, 148.8, 160.1, 161.3, 162.1.

ESCI MS: *m*/*z* = 274.78, 276.71 $[M + H - Boc]^+$, 318.73, 320.73 $[M + H - t\text{-Bu}]^+$.

2-(2-Methoxyphenyl)pyridine (14)
Prepared from anisole (0.44 mL) using BuLi at 25 °C and 2-chloropyridine (0.38 mL); eluent: CH_2Cl_2; yield: 0.43 g (64%); colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 7.02 (d, *J* = 8.3 Hz, 1 H), 7.09 (t, *J* = 7.5 Hz, 1 H), 7.2 (m, 1 H), 7.37 (dt, *J* = 7.8, 1.7 Hz, 1 H), 7.7 (m, 3 H), 8.71 (dd, *J* = 4.3, 1.2 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 56.0, 111.7, 121.4, 122.0, 125.5, 129.5, 130.3, 131.5, 136.0, 149.8, 156.4, 157.2.

The spectral data were identical to those previously described.[52]

2-Fluoro-3-(2-pyridyl)pyridine (15)
Prepared from 2-fluoropyridine (0.34 mL) using LiTMP at –75 °C and 2-chloropyridine (0.38 mL); eluent: heptane–CH_2Cl_2 (60:40 to 0:100); yield: 0.43 g (62%); beige powder; mp <50 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.25–7.37 (m, 2 H), 7.72–7.91 (m, 2 H), 8.25 (d, *J* = 3.2 Hz, 1 H), 8.47–8.58 (m, 1 H), 8.72 (d, *J* = 4.8 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 122.1 (d, *J* = 4.3 Hz), 122.6, 123.2, 124.3 (d, *J* = 10 Hz), 136.8, 141.6 (d, *J* = 3.8 Hz), 147.7 (d, *J* = 15 Hz), 150.0, 151.4 (d, *J* = 6.8 Hz), 160.9 (d, *J* = 241 Hz).

HRMS: *m*/*z* calcd for $C_{10}H_7FN_2$ (M^+): 174.0593; found: 174.0595.

Deprotonation/Cross-Coupling Sequence (Compounds 1b and 5b); General Procedure

To a stirred and cooled solution (temperature given in the product description) of the appropriate reagent (4.0 mmol) in anhyd THF (5 mL) under argon were added the required base (4.0 mmol) and, 1 h later, $ZnCl_2$·TMEDA[34] (0.33 g, 1.3 mmol). The mixture was slowly warmed to r.t. (1 h) before the addition of the appropriate aromatic halide (4.0 mmol), $PdCl_2$ (14 mg, 80 μmol), dppf (44 mg, 80 μmol), and 1,2-dimethoxyethane (2.1 mL, 20 mmol), and heated at 55 °C for 12 h. The mixture was cooled before the addition of H_2O (0.5 mL). Extraction with EtOAc (2 × 25 mL), drying (Na_2SO_4), and removal of the solvents under reduced pressure afforded a crude compound, which was purified by chromatography on silica gel (the eluent is given in the product description) (Tables 1 and 2).

2-(4-Nitrophenyl)thiophene (1b)

Prepared from thiophene (0.32 mL) using BuLi at –75 °C and 1-bromo-4-nitrobenzene (0.81 g); eluent: heptane–EtOAc (100:0 to 90:10); yield: 0.62 g (76%); yellow powder; mp 135 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.15 (t, *J* = 4.4 Hz, 1 H), 7.44 (d, *J* = 5.2 Hz, 1 H), 7.48 (d, *J* = 4.0 Hz, 1 H), 7.74 (d, *J* = 9.5 Hz, 2 H), 8.23 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 124.4, 125.7 (2 C), 126.0, 127.7, 128.7 (2 C), 140.6, 141.6, 146.6.

The spectral data were identical to those previously described.[53]

2-(2-Benzo[*b*]furyl)pyridine (5b)

Prepared from benzo[*b*]furan (0.44 mL) using BuLi at –15 °C and 2-chloropyridine (0.38 mL); eluent: heptane–CH_2Cl_2 (60:40); yield: 0.60 g (76%); white powder; mp 88 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20–7.39 (m, 3 H), 7.43 (d, *J* = 1.0 Hz, 1 H), 7.57 (dq, *J* = 8.1, 1.0 Hz, 1 H), 7.62–7.68 (m, 1 H), 7.78 (ddd, *J* = 9.3, 8.1, 1.5 Hz, 1 H), 7.91 (dt, *J* = 9.3, 1.0 Hz, 1 H), 8.69 (m, 1 H).

The spectral data were identical to those previously described.[54]

Substitution of the Chloro Group of Compounds 2d, 9a, 5a, 6, 7a, and 1e with Allylamine and Subsequent Allyl Cleavage (Compounds 16–21); General Procedure

A stirred solution of the aromatic chloride (1.0 mmol) in allylamine (5 mL) was heated under reflux for 2 h. After concentration under reduced pressure, H_2O (10 mL) and aq 1 M NaOH (1 mL) were added before extraction with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and the solvents were removed under reduced pressure. After checking the purity by NMR spectroscopy, the crude allylated compound was directly dissolved in EtOH (5 mL), and $MeSO_3H$ (85 μL, 1.3 mmol) and 10% Pd/C (0.10 g) were added at r.t. The mixture was then heated under reflux for 3 days, filtrated over Celite, and the solvents were removed under reduced pressure. Sat. aq $NaHCO_3$ (10 mL) was added to the residue before extraction with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (10 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure before purification by chromatography on silica gel (eluent given in the product description) (Table 3).

4-(2-Indolyl)-2-pyrimidinamine (Isomeridianin G, 16)

Precursor *N*-allyl-4-(2-indolyl)-2-pyrimidinamine was prepared from *N*-Boc-2-(2-chloro-4-pyrimidyl)indole (**2d**; 0.33 g), and identified by NMR spectroscopy.

N-Allyl-4-(2-indolyl)-2-pyrimidinamine

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.14–4.22 (m, 2 H), 5.19 (dq, *J* = 11, 1.5 Hz, 1 H), 5.26 (s, 1 H), 5.31 (dq, *J* = 17, 1.5 Hz, 1 H), 5.96–6.11 (m, 1 H), 7.00 (d, *J* = 5.3 Hz, 1 H), 7.09–7.16 (m, 2 H), 7.27 (ddd, *J* = 8.3, 7.0, 1.5 Hz, 1 H), 7.44 (d, *J* = 8.3 Hz, 1 H), 7.66 (d, *J* = 7.5 Hz, 1 H), 8.29 (d, *J* = 5.3 Hz, 1 H), 9.36 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.0, 103.6, 106.1, 111.5, 115.8, 120.4, 121.6 (2C), 128.7, 135.0, 135.1, 136.5, 157.4, 158.1, 162.1.

Isomeridianin G (16)

Eluent: EtOAc–CH_2Cl_2 (70:30); yield: 0.10 g (2 steps, 48%); yellow powder; mp 225 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.07 (s, 2 H), 7.07 (d, *J* = 5.3 Hz, 1 H), 7.09–7.16 (m, 2 H), 7.27 (td, *J* = 8.3, 1.5 Hz, 1 H), 7.43 (d, *J* = 8.3 Hz, 1 H), 7.66 (d, *J* = 8.3 Hz, 1 H), 8.28 (d, *J* = 5.3 Hz, 1 H), 9.40 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 104.2, 106.9, 111.6, 120.5, 121.7, 124.5, 128.6, 134.2, 136.7, 157.5, 158.0, 162.9.

HRMS: *m*/*z* calcd for $C_{12}H_{10}N_4$ (M^+): 210.0905; found: 210.0884.

The physical and spectral data were identical to those previously described.[31]

4-(2-Pyrryl)-2-pyrimidinamine (17)[55]

Precursor *N*-allyl-4-(2-pyrryl)-2-pyrimidinamine was prepared from *N*-Boc-2-(2-chloro-4-pyrimidyl)pyrrole (**9a**; 0.28 g), and identified by NMR spectroscopy.

N-Allyl-4-(2-pyrryl)-2-pyrimidinamine

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.06–4.16 (m, 2 H), 5.15 (dq, *J* = 10, 1.5 Hz, 1 H), 5.27 (dq, *J* = 17, 1.5 Hz, 1 H), 5.30 (s, 1 H), 5.87–6.10 (m, 1 H), 6.30 (m, 1 H), 6.76 (d, *J* = 5.1 Hz, 1 H), 6.81 (ddd, *J* = 3.5, 2.5, 1.2 Hz, 1 H), 6.96 (ddd, *J* = 3.5, 2.5, 1.2 Hz, 1 H), 8.18 (d, *J* = 5.1 Hz, 1 H), 9.55 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.9, 104.6, 110.3, 110.8, 115.6, 121.1, 129.7, 135.2, 157.0, 157.6, 161.8.

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Eluent: EtOAc–CH_2Cl_2 (50:50); yield: 0.11 g (2 steps, 70%); beige powder; mp 183 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ = 5.80 (s, 2 H), 6.18–6.24 (m, 1 H), 6.88 (d, *J* = 5.1 Hz, 1 H), 6.84–6.89 (m, 1 H), 6.97–7.01 (m, 1 H), 8.13 (d, *J* = 5.1 Hz, 1 H), 10.6 (s, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 106.6, 112.3, 112.7, 124.1, 132.5, 159.8, 160.9, 165.8.

HRMS: *m*/*z* calcd for $C_8H_8N_4$ (M^+): 160.0749; found: 160.0743.

4-(2-Benzo[*b*]furyl)-2-pyrimidinamine (18)

Precursor *N*-allyl-4-(2-benzo[*b*]furyl)-2-pyrimidinamine was prepared from 4-(2-benzo[*b*]furyl)-2-chloropyrimidine (**5a**; 0.23 g), and identified by NMR spectroscopy.

N-Allyl-4-(2-benzo[*b*]furyl)-2-pyrimidinamine

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.11–4.20 (m, 2 H), 5.17 (dq, *J* = 11, 1.5 Hz, 1 H), 5.30 (dq, *J* = 17, 1.5 Hz, 1 H), 5.35 (s, 1 H), 5.90–6.12 (m, 1 H), 7.10 (d, *J* = 5.1 Hz, 1 H), 7.26 (ddd, *J* = 8.6, 7.6, 1.0 Hz, 1 H), 7.37 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1 H), 7.52 (s, 1 H), 7.56 (d, *J* = 7.0 Hz, 1 H), 7.66 (dd, *J* = 7.6, 1.5 Hz, 1 H), 8.40 (d, *J* = 5.1 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.8, 105.9, 107.4, 111.7, 115.7, 121.9, 123.3, 125.9, 128.2, 134.9, 153.7, 155.5, 156.3, 158.9, 162.2.

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Eluent: EtOAc; yield: 0.12 g (2 steps, 55%); pale yellow powder; mp 205 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.24 (s, 2 H), 7.17 (d, *J* = 5.3 Hz, 1 H), 7.29 (t, *J* = 7.5 Hz, 1 H), 7.39 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1 H), 7.53 (s, 1 H), 7.58 (d, *J* = 8.5 Hz, 1 H), 7.66 (d, *J* = 7.6 Hz, 1 H), 8.39 (d, *J* = 5.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 106.9, 108.0, 111.8, 122.1, 123.5, 126.3, 128.2, 152.7, 155.1, 156.3, 158.9, 162.5.

HRMS: *m*/*z* calcd for $C_{12}H_9N_3O$ (M^+): 211.0746; found: 211.0745.

4-(2-Furyl)-2-pyrimidinamine (19)[55]

Precursor *N*-allyl-4-(2-furyl)-2-pyrimidinamine was prepared from 4-(2-furyl)-2-chloropyrimidine (**6**; 0.18 g), and identified by NMR spectroscopy.

***N*-Allyl-4-(2-furyl)-2-pyrimidinamine**

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.07–4.17 (m, 2 H), 5.15 (dq, *J* = 11, 1.5 Hz, 1 H), 5.28 (dq, *J* = 17, 1.5 Hz, 1 H), 5.30 (s, 1 H), 5.88–6.10 (m, 1 H), 6.54 (dd, *J* = 3.6, 1.5 Hz, 1 H), 6.90 (d, *J* = 5.1 Hz, 1 H), 7.16 (d, *J* = 3.6 Hz, 1 H), 7.57 (m, 1 H), 8.31 (d, *J* = 5.1 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.8, 104.9, 111.5, 112.1, 115.7, 135.0, 144.5, 152.2, 156.1, 158.5, 162.2.

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Eluent: EtOAc; yield: 42 mg (2 steps, 26%); dark yellow powder (degradation before melting).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.15 (s, 2 H), 6.54 (dd, *J* = 3.8, 2.2 Hz, 1 H), 6.96 (d, *J* = 5.1 Hz, 1 H), 7.14 (d, *J* = 3.8 Hz, 1 H), 7.57 (s, 1 H), 8.30 (d, *J* = 5.1 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 104.7, 110.9, 111.3, 143.5, 152.5, 156.2, 158.4, 162.6.

HRMS: *m*/*z* calcd for $C_8H_7N_3O$ (M^+): 161.0589; found: 161.0577.

4-(2-Benzo[*b*]thienyl)-2-pyrimidinamine (20)

Precursor *N*-allyl-4-(2-benzo[*b*]thienyl)-2-pyrimidinamine was prepared from 4-(2-benzo[*b*]thienyl)-2-chloropyrimidine (**7a**; 0.22 g), and identified by NMR spectroscopy.

***N*-Allyl-4-(2-benzo[*b*]thienyl)-2-pyrimidinamine**

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.04–4.14 (m, 2 H), 5.11 (dq, *J* = 11, 1.5 Hz, 1 H), 5.26 (dq, *J* = 17, 1.5 Hz, 1 H), 5.25 (s, 1 H), 5.84–6.06 (m, 1 H), 6.95 (d, *J* = 5.1 Hz, 1 H), 7.27–7.35 (m, 2 H), 7.72–7.84 (m, 2 H), 7.88 (s, 1 H), 8.25 (d, *J* = 5.1 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.9, 105.7, 115.9, 122.6, 123.7, 124.5, 124.6, 125.7 (2 C), 134.9, 139.9, 140.9, 158.3, 159.8, 162.2.

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Eluent: EtOAc; yield: 0.13 g (2 steps, 58%); white powder; mp 230 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.11 (s, 2 H), 7.08 (d, *J* = 5.3 Hz, 1 H), 7.34–7.43 (m, 2 H), 7.78–7.91 (m, 2 H), 7.96 (s, 1 H), 8.33 (d, *J* = 5.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 105.2, 123.5, 124.4, 124.5, 125.6 (2 C), 139.8, 140.8, 143.4, 158.2, 159.9, 162.3.

HRMS: *m*/*z* calcd for $C_{12}H_9N_3S$ (M^+): 227.0517; found: 227.0531.

4-(2-Thienyl)-2-pyrimidinamine (21)

Precursor *N*-allyl-4-(2-thienyl)-2-pyrimidinamine was prepared from 4-(2-thienyl)-2-chloropyrimidine (**1e**; 0.20 g), and identified by NMR spectroscopy.

***N*-Allyl-4-(2-thienyl)-2-pyrimidinamine**

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.00–4.11 (m, 2 H), 5.08 (dq, *J* = 10, 1.5 Hz, 1 H), 5.22 (dq, *J* = 17, 1.5 Hz, 1 H), 5.23 (s, 1 H), 5.82–6.03 (m, 1 H), 6.86 (d, *J* = 5.1 Hz, 1 H), 7.11 (dd, *J* = 5.0, 3.5 Hz, 1 H), 7.44 (dd, *J* = 5.0, 1.0 Hz, 1 H), 7.66 (dd, *J* = 3.5, 1.0 Hz, 1 H), 8.27 (d, *J* = 5.1 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.9, 104.6, 115.8, 126.9, 127.9, 129.5, 134.7, 140.5, 158.6, 159.4, 162.6.

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Eluent: EtOAc–CH_2Cl_2 (50:50); yield: 51 mg (2 steps, 29%); pale yellow powder; mp 181 °C (Lit.[56] mp 174 °C).

^{1}H NMR (300 MHz, acetone-d_6): δ = 6.06 (s, 2 H), 7.05 (d, *J* = 5.3 Hz, 1 H), 7.16 (dd, *J* = 5.3, 3.8 Hz, 1 H), 7.63 (dd, *J* = 5.3, 1.5 Hz, 1 H), 7.83 (dd, *J* = 3.8, 1.5 Hz, 1 H), 8.25 (d, *J* = 5.3 Hz, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 105.6, 127.9, 128.9, 130.2, 144.2, 159.6, 160.4, 164.8.

HRMS: *m*/*z* calcd for $C_8H_7N_3S$ (M^+): 177.0361; found: 177.0373.

Deprotection of *N*-Boc-Indoles Using TFA (Compounds 22, 23, 25–27); General Procedure

Method A: To a stirred solution of the appropriate *N*-Boc-indole (2.0 mmol) in CH_2Cl_2 (10 mL) at r.t. was added TFA (30 mmol). After 2 h at r.t., sat. aq $NaHCO_3$ (10 mL) was added. Extraction with EtOAc (3 × 10 mL), washing with brine (10 mL), drying (Na_2SO_4), and removal of the solvents under reduced pressure afforded a crude product, which was purified by chromatography on silica gel (eluent given in the product description) (Table 4).

2-(4-Methoxycarbonylphenyl)indole (22)

Prepared from *N*-Boc-2-(4-methoxycarbonylphenyl)indole (**2a**; 0.71 g); eluent: CH_2Cl_2; yield: 0.27 g (52%,); yellow powder; mp 200 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 6.95 (dd, *J* = 2.5, 1.0 Hz, 1 H), 7.14 (ddd, *J* = 8.6, 7.5, 1.5 Hz, 1 H), 7.24 (ddd, *J* = 8.6, 8.0, 1.5 Hz, 1 H), 7.42 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.65 (d, *J* = 7.5 Hz, 1 H), 7.72 (dt, *J* = 8.6, 2.0 Hz, 2 H), 8.10 (dt, *J* = 8.6, 2.0 Hz, 2 H), 8.47 (s, 1 H).

These spectral data were identical to those previously described.[57]

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.2, 101.8, 111.1, 120.6, 121.0, 123.1, 124.6 (2 C), 128.8, 129.0, 130.3 (2 C), 136.4, 137.2, 141.3, 166.7.

HRMS: *m*/*z* calcd for $C_{16}H_{13}NO_2$ (M^+): 251.0946; found: 251.0968.

Anal. Calcd for $C_{16}H_{13}NO_2$ (251.28): C, 76.48; H, 5.21; N, 5.57. Found: C, 76.27; H, 5.23; N, 5.54.

2-(4-Cyanophenyl)indole (23)

Prepared from *N*-Boc-2-(4-cyanophenyl)indole (**2b**; 0.64 g); eluent: CH_2Cl_2; yield: 0.20 g (46%); yellow powder; mp 192 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 2.2 Hz, 1 H), 7.10–7.28 (m, 2 H), 7.42 (dd, *J* = 8.1, 7.5 Hz, 1 H), 7.65 (d, *J* = 7.5 Hz, 1 H), 7.68–7.74 (m, 2 H), 7.85–7.88 (m, 2 H), 8.37 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 101.1, 111.5, 112.7, 117.8, 120.7, 121.6, 123.2, 128.7, 131.5 (2 C), 133.3 (2 C), 136.1, 136.9, 141.3.

HRMS: *m*/*z* calcd for $C_{15}H_{10}N_2$ (M^+): 218.0844; found: 218.0858.

These data were identical to those previously described.[58]

5-Fluoro-2-(4-trifluoromethylphenyl)indole (25)

Prepared from *N*-Boc-5-fluoro-2-(4-trifluoromethylphenyl)indole (**3**; 0.77 g); eluent: heptane–CH_2Cl_2 (50:50); yield: 0.26 g (46%); yellow powder; mp 162 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.88 (d, *J* = 1.5 Hz, 1 H), 6.98 (ddd, *J* = 11.6, 9.1, 2.5 Hz, 1 H), 7.24–7.38 (m, 2 H), 7.65–7.80 (m, 4 H), 8.36 (s, 1 H).

HRMS: *m*/*z* calcd for $C_{15}H_9F_4N$ (M^+): 279.0671; found: 279.0652.

These data were identical to those previously described.[59]

5-Bromo-2-(4-methoxycarbonylphenyl)indole (26)

Prepared from *N*-Boc-5-bromo-2-(4-methoxycarbonylphenyl)indole (**4a**; 0.88 g); eluent: heptane–CH_2Cl_2 (50:50); yield: 0.20 g (31%); yellow powder; mp 204 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 6.88 (d, *J* = 2.0 Hz, 1 H), 7.25–7.33 (m, 2 H), 7.66–7.79 (m, 3 H), 8.12 (d, *J* = 8.6 Hz, 2 H), 8.46 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.2, 101.2, 112.5, 113.7, 123.4, 124.8 (2 C), 125.9, 129.3, 130.4 (2 C), 130.8, 135.8, 135.9, 137.9, 167.3.

HRMS: *m*/*z* calcd for $C_{16}H_{12}{}^{79}BrNO_2$ (M^+): 329.0051; found: 329.0320.

5-Bromo-2-(4-trifluoromethylphenyl)indole (27)

Prepared from *N*-Boc-5-bromo-2-(4-trifluoromethylphenyl)indole (**4b**; 0.89 g); eluent: heptane–CH_2Cl_2 (60:40); yield: 0.20 g (30%); yellow powder; mp 190 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 2.0 Hz, 1 H), 7.23 (d, *J* = 2.0 Hz, 2 H), 7.58–7.73 (m, 5 H), 8.34 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 101.3, 111.8, 114.7, 123.5, 124.5 (q, *J* = 253 Hz), 125.6 (q, *J* = 3.6 Hz, 2 C), 125.9, 127.7 (2 C), 129.3, 129.8 (q, *J* = 32 Hz), 135.7, 136.0, 140.8.

HRMS: *m*/*z* calcd for $C_{15}H_9{}^{79}BrF_3N$ (M^+): 338.9870; found: 338.9893.

Deprotection of *N*-Boc-Indoles Using TBAF (Compounds 24, 28); General Procedure

Method B: To a stirred solution of the appropriate *N*-Boc-indole (2.0 mmol) in THF (5 mL) at r.t. was added TBAF (8.0 mmol). The mixture was then heated under reflux for 10 h, and cooled at r.t. before addition of brine (10 mL), extraction with EtOAc (3 × 10 mL), and drying (Na_2SO_4). The solvents were removed under reduced pressure before purification by chromatography over silica gel (eluent given in the product description) (Table 4).

2-(4-Trifluoromethylphenyl)indole (24)

Prepared from *N*-Boc-2-(4-trifluoromethylphenyl)indole (**2c**; 0.76 g); eluent: heptane–CH_2Cl_2 (50:50); yield: 0.29 g (55%); white powder; mp 228 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.93 (dd, *J* = 2.0, 1.0 Hz, 1 H), 7.10–7.29 (m, 2 H), 7.43 (d, *J* = 7.5 Hz, 1 H), 7.62–7.81 (m, 5 H), 8.39 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 101.5, 110.7, 110.8, 119.5, 120.2, 122.4, 123.9 (q, *J* = 226 Hz), 124.6 (2 C), 125.3 (q, *J* = 4.1 Hz, 2 C), 128.3 (q, *J* = 38 Hz), 135.5, 135.8, 137.4.

HRMS: *m*/*z* calcd for $C_{15}H_{10}F_3N$ (M^+): 261.0765; found: 261.0745.

These data were identical to those previously described.[59]

2-(2-Pyridyl)indole (28)

Prepared from *N*-Boc-2-(2-pyridyl)indole (**2e**; 0.60 g); eluent: CH_2Cl_2; yield: 0.26 g (67%); beige powder; mp 153 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.04 (d, *J* = 1.5 Hz, 1 H), 7.07–7.28 (m, 3 H), 7.39 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.67 (dd, *J* = 7.5, 2.0 Hz, 1 H), 7.75 (dd, *J* = 8.1, 2.0 Hz, 1 H), 7.84 (td, *J* = 8.1, 1.5 Hz, 1 H), 8.59 (m, 1 H), 9.95 (s, 1 H).

These data were identical to those previously described.[60]

^{13}C NMR (75 MHz, $CDCl_3$): δ = 100.6, 111.4, 119.8, 120.1, 121.1, 121.9, 123.1, 129.0, 136.5, 136.6, 136.7, 148.9, 150.3.

HRMS: *m*/*z* calcd for $C_{13}H_{10}N_2$ (M^+): 194.0844; found: 194.0851.

Deprotection of *N*-Boc-Indoles Using TFA Followed by the Substitution of the Chloro Group with Amines (Compounds 29–47); General Procedure

To a stirred solution of *N*-Boc-2-(2-chloro-4-pyrimidyl)indole (**2d**; 0.33 g, 1.0 mmol) in CH_2Cl_2 (5 mL) at r.t. was added TFA (15 mmol). After 2 h at r.t., sat. aq $NaHCO_3$ (5 mL) was added. Extraction with EtOAc (3 × 5 mL), washing with brine (5 mL), drying (Na_2SO_4), and removal of the solvents under reduced pressure afforded crude 2-chloro-4-(2-indolyl)pyrimidine, which was further dissolved in a mixture of pyridine (3 mL) and EtOH (3 mL). The required amine (3.0 mmol) was then added, and the reaction mixture was heated at 150 °C for 20 min in the microwave oven. After removal of the solvents under reduced pressure, the crude product was purified by MDAP (Table 5).

4-(2-Indolyl)-*N*-propyl-2-pyrimidinamine (29)

Prepared using *N*-propylamine (0.25 mL); yield: 0.11 g (44%); beige powder; mp 138 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.5 Hz, 3 H), 1.68 (m, 2 H), 3.47 (dt, *J* = 7.5, 4.4 Hz, 2 H), 5.23 (s, 1 H), 6.97 (d, *J* = 5.2 Hz, 1 H), 7.09 (dd, *J* = 2.2, 0.9 Hz, 1 H), 7.12 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1 H), 7.26 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.43 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.66 (dd, *J* = 7.9, 1.3 Hz, 1 H), 8.29 (d, *J* = 5.2 Hz, 1 H), 9.47 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5, 22.9, 43.4, 103.5, 105.7, 111.5, 120.4, 121.6, 124.1, 128.7, 135.0, 136.5, 157.4, 158.0, 162.3.

ESCI MS: *m*/*z* = 253.19 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{16}N_4$ (252.31): C, 71.40; H, 6.39; N, 22.21. Found: C, 71.33; H, 6.38; N, 22.26.

4-(2-Indolyl)-*N*-isobutyl-2-pyrimidinamine (30)

Prepared using isobutylamine (0.30 mL); yield: 0.13 g (48%); beige powder; mp 129 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.6 Hz, 6 H), 1.94 (m, 1 H), 3.34 (t, *J* = 6.6 Hz, 2 H), 5.29 (s, 1 H), 6.97 (d, *J* = 5.3 Hz, 1 H), 7.10–7.16 (m, 2 H), 7.26 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.42 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.66 (dd, *J* = 7.9, 1.3 Hz, 1 H), 8.28 (d, *J* = 5.3 Hz, 1 H), 9.49 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (2 C), 28.5, 49.1, 103.5, 105.7, 111.5, 120.4, 121.6, 124.1, 128.7, 135.0, 136.5, 157.4, 158.0, 162.5.

ESCI MS: *m*/*z* = 267.24 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{18}N_4$ (266.34): C, 72.15; H, 6.81; N, 21.04. Found: C, 72.09; H, 6.80; N, 20.98.

4-(2-Indolyl)-*N*-neopentyl-2-pyrimidinamine (31)

Prepared using neopentylamine (0.35 mL); yield: 0.17 g (59%); pale yellow powder; mp 134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (s, 9 H), 3.36 (d, *J* = 6.1 Hz, 2 H), 5.22 (s, 1 H), 6.96 (d, *J* = 5.3 Hz, 1 H), 7.09–7.16 (m, 2 H), 7.26 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.44 (d, *J* = 8.3 Hz, 1 H), 7.66 (dd, *J* = 7.9, 1.3 Hz, 1 H), 8.27 (d, *J* = 5.3 Hz, 1 H), 9.43 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5 (3 C), 32.0, 52.8, 103.5, 105.7, 111.6, 120.4, 121.7, 124.1, 128.8, 135.0, 136.5, 157.4, 158.0, 162.8.

ESCI MS: *m*/*z* = 281.03 $[M + H]^+$.

4-(2-Indolyl)-*N*-(2-trifluoromethylbenzyl)-2-pyrimidinamine (32)

Prepared using 2-(trifluoromethyl)benzylamine (0.42 mL); yield: 0.17 g (45%); beige powder; mp 150 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.96 (d, *J* = 6.1 Hz, 2 H), 5.69 (s, 1 H), 7.05 (d, *J* = 5.0 Hz, 1 H), 7.08–7.15 (m, 2 H), 7.26 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.32–7.45 (m, 2 H), 7.48 (ddd, *J* = 8.1, 7.9, 1.3 Hz, 1 H), 7.60–7.73 (m, 3 H), 8.29 (d, *J* = 5.0 Hz, 1 H), 9.29 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.9, 103.6, 106.4, 111.6, 120.5 (2 C), 121.6, 123.9 (q, *J* = 225 Hz), 124.2, 126.2 (q, *J* = 3.6 Hz), 127.2, 128.8, 129.1 (q, *J* = 31 Hz), 132.2, 134.7, 136.5, 138.2, 157.4, 158.3, 161.9.

ESCI MS: *m*/*z* = 368.99 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{15}F_3N_4$ (368.36): C, 65.21; H, 4.10; N, 15.21. Found: C, 65.23; H, 4.21; N, 15.28.

4-(2-Indolyl)-*N*-(3-trifluoromethylbenzyl)-2-pyrimidinamine (33)

Prepared using 3-(trifluoromethyl)benzylamine (0.43 mL); yield: 0.12 g (33%); beige powder, mp 157 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79 (d, *J* = 6.1 Hz, 2 H), 5.59 (s, 1 H), 7.04 (d, *J* = 5.3 Hz, 1 H), 7.10–7.16 (m, 2 H), 7.26 (ddd, *J* = 8.3, 7.0, 0.9 Hz, 1 H), 7.41 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.54 (d, *J* = 7.5 Hz, 1 H), 7.60 (d, *J* = 7.5 Hz, 1 H), 7.66 (dd, *J* = 7.9, 0.9 Hz, 1 H), 7.68 (s, 1 H), 8.31 (d, *J* = 5.3 Hz, 1 H), 9.24 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.5, 104.0, 106.8, 111.8, 120.7, 121.9, 124.3 (q, *J* = 3.7 Hz, 2 C), 124.6 (q, *J* = 224 Hz), 124.6, 128.9, 129.4, 130.6 (q, *J* = 1.5 Hz), 130.9 (q, *J* = 32 Hz), 134.8, 136.8, 140.8, 157.7, 158.4, 162.3.

ESCI MS: *m*/*z* = 369.04 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{15}F_3N_4$ (368.36): C, 65.21; H, 4.10; N, 15.21. Found: C, 65.01; H, 4.10; N, 15.11.

4-(2-Indolyl)-*N*-(4-trifluoromethylbenzyl)-2-pyrimidinamine (34)

Prepared using 4-(trifluoromethyl)benzylamine (0.43 mL); yield: 0.18 g (49%); beige powder; mp 131 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79 (d, *J* = 6.1 Hz, 2 H), 5.67 (s, 1 H), 7.04 (d, *J* = 5.2 Hz, 1 H), 7.10–7.16 (m, 2 H), 7.26 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.39 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.50 (d, *J* = 8.1 Hz, 2 H), 7.60 (d, *J* = 8.1 Hz, 2 H), 7.67 (dd, *J* = 7.9, 0.9 Hz, 1 H), 8.29 (d, *J* = 5.2 Hz, 1 H), 9.33 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.3, 103.9, 106.7, 111.6, 120.7, 121.8, 124.1 (q, *J* = 273 Hz), 124.5, 125.6 (q, *J* = 3.7 Hz, 2 C), 127.6 (2 C), 128.8, 129.5 (q, *J* = 32 Hz), 134.7, 136.7, 143.7, 157.6, 158.3, 162.1.

ESCI MS: *m*/*z* = 368.87 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{15}F_3N_4$ (368.36): C, 65.21; H, 4.10; N, 15.21. Found: C, 65.16; H, 4.18; N, 15.17.

4-(2-Indolyl)-*N*-(2-methoxybenzyl)-2-pyrimidinamine (35)

Prepared using 2-methoxybenzylamine (0.39 mL); yield: 0.17 g (50%); beige powder; mp 149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 3 H), 4.73 (d, *J* = 6.1 Hz, 2 H), 5.64 (s, 1 H), 6.90–6.96 (m, 2 H), 6.98 (d, *J* = 5.3 Hz, 1 H), 7.09 (dd, *J* = 2.2, 0.9 Hz, 1 H), 7.12 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1 H), 7.23–7.30 (m, 2 H), 7.38 (dd, *J* = 7.5, 1.3 Hz, 1 H), 7.43 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.66 (dd, *J* = 7.9, 0.9 Hz, 1 H), 8.28 (d, *J* = 5.3 Hz, 1 H), 9.42 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1, 55.4, 103.4, 105.9, 110.4, 111.5, 120.4, 120.6, 121.6, 124.1, 127.3, 128.6, 128.8, 129.2, 135.0, 136.5, 157.3, 157.6, 158.1, 162.3.

ESCI MS: *m*/*z* = 330.91 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{18}N_4O$ (330.38): C, 72.71; H, 5.49; N, 16.96. Found: C, 72.73; H, 5.57; N, 16.96.

4-(2-Indolyl)-*N*-(3-methoxybenzyl)-2-pyrimidinamine (36)

Prepared using 3-methoxybenzylamine (0.37 mL); yield: 0.14 g (43%); white powder; mp 140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 4.70 (d, *J* = 5.7 Hz, 2 H), 5.57 (s, 1 H), 6.82 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1 H), 6.95–7.02 (m, 2 H), 7.00 (d, *J* = 5.3 Hz, 1 H), 7.09–7.15 (m, 2 H), 7.23–7.31 (m, 2 H), 7.41 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.65 (dd, *J* = 7.9, 0.9 Hz, 1 H), 8.28 (d, *J* = 5.3 Hz, 1 H), 9.32 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.7, 55.2, 103.5, 106.2, 111.5, 112.6, 113.1, 119.6, 120.4, 121.6, 124.2, 128.7, 129.7, 134.8, 136.5, 141.1, 157.4, 158.2, 159.9, 162.1.

ESCI MS: *m*/*z* = 330.91 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{18}N_4O$ (330.38): C, 72.71; H, 5.49; N, 16.96. Found: C, 72.77; H, 5.54; N, 17.04.

4-(2-Indolyl)-*N*-(4-methoxybenzyl)-2-pyrimidinamine (37)

Prepared using 4-methoxybenzylamine (0.39 mL); yield: 0.14 g (42%); beige powder; mp 161 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 4.66 (d, *J* = 5.7 Hz, 2 H), 5.44 (s, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 7.01 (d, *J* = 5.3 Hz, 1 H), 7.10–7.15 (m, 2 H), 7.26 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.33 (d, *J* = 8.8 Hz, 2 H), 7.41 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.66 (dd, *J* = 7.9, 0.9 Hz, 1 H), 8.28 (d, *J* = 5.3 Hz, 1 H), 9.33 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.2, 55.3, 103.5, 106.1, 111.5, 114.1 (2 C), 120.4, 121.6, 124.2, 128.7, 128.8 (2 C), 131.3, 134.9, 136.5, 157.4, 158.2, 158.9, 162.1.

ESCI MS: *m*/*z* = 330.91 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{18}N_4O$ (330.38): C, 72.71; H, 5.49; N, 16.96. Found: C, 72.65; H, 5.47; N, 16.87.

***N*-(2-Chlorobenzyl)-4-(2-indolyl)-2-pyrimidinamine (38)**

Prepared using 2-chlorobenzylamine (0.36 mL); yield: 0.12 g (36%); white powder; mp 153 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.83 (d, *J* = 6.1 Hz, 2 H), 5.66 (s, 1 H), 7.01 (d, *J* = 5.1 Hz, 1 H), 7.10 (dd, *J* = 1.7, 0.9 Hz, 1 H), 7.12 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1 H), 7.20–7.29 (m, 3 H), 7.38–7.50 (m, 3 H), 7.65 (dd, *J* = 7.9, 0.9 Hz, 1 H), 8.29 (d, *J* = 5.1 Hz, 1 H), 9.38 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.5, 103.8, 106.6, 111.8, 120.7, 121.9, 124.4, 127.2, 128.8, 128.9, 129.5, 129.8, 133.6, 135.0, 136.8, 137.0, 157.7, 158.4, 162.3.

ESCI MS: *m*/*z* = 334.91, 336.85 $[M + H]^+$.

Anal. Calcd for $C_{19}H_{15}ClN_4$ (334.80): C, 68.16; H, 4.52; N, 16.73. Found: C, 68.12; H, 4.62; N, 16.58.

***N*-(3-Chlorobenzyl)-4-(2-indolyl)-2-pyrimidinamine (39)**

Prepared using 3-chlorobenzylamine (0.37 mL); yield: 33 mg (10%); white powder; mp 160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.73 (d, *J* = 5.8 Hz, 2 H), 5.57 (s, 1 H), 7.02 (d, *J* = 5.3 Hz, 1 H), 7.11 (dd, *J* = 2.2, 0.9 Hz, 1 H), 7.13 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1 H), 7.24–7.33 (m, 4 H), 7.41–7.43 (m, 2 H), 7.66 (dd, *J* = 7.9, 0.9 Hz, 1 H), 8.30 (d, *J* = 5.3 Hz, 1 H), 9.24 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.2, 103.8, 106.6, 111.7, 120.6, 121.8, 124.3, 125.5, 127.5 (2 C), 128.8, 130.0, 134.6, 134.8, 136.6, 141.7, 157.6, 158.3, 162.1.

ESCI MS: *m*/*z* = 334.99, 336.97 $[M + H]^+$.

_N_-(4-Chlorobenzyl)-4-(2-indolyl)-2-pyrimidinamine (40)
Prepared using 4-chlorobenzylamine (0.37 mL); yield: 40 mg (12%); beige powder; mp 162 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.70 (d, *J* = 6.1 Hz, 2 H), 5.51 (s, 1 H), 7.03 (d, *J* = 5.3 Hz, 1 H), 7.12 (dd, *J* = 2.1, 0.9 Hz, 1 H), 7.13 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1 H), 7.26 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.30–7.36 (m, 4 H), 7.41 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.66 (dd, *J* = 7.9, 1.3 Hz, 1 H), 8.29 (d, *J* = 5.3 Hz, 1 H), 9.27 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.2, 104.0, 106.7, 111.8, 120.7, 121.9, 124.5, 128.9, 129.0 (2 C), 129.1 (2 C), 133.2, 134.9, 136.8, 138.1, 157.7, 158.4, 162.3.

ESCI MS: *m*/*z* = 335.03, 337.02 $[M + H]^+$.

_N_-(2-Fluorobenzyl)-4-(2-indolyl)-2-pyrimidinamine (41)
Prepared using 2-fluorobenzylamine (0.34 mL); yield: 0.13 g (41%); white powder; mp 146 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78 (d, *J* = 6.1 Hz, 2 H), 5.71 (s, 1 H), 7.01 (d, *J* = 5.3 Hz, 1 H), 7.05–7.15 (m, 4 H), 7.22–7.29 (m, 2 H), 7.40–7.47 (m, 2 H), 7.66 (dd, *J* = 7.9, 0.9 Hz, 1 H), 8.28 (d, *J* = 5.3 Hz, 1 H), 9.45 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.2, 103.8, 106.5, 111.8, 115.3 (d, *J* = 21 Hz), 120.6, 121.9, 124.4, 124.5 (d, *J* = 3.7 Hz), 126.3 (d, *J* = 15 Hz), 129.0 (d, *J* = 8.1 Hz), 129.2, 129.9 (d, *J* = 4.4 Hz), 135.0, 136.8, 157.6, 158.4, 161.0 (d, *J* = 245 Hz), 162.3.

ESCI MS: *m*/*z* = 318.86 $[M + H]^+$.

Anal. Calcd for $C_{19}H_{15}FN_4$ (318.35): C, 71.68; H, 4.75; N, 17.60. Found: C, 71.52; H, 4.83; N, 17.58.

4-(2-Indolyl)-_N_-(4-*tert*-butylbenzyl)-2-pyrimidinamine (42)
Prepared using 4-*tert*-butylbenzylamine (0.53 mL); yield: 0.15 g (43%); white powder; mp 162 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9 H), 4.71 (d, *J* = 5.7 Hz, 2 H), 5.54 (s, 1 H), 7.01 (d, *J* = 5.3 Hz, 1 H), 7.11 (dd, *J* = 2.2, 0.9 Hz, 1 H), 7.13 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1 H), 7.26 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.33–7.44 (m, 5 H), 7.66 (dd, *J* = 7.9, 1.3 Hz, 1 H), 8.28 (d, *J* = 5.3 Hz, 1 H), 9.34 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.6 (3 C), 34.7, 45.6, 103.7, 106.3, 111.8, 120.6, 121.7, 124.4, 125.8 (2 C), 127.4 (2 C), 128.9, 135.1, 136.5, 136.7, 150.6, 157.6, 158.4, 162.4.

Anal. Calcd for $C_{23}H_{24}N_4$ (356.46): C, 77.50; H, 6.79; N, 15.72. Found: C, 77.62; H, 6.97; N, 15.29.

4-(2-Indolyl)-_N_-(3,4,5-trimethoxybenzyl)-2-pyrimidinamine (43)
Prepared using 3,4,5-trimethoxybenzylamine (0.51 mL); yield: 0.14 g (37%); beige powder; mp 143 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 6 H), 3.84 (s, 3 H), 4.65 (d, *J* = 5.7 Hz, 2 H), 5.65 (s, 1 H), 6.62 (s, 2 H), 7.02 (d, *J* = 5.3 Hz, 1 H), 7.10–7.15 (m, 2 H), 7.25 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.39 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.66 (dd, *J* = 7.9, 0.9 Hz, 1 H), 8.29 (d, *J* = 5.3 Hz, 1 H), 9.44 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.3, 56.3 (2 C), 61.1, 103.9, 104.5 (2 C), 106.5, 111.7, 120.7, 121.9, 124.5, 128.7, 134.7, 135.0, 136.6, 137.1, 153.4 (2C), 157.5, 158.1, 162.1.

ESCI MS: *m*/*z* = 391.04 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{22}N_4O_3$ (390.44): C, 67.68; H, 5.68; N, 14.35. Found: C, 67.51; H, 5.72; N, 14.01.

4-(2-Indolyl)-_N_-(2-pyridylmethyl)-2-pyrimidinamine (44)
Prepared using 2-(aminomethyl)pyridine (0.31 mL); yield: 0.22 g (73%); beige powder; mp 178 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.84 (d, *J* = 5.7 Hz, 2 H), 6.22 (s, 1 H), 7.01 (d, *J* = 5.1 Hz, 1 H), 7.09 (dd, *J* = 2.2, 0.9 Hz, 1 H), 7.11 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1 H), 7.17–7.22 (m, 1 H), 7.26 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.37 (d, *J* = 7.9 Hz, 1 H), 7.43 (ddd, *J* = 8.3, 1.7, 0.9 Hz, 1 H), 7.63–7.68 (m, 2 H), 8.31 (d, *J* = 5.1 Hz, 1 H), 8.61 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1 H), 9.49 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.2, 103.7, 106.4, 111.8, 120.6, 121.7, 121.8, 122.4, 124.4, 128.9, 135.1, 136.8, 136.9, 149.3, 157.6, 158.3, 158.4, 162.3.

ESCI MS: *m*/*z* = 302.05 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{15}N_5$ (301.35): C, 71.74; H, 5.02; N, 23.24. Found: C, 71.48; H, 4.98; N, 23.26.

_N_-(3-Furylmethyl)-4-(2-indolyl)-2-pyrimidinamine (45)
Prepared using 3-furylmethylamine (0.26 mL); yield: 0.19 g (65%); pale brown powder; mp 144 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.72 (d, *J* = 5.7 Hz, 2 H), 5.53 (s, 1 H), 6.27–6.36 (m, 2 H), 7.03 (d, *J* = 5.3 Hz, 1 H), 7.12 (dd, *J* = 2.2, 0.9 Hz, 1 H), 7.13 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1 H), 7.27 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.38 (dd, *J* = 1.8, 0.9 Hz, 1 H), 7.43 (ddd, *J* = 8.3, 1.7, 0.9 Hz, 1 H), 7.66 (dd, *J* = 7.9, 0.9 Hz, 1 H), 8.30 (d, *J* = 5.3 Hz, 1 H), 9.41 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.1, 103.8, 106.6, 107.1, 110.7, 111.8, 120.7, 121.9, 124.5, 128.9, 135.0, 136.8, 142.2, 152.8, 157.6, 158.3, 162.1.

ESCI MS: *m*/*z* = 291.05 $[M + H]^+$.

_N_-Cyclohexyl-4-(2-indolyl)-2-pyrimidinamine (46)
Prepared using cyclohexylamine (0.34 mL); yield: 0.20 g (70%); pale yellow powder; mp 114 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.35 (m, 2 H), 1.39–1.53 (m, 2 H), 1.60–1.72 (m, 2 H), 1.73–1.84 (m, 2 H), 2.01–2.14 (m, 2 H), 3.87–4.00 (m, 1 H), 5.08 (d, *J* = 7.9 Hz, 1 H), 6.95 (d, *J* = 5.3 Hz, 1 H), 7.10 (dd, *J* = 1.8, 0.9 Hz, 1 H), 7.13 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1 H), 7.26 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1 H), 7.43 (dd, *J* = 8.3, 0.9 Hz, 1 H), 7.66 (dd, *J* = 7.9, 1.3 Hz, 1 H), 8.27 (d, *J* = 5.3 Hz, 1 H), 9.36 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1 (2 C), 26.0, 33.5 (2 C), 49.9, 103.7, 105.8, 111.7, 120.6, 121.8, 124.3, 129.0, 135.2, 136.7, 157.6, 158.3, 161.8.

ESCI MS: *m*/*z* = 292.89 $[M + H]^+$.

4-(2-Indolyl)-_N_-(_N_-methyl-4-piperidyl)-2-pyrimidinamine (47)
Prepared using 4-amino-*N*-methylpiperidine (0.34 g); yield: 0.15 g (50%); pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57–1.71 (m, 2 H), 2.07–2.16 (m, 2 H), 2.23 (t, *J* = 11 Hz, 2 H), 2.33 (s, 3 H), 2.82 (d, *J* = 11 Hz, 2 H), 3.95 (m, 1 H), 5.06 (d, *J* = 7.9 Hz, 1 H), 6.98 (d, *J* = 5.3 Hz, 1 H), 7.11 (dd, *J* = 1.8, 0.9 Hz, 1 H), 7.13 (ddd, *J* = 7.9, 7.0, 1.3 Hz, 1 H), 7.26 (ddd, *J* = 8.1, 7.0, 0.9 Hz, 1 H), 7.43 (d, *J* = 8.1 Hz, 1 H), 7.66 (dd, *J* = 7.9, 0.9 Hz, 1 H), 8.28 (d, , *J* = 5.3 Hz, 1 H), 9.36 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.6 (2 C), 46.5, 47.6, 54.7 (2 C), 103.8, 106.1, 111.8, 120.7, 121.9, 124.4, 130.0, 135.1, 136.7, 157.7, 158.3, 161.9.

ESCI MS: *m*/*z* = 292.89 $[M + H]^+$.

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