Rapid Synthesis of 3-Aminoisoquinoline-5-sulfonamides Using the Buchwald–Hartwig Reaction

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Dedicated to Professor Andrew B. Holmes on the occasion of his 65th birthday

Abstract: A rapid synthesis of previously unreported 3-aminoisoquinoline-5-sulfonamides related to known kinase inhibitors was achieved by a two-step sequential reaction of 3-chloro-5-isoquinolinesulfonyl chloride with amines. Palladium-catalysed C–N bond formation was used to introduce arylamine, alkylamine, and unsubstituted amino groups at C-3 of the isoquinoline.

Key words: palladium catalysis, amination, isoquinolines, sulfonamides

Isoquinolines are an important class of heterocyclic compounds widely represented in natural products, and which show a range of biological activities.[1] The isoquinoline bicycle has been widely used in the design of biologically active molecules. In particular, isoquinoline-5-sulfonamides have been researched as a scaffold for new inhibitors of kinase enzymes for the treatment of human disease.[2] For example, the rho kinase inhibitor fasudil (**1**, Figure 1) is approved for the treatment of cerebral vasospasm.[3] Other isoquinoline-5-sulfonamides have been investigated as inhibitors of kinases involved in the deregulated intracellular signalling leading to cancer, for example, H-89 (**2**).[2,4,5] We have described the preparation of isoquinoline-5-sulfonamide inhibitors of protein kinase B, such as **3**, as potential anticancer agents.[5] As part of a program to develop novel kinase inhibitors, we required a straightforward parallel synthesis[6] of previously unreported 3-(alkylamino)- and 3-(arylamino)isoquinoline-5-sulfonamides. The introduction of amino functionality at C-3 of isoquinolines related to **1**–**3** is of particular interest as hydrogen bonding to the kinase active site by this region of the inhibitors is a key determinant of their biological activity.[7]

Various synthetic routes have been developed to access polysubstituted isoquinolines.[8] However, while nucleophilic substitution of halides by amines at the C-1 position of isoquinolines has been extensively reported, the equivalent introduction of amines at the C-3 position has fewer examples. Existing strategies involve intramolecular cyclisation,[9] or intermolecular reactions requiring the presence of a strongly activating 2-substituent on the isoquinoline[10] and harsh reaction conditions.[10,11] To the best of our knowledge, palladium-catalysed C–N bond formation has not previously been reported for the introduction of a range of substituted amines at C-3 of 3-haloisoquinolines. In contrast, C–C bond formation to 3-haloisoquinolines through palladium-catalysed Suzuki, Stille, or Sonogashira reactions is better precedented.[12] In this paper, we describe the synthesis of various substituted 3-aminoisoquinoline-5-sulfonamides by sequential reaction of the useful bifunctional intermediate 3-chloroisoquinoline-5-sulfonyl chloride (**5**) with cyclic amines, followed by Buchwald–Hartwig amination[13] at C-3 of the isoquinoline.

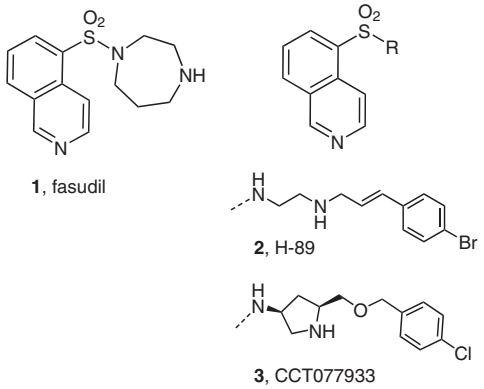

Figure 1 Representative isoquinoline-5-sulfonamide kinase inhibitors

The synthesis of our isoquinoline derivatives started with the introduction of the chlorosulfonyl group at the C-5 position of 3-chloroisoquinoline (**4**) (Scheme 1). The starting material **4** was prepared in good yield by selective reduction of 1,3-dichloroisoquinoline[14] with red phosphorous.[15] Regioselective sulfonylation of **4** was achieved by high temperature reaction with neat chlorosulfonic acid.[16] Depending on the functionalities present on the isoquinoline, isoquinoline-5-sulfonic acids or isoquinoline-5-sulfonyl chlorides have been obtained from this reaction.[16] In the case of 3-chloroisoquinoline (**4**), the novel chlorosulfonyl derivative **5** was obtained in good yield without any formation of the hydrolysed product.

Preparation of the 3-chloroisoquinoline-5-sulfonamides **6**–**8** using various cyclic amines proceeded in satisfactory yields, allowing a first degree of substitution to be introduced. The amines (morpholine, piperidine, and *N*-Boc-piperazine) were chosen in order to assess their compati-

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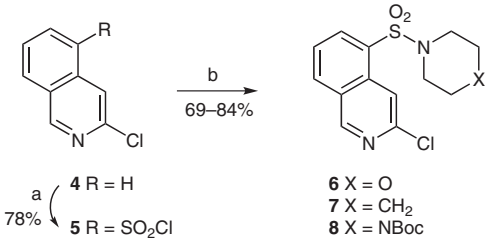


Scheme 1 *Reagents and conditions*: a) $ClSO_3H$, 160 °C; b) amine, Et_3N, CH_2Cl_2, r.t.

bility with subsequent reaction at the C-3 position of the isoquinoline, and for their similarity to preferred substituents in kinase inhibitors related to **1**.[2–5] The regiochemistry of the initial sulfonylation was confirmed from the ^1H NMR spectrum of sulfonamide **6** (Figure 2). The distinctive singlet at δ = 9.18 for H-1 of the isoquinoline showed an NOE to H-8, while the singlet at δ = 8.59 corresponding to H-4 showed an NOE to the protons adjacent to nitrogen on the morpholine ring.

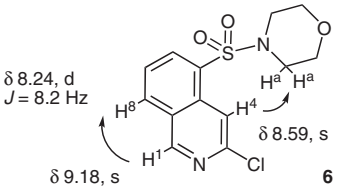


Figure 2 Regiochemistry of sulfonylation reaction confirmed by ^1H NMR and NOE determination

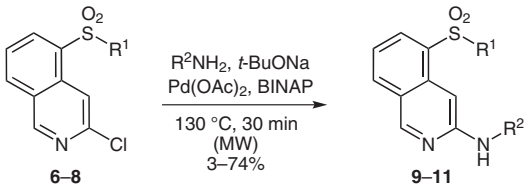
While intramolecular cyclisation of amines to 3-chloroisoquinolines has been achieved in good yields,[9] harsh reaction conditions are generally needed when no additional activating functionality is present on the heterocyclic aromatic ring, for example, 150 °C, 72 hours.[11a] We first attempted nucleophilic substitution of the 3-chloroisoquinoline-5-sulfonamides **6–8** with aniline using various bases with heating, for example, Et_3N, NMP, 150 °C (microwave), 30 minutes; NaH, DMF, 60 °C (microwave), 120 minutes. Under these conditions, no formation of product was observed and the starting materials were recovered unchanged. However, a limited catalyst and ligand screen of potential Buchwald–Hartwig conditions[13] to achieve the introduction of aniline to **6** was successful (Table 1). Some sensitivity to the catalyst and base combination was observed. Although $Pd_2(dba)_3$, BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl], and LiHMDS (entry 3) gave complete conversion of starting material, the product **9a** proved more difficult to isolate from this mixture. Thus, palladium acetate, BINAP, and sodium *tert*-butoxide (entry 1) were selected as the most suitable reagent combination, and these conditions were used for the functionalisation of **6–8** with a set of aryl and alkyl amines (Equation 1, Table 2).

Reactions were conducted in parallel in an automated microwave reactor and the crude products were isolated by solid-phase extraction using acidic resin cartidges. The

Table 1 Screen of Reagents for Buchwald–Hartwig Coupling of Aniline to **6**

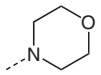
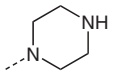
Entry	Reagents[a]	Conversion to **9a**[b]
1	$Pd(OAc)_2$, BINAP, *t*-BuONa	100%
2	$Pd(OAc)_2$, biphenyl-2-yl-di-*tert*-butylphosphine, *t*-BuONa	0%
3	$Pd_2(dba)_3$, BINAP, LiHMDS	100%
4	$Pd_2(dba)_3$, Xantphos, Cs_2CO_3	0%

[a] All reactions conducted in toluene at 130 °C (microwave) for 30 min.
[b] Determined by HPLC-MS analysis of the crude reaction mixture.



Equation 1 C–N bond formation to 3-chloroisquinoline-5-sulfonamides **6–8**. See Table 2 for products and yields.

Table 2 Buchwald–Hartwig Coupling of Alkyl and Aryl Amines to the 3-Chloroisoquinoline-5-sulfonamides **6–8**[a]

	6 → **9a–f**	**7** → **10a–f**	**8** → **11a–f**[b]
R1 / R2			
Ph	**9a** 15%	**10a** 25%	**11a** 18%
4-$MeOC_6H_4$	**9b** 54%	**10b** 61%	**11b** 53%
4-$NO_2C_6H_4$	**9c** 61%	**10c** 68%	**11c** 60%
$PhCH_2$	**9d** 3%	**10d** 74%	**11d** 62%
n-Bu	**9e** 4%	**10e** 35%	**11e** 18%
H	**9f**[c] 48%	**10f**[c] 33%	**11f**[c] 30%

[a] Yields refer to isolated and purified material.
[b] Yields of free amine following deprotection of piperazine *N*-Boc using CF_3CO_2H in CH_2Cl_2.
[c] From coupling of benzophenone imine followed by hydrolysis with aq HCl.

products were further purified by chromatography as necessary. As shown in Table 2, the yields for the formation of the disubstituted isoquinolines **9–11** were variable, but in all cases the standard procedure was successful. Isolation of the morpholine sulfonamides **9d** and **9e** was achieved in substantially lower yields than for the corresponding piperidine and piperazine derivatives. This was principally a result of poor solubility of the morpholine derivatives **9d** and **9e**, which led to a reduced efficiency of isolation and purification. The *N*-Boc protecting group of the piperazine derivatives was removed by treatment with trifluoroacetic acid in dichloromethane following the C–

N bond formation and the products **11a–f** were isolated as the free amines. Representative electron-rich and electron-poor anilines gave satisfactory yields for the C–N bond formation, as did benzylamine. The introduction of *n*-butylamine to the three scaffolds, while lower yielding, showed the sequence could accommodate nonaromatic amines. An unsubstituted 3-amino group was introduced into the molecules through the coupling of benzophenone imine as an ammonia equivalent,[17] followed by hydrolysis in situ with hydrochloric acid prior to isolation.

In summary, the straightforward parallel synthesis of a small set of previously unreported 3-aminoisoquinoline-5-sulfonamides related to known kinase inhibitors was achieved by a two-step sequential reaction of 3-chloro-5-isoquinolinesulfonyl chloride with various amines. Palladium-catalysed C–N bond formation was used to introduce arylamine, alkylamine, and unsubstituted amino groups to C-3 of the isoquinoline.

Reagents and anhyd solvents were obtained from commercial suppliers and used without further purification, unless otherwise noted. Flash column chromatography was carried out on Merck silica gel 60 (0.015–0.040 mm). Preparative TLC was performed on Macherey-Nagel or Analtech precoated silica plates. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 126 Hz, respectively, on Bruker AMX500 spectrometers using an internal deuterium lock. HPLC-MS analyses were performed on a Micromass LCT/Waters Alliance 2795 HPLC with a Discovery column from Supelco at a temperature of 22 °C. A solvent gradient of 10–90% MeOH in 0.1% aq formic acid was run over 6 min. UV detection was at 254 nm. Ionisation was by positive or negative ion electrospray and the molecular weight scan range was 50–1000 Da. HRMS were recorded on an Agilent 6210 (ToF) mass spectrometer.

3-Chloroisoquinoline-5-sulfonyl Chloride (5)

3-Chloroisoquinoline (**4**;[15] 1.00 g, 6.11 mmol) and $ClSO_3H$ (3.6 mL) were stirred at 160 °C under reflux for 22 h. The mixture was cooled to r.t. and ice was added portionwise to the stirred solution until effervescence ceased. The mixture was diluted with H_2O (20 mL) and stirred at 0 °C for 10 min. The resulting precipitate was collected and dried in vacuo to give **5** as a tan solid (1.254 g, 78%); mp 138–139 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79 (dd, *J* = 7.6, 8.1 Hz, 1 H), 8.39 (d, *J* = 8.1 Hz, 1 H), 8.60 (dd, *J* = 7.6, 1.1 Hz, 1 H), 8.62 (d, *J* = 1.1 Hz, 1 H), 9.27 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 116.4, 125.9, 127.7, 132.3, 134.1, 136.3, 138.1, 149.7, 153.6.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_9H_5Cl_2NO_2S$: 261.94908; found: 261.94894.

Sulfonamides 6–8; 4-(3-Chloroisoquinolin-5-ylsulfonyl)morpholine (6); Typical Procedure

Morpholine (0.150 mL, 1.71 mmol) was added dropwise to a mixture of **5** (0.300 g, 1.14 mmol) and Et_3N (0.240 mL, 1.71 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred at r.t. for 30 min, and then left to stand for a further 30 min. The crude mixture was partitioned between aq $NaHCO_3$ (15 mL) and CH_2Cl_2 (15 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc–hexanes (3:7), to give **6** as a colourless solid (0.301 g, 84%); mp 189–190 °C; HPLC: t_R = 3.94 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.15–3.17 (m, 4 H, CH_2), 3.72–3.74 (m, 4 H, CH_2), 7.3 (dd, *J* = 7.5, 8.2 Hz, 1 H, CH), 8.24 (dd, *J* = 8.2, 0.9 Hz, 1 H, CH), 8.39 (d, *J* = 7.5 Hz, 1 H, CH), 8.59 (br s, 1 H), 9.18 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.6, 66.2, 117.3, 126.0, 127.8, 131.3, 133.9, 134.0, 135.2, 148.6, 153.3.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}ClN_2O_3S$: 313.04082; found: 313.04106.

3-Chloro-5-(piperidin-1-ylsulfonyl)isoquinoline (7)

Yield: 73%; mp 157–159 °C; HPLC: t_R = 4.56 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46–1.64 (m, 6 H, CH_2), 3.17–3.19 (m, 4 H, CH_2), 7.71 (dd, *J* = 7.4, 8.1 Hz, 1 H), 8.21 (d, *J* = 8.2 Hz, 1 H), 8.40 (dd, *J* = 1.2, 7.4 Hz, 1 H), 8.59 (br s, 1 H), 9.17 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.5, 25.4, 46.3, 117.6, 126.0, 127.8, 132.6, 133.4, 133.8, 134.8, 148.3, 153.2.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{16}ClN_2O_2S$: 311.0615; found: 311.0616.

***tert*-Butyl 4-(3-Chloroisoquinolin-5-ylsulfonyl)piperazine-1-carboxylate (8)**

Yield: 69%; mp 163–165 °C; HPLC: t_R = 4.88 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, CH_3), 3.14–3.16 (m, 4 H, CH_2), 3.49–3.56 (m, 4 H, CH_2), 7.73 (dd, *J* = 7.1, 8.1 Hz, 1 H), 8.24 (d, *J* = 8.1 Hz, 1 H), 8.40 (dd, *J* = 1.2, 8.1 Hz, 1 H), 8.59 (br s, 1 H), 9.19 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.3, 43.0, 45.5, 80.6, 117.3, 126.0, 127.8, 131.6, 133.6, 134.0, 135.1, 148.7, 153.4, 154.1.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}ClN_3O_4S$: 412.10923; found: 412.10902.

Palladium-Catalysed Aminations of Sulfonamides 6,7; *N*-Phenyl-5-(piperidin-1-ylsulfonyl)isoquinolin-3-amine (10a); Typical Procedure

A mixture of **7** (0.100 g, 0.320 mmol), $Pd(OAc)_2$ (0.007 g, 0.032 mmol), BINAP (0.060 g, 0.096 mmol), *t*-BuONa (0.092 g, 0.959 mmol) in toluene (2.1 mL) was stirred under N_2 for 5 min at r.t. Aniline (0.070 mL, 0.735 mmol) was added and the mixture was heated at 130 °C for 30 min under microwave irradiation. The mixture was purified by ion exchange on SCX-II acidic resin (0.5 g) eluting with MeOH–CH_2Cl_2 (1:1), then 2 M NH_3 in MeOH. The basic fractions were combined and concentrated. The crude product was purified by preparative TLC, eluting with EtOAc–hexanes (3:7), to give **10a** as a yellow solid (0.029 g, 25%); mp 182–183 °C; HPLC: t_R = 4.97 min (Table 1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42–1.50 (m, 6 H, CH_2), 3.10 (t, *J* = 5.5 Hz, 4 H, CH_2), 7.05 (s, 1 H, NH), 7.11–7.14 (m, 1 H, CH), 7.29–7.35 (m, 1 H, CH), 7.38–7.41 (m, 4 H, CH), 7.92 (s, 1 H, CH), 8.01 (d, *J* = 8.1 Hz, 1 H, CH), 8.24 (dd, *J* = 7.3, 1.2 Hz, 1 H, CH), 9.00 (s,1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.6, 25.2, 46.1, 96.3, 120.9, 121.4, 123.6, 124.8, 129.4, 130.6, 133.8, 134.7, 135.0, 140.0, 152.9, 153.7.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}N_3O_2S$: 368.14272; found: 368.14235.

5-(Morpholinosulfonyl)-*N*-phenylisoquinolin-3-amine (9a)

Mp 232–233 °C; HPLC: t_R = 2.40 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.94–3.17 (m, 4 H), 3.50–3.66 (m, 4 H, CH_2), 6.84 (s, 1 H, CH), 7.36 (dd, *J* = 7.7, 15.1 Hz, 1 H, CH), 7.38–7.46 (m, 4 H, CH), 7.87 (s, 1 H, CH), 8.04 (d, *J* = 8.3 Hz, 1 H, CH), 8.25 (d, *J* = 8.3 Hz, 1 H, CH), 9.03 (s, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.3, 66.1, 95.7, 121.3, 121.4, 123.9, 124.8, 129.3, 129.4, 134.4, 134.7, 135.4, 139.8, 153.2, 153.9.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}N_3O_3S$: 370.12199; found: 370.11665.

_N_-(4-Methoxyphenyl)-5-(morpholinosulfonyl)isoquinolin-3-amine (9b)

Mp 208–209 °C; HPLC: t_R = 2.36 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.07–3.08 (m, 4 H, CH_2), 3.60–3.61 (m, 4 H, CH_2), 3.84 (s, 3 H, CH_3), 6.73 (s, 1 H, NH), 6.97 (d, *J* = 8.9 Hz, 2 H, CH), 7.22–7.40 (m, 3 H, CH), 7.59 (s, 1 H, CH), 8.01 (d, *J* = 8.1 Hz, 1 H, CH), 8.23 (d, *J* = 7.3 Hz, 1 H, CH), 8.98 (s, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.3, 55.6, 66.1, 94.8, 114.8, 120.9, 124.5, 125.0, 129.2, 132.4, 134.4, 134.8, 135.4, 153.1, 155.3, 157.0.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}N_3O_4S$: 400.13255; found: 400.13286.

5-(Morpholinosulfonyl)-_N_-(4-nitrophenyl)isoquinolin-3-amine (9c)

Mp 269–270 °C; HPLC: t_R = 2.64 min.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.08–3.09 (m, 4 H, CH_2), 3.60–3.61 (m, 4 H, CH_2), 7.58 (t, *J* = 7.8 Hz, 1 H, CH), 7.89 (d, *J* = 9.2 Hz, 2 H, CH), 8.03 (s, 1 H, CH), 8.19–8.24 (m, 3 H, CH), 8.38 (d, *J* = 7.8 Hz, 1 H, CH), 9.32 (s, 1 H, CH), 10.33 (s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 45.5, 65.4, 101.5, 116.7, 122.9, 124.8, 125.3, 128.9, 133.5, 134.8, 138.2, 139.5, 148.2, 152.0, 152.8.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}N_4O_5S$: 415.10707; found: 415.10702.

_N_-Benzyl-5-(morpholinosulfonyl)isoquinolin-3-amine (9d)

Mp 148–150 °C; HPLC: t_R = 4.45 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.77–2.79 (m, 4 H, CH_2), 3.49–3.51 (m, 4 H, CH_2), 4.60 (d, *J* = 4.4 Hz, 2 H, CH_2), 5.53 (br s, 1 H, NH), 7.25–7.30 (m, 3 H, CH), 7.34–7.37 (m, 2 H, CH), 7.44–7.45 (m, 2 H, CH), 7.98 (dt, *J* = 8.2, 1.0 Hz, 1 H, CH), 8.13 (dd, *J* = 7.6, 1.3 Hz, 1 H, CH), 8.93 (br s, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.4, 46.7, 66.1, 93.7, 120.4, 124.0, 127.0, 127.3, 128.5, 128.7, 134.5, 135.1, 135.2, 138.2, 153.1, 156.4.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{22}N_3O_3S$: 313.04082; found: 313.04106.

_N_-Butyl-5-(morpholinosulfonyl)isoquinolin-3-amine (9e)

Mp 121–122 °C; HPLC: t_R = 4.54 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.48–1.74 (m, 4 H, CH_2), 3.17–3.19 (m, 4 H, CH_2), 3.33 (t, *J* = 7.4 Hz, 2 H, CH_2), 3.72 (t, *J* = 4.7 Hz, 4 H, CH_2), 4.99 (s, 1 H, NH), 7.23–7.25 (m, 1 H, CH), 7.32 (s, 1 H, CH), 7.97 (dt, *J* = 7.5, 1.1 Hz, 1 H, CH), 8.18 (dd, *J* = 7.5, 1.1 Hz, 1 H, CH), 8.90 (s, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 20.2, 31.2, 42.5, 45.7, 66.3, 92.8, 120.0, 123.8, 128.3, 134.7, 135.3, 135.4, 153.1, 156.8.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}N_3O_3S$: 350.15329; found: 350.15310.

_N_-(4-Methoxyphenyl)-5-(piperidin-1-ylsulfonyl)isoquinolin-3-amine (10b)

Mp 173–175 °C; HPLC: t_R = 2.59 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44–1.46 (m, 6 H, CH_2), 3.04–3.06 (m, 4 H, CH_2), 3.85 (s, 3 H, CH_3), 6.73 (s, 1 H, NH), 6.97 (d, *J* = 8.8 Hz, 2 H, CH), 7.25–7.36 (m, 3 H, CH), 7.65 (s, 1 H, CH), 7.98 (d, *J* = 8.1 Hz, 1 H, CH), 8.22 (d, *J* = 7.3 Hz, 1 H, CH), 8.96 (s, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.6, 25.2, 46.1, 55.6, 95.3, 114.7, 121.0, 124.5, 124.6, 130.5, 132.6, 133.8, 134.8, 135.0, 152.8, 155.0, 156.9.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{24}N_3O_3S$: 398.15329; found: 398.15398.

_N_-(4-Nitrophenyl)-5-(piperidin-1-ylsulfonyl)isoquinolin-3-amine (10c)

Mp 155–156 °C; HPLC: t_R = 2.78 min.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.35–1.53 (m, 6 H, CH_2), 3.10–3.12 (m, 4 H, CH_2), 7.57 (t, *J* = 7.7 Hz, 1 H, CH), 7.85–7.92 (m, 2 H, CH), 8.05 (s, 1 H, CH), 8.12-8.21 (m, 3 H, CH), 8.35 (d, *J* = 7.7 Hz, 1 H, CH), 9.31 (s, 1 H, CH), 10.34 (s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.8, 24.9, 46.1, 101.7, 112.3, 116.6, 122.9, 124.8, 125.3, 126.3, 133.5, 134.6, 134.8, 139.5, 152.7, 155.6.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}N_4O_4$: 413.12780; found: 413.10969.

_N_-Benzyl-5-(piperidin-1-ylsulfonyl)isoquinolin-3-amine (10d)

Mp 166–168 °C; HPLC: t_R = 4.45 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34–1.48 (m, 6 H, CH_2), 2.91 (t, *J* = 5.5 Hz, 4 H, CH_2), 4.59 (d, *J* = 5.6 Hz, 2 H, CH_2), 5.44 (t, *J* = 5.6 Hz, 1 H, NH), 7.23–7.30 (m, 3 H, CH), 7.36–7.37 (m, 2 H, CH), 7.43–7.45 (m, 2 H, CH), 7.94 (d, *J* = 8.2 Hz, 1 H, CH), 8.19 (dd, *J* = 7.2, 1.0 Hz, 1 H, CH), 8.91 (s, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.5, 25.3, 46.3, 46.8, 93.9, 120.4, 124.1, 127.2, 127.4, 128.7, 129.8, 133.9, 134.8, 135.1, 138.3, 153.0, 156.4.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{24}N_3O_2S$: 382.15451; found: 382.15500.

_N_-Butyl-5-(piperidin-1-ylsulfonyl)isoquinolin-3-amine (10e)

Mp 118–119 °C; HPLC: t_R = 4.54 min.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.43–1.72 (m, 10 H, CH_2), 3.17 (t, *J* = 5.3 Hz, 4 H, CH_2), 3.00–3.33 (m, 2 H, CH_2), 5.01 (s, 1 H, NH), 7.20 (t, *J* = 7.5 Hz, 1 H, CH), 7.29 (s, 1 H, CH), 7.91 (d, *J* = 8.2 Hz, 1 H, CH), 8.16 (dd, *J* = 7.5, 1.2 Hz, 1 H, CH), 8.86 (s, 1 H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 20.2, 23.6, 25.4, 31.2, 42.5, 46.4, 93.1, 120.0, 123.8, 129.7, 134.1, 134.8, 135.1, 153.0, 156.8.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{26}N_3O_2S$: 348.17402; found: 348.17492.

Palladium-Catalysed Aminations of Sulfonamide 8; _N_-Phenyl-5-(piperazin-1-ylsulfonyl)isoquinolin-3-amine (11a); Typical Procedure

A mixture of **8** (0.060 g, 0.1460 mmol), $Pd(OAc)_2$ (0.003 g, 0.015 mmol), BINAP (0.027 g, 0.044 mmol), *t*-BuONa (0.042 g, 0.437 mmol) in toluene (1.2 mL) was stirred under N_2 at r.t. for 5 min. Aniline (0.031 mL, 0.340 mmol) was added and the mixture was heated at 130 °C for 30 min under microwave irradiation. The mixture was purified by ion exchange on SCX-II acidic resin (2 g), eluting with MeOH–CH_2Cl_2 (1:1), and then with 2 M NH_3 in MeOH. The basic fractions were combined and concentrated. The residue was dissolved in CH_2Cl_2 (2 mL) and CF_3CO_2H (0.10 mL) was added. The mixture was stirred at r.t. for 20 min. The mixture was concentrated and purified by preparative TLC, eluting with EtOAc–hexanes (6:4), to give **11a** as a yellow solid (0.009 g, 18%); mp 172–173 °C; HPLC: t_R = 1.84 min (Table 1).

^{1}H NMR (500 MHz, MeOD): δ = 2.79–2.94 (m, 4 H, CH_2), 3.11–3.23 (m, 4 H, CH_2), 7.09 (t, *J* = 7.4 Hz, 1 H, CH), 7.36–7.41 (m, 3 H, CH), 7.49–7.50 (m, 2 H, CH), 7.83 (s, 1 H, CH), 8.18 (d, *J* = 8.1 Hz, 1 H, CH), 8.25 (dd, *J* = 7.4, 1.2 Hz, 1 H, CH), 9.07 (s, 1 H, CH).

^{13}C NMR (125 MHz, MeOD): δ = 45.5, 46.2, 97.8, 121.8, 122.4, 124.0, 125.9, 130.2, 130.5, 135.8, 135.9, 136.7, 142.2, 154.3, 155.8.

HRMS-TOF: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{21}N_4O_2S$: 371.15122; found: 371.13244.

_N_-(4-Methoxyphenyl)-5-(piperazin-1-ylsulfonyl)isoquinolin-3-amine (11b)

Mp 202–203 °C; HPLC: t_R = 1.95 min.

^{1}H NMR (500 MHz, MeOD): δ = 2.70–2.72 (m, 4 H, CH_2), 3.04–3.06 (m, 4 H, CH_2), 3.83 (s, 3 H, CH_3), 6.97–7.00 (m, 2 H, CH), 7.33–7.37 (m, 3 H, CH), 7.60 (s, 1 H, CH), 8.13 (d, *J* = 8.1 Hz, 1 H, CH), 8.20 (dd, *J* = 7.3, 1.2 Hz, 1 H, CH), 9.00 (s, 1 H, CH).

^{13}C NMR (125 MHz, MeOD): δ = 45.8, 46.8, 56.0, 96.6, 115.6, 121.9, 125.4, 125.7, 130.5, 134.8, 135.8, 136.0, 136.7, 154.3, 156.9, 158.00.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}N_4O_3S$: 399.14854; found: 399.14784.

_N_-(4-Nitrophenyl)-5-(piperazin-1-ylsulfonyl)isoquinolin-3-amine (11c)

Mp 285–287 °C; HPLC: t_R = 2.09 min.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.71–2.72 (m, 4 H, CH_2), 3.02–3.04 (m, 4 H, CH_2), 6.60 (d, *J* = 9.1 Hz, 1 H), 6.69 (s, 1 H), 7.58 (t, *J* = 7.7 Hz, 1 H, CH), 8.06 (s, 1 H, CH), 8.19–8.21 (m, 3 H, CH), 8.37 (d, *J* = 8.2 Hz, 1 H, CH), 9.32 (s, 1 H, CH), 10.30 (s, 1 H, NH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 44.6, 46.0, 101.7, 112.3, 116.6, 122.9, 124.8, 125.3, 129.4, 133.5, 139.5, 148.2, 151.9, 152.7, 155.7.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}N_5O_4$: 414.12305; found: 414.12294.

_N_-Benzyl-5-(piperazin-1-ylsulfonyl)isoquinolin-3-amine (11d)

Mp 142–143 °C; HPLC: t_R = 3.83 min.

^{1}H NMR (500 MHz, MeOD): δ = 2.83–2.99 (m, 8 H, CH_2), 4.60 (s, 2 H, CH_2), 7.24–7.33 (m, 3 H, CH), 7.37 (t, *J* = 7.6 Hz, 2 H, CH), 7.46–7.48 (m, 2 H, CH), 8.12–8.17 (m, 2 H, CH), 8.97 (s, 1 H, CH).

^{13}C NMR (125 MHz, MeOD): δ = 44.8, 47.1, 49.1, 94.7, 121.4, 125.2, 128.1, 129.0, 129.7, 136.2, 136.4, 136.9, 140.5, 154.8, 158.2.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}N_4O_2S$: 383.15362; found: 383.15363.

_N_-Butyl-5-(piperazin-1-ylsulfonyl)isoquinolin-3-amine (11e)

Mp 103–104 °C; HPLC: t_R = 1.95 min.

^{1}H NMR (500 MHz, MeOD): δ = 1.00 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.45–1.68 (m, 4 H, CH_2), 3.27–3.34 (m, 6 H, CH_2), 3.37–3.49 (m, 4 H, CH_2), 7.26–7.30 (m, 2 H, CH), 8.11 (d, *J* = 7.4 Hz, 1 H, CH), 8.21 (dd, *J* = 7.4, 1.2 Hz, 1 H, CH), 8.92 (s, 1 H, CH).

^{13}C NMR (125 MHz, MeOD): δ = 14.2, 21.3, 32.4, 43.0, 43.8, 44.4, 94.7, 119.4, 121.5, 128.9, 136.1, 136.7, 137.1, 154.4, 162.9

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}N_3O_3S$: 349.16927; found: 349.16819.

Introduction of a Primary Amine to Sulfonamides 6–8; 5-(Morpholinosulfonyl)isoquinolin-3-amine (9f); Typical Procedure

A mixture of **6** (0.100 g, 0.320 mmol), $Pd(OAc)_2$ (0.007 g, 0.032 mmol), BINAP (0.060 g, 0.096 mmol), *t*-BuONa (0.092 g, 0.959 mmol) in toluene (2.1 mL) was stirred under N_2 at r.t. for 5 min. Benzophenone imine (0.107 mL, 0.639 mmol) was added and the mixture was heated at 130 °C for 30 min under microwave irradiation. The mixture was cooled, aq 1 M HCl (0.1 mL) was added and stirred for 30 min. The mixture was concentrated and purified by ion exchange on SCX-II acidic resin (2 g), eluting with MeOH–CH_2Cl_2 (1:1), and then with 2 M NH_3 in MeOH. The basic fractions were combined and concentrated. The crude product was purified by preparative TLC, eluting with MeOH–CH_2Cl_2 (1:19), to give **9f** as a yellow solid (0.045 g, 48%); mp 235–237 °C; HPLC: t_R = 2.85 min (Table 1).

^{1}H NMR (500 MHz, MeOD): δ = 3.14–3.16 (m, 4 H, CH_2), 3.65–3.67 (m, 4 H, CH_2), 7.31 (dd, *J* = 8.0, 7.4 Hz, 1 H, CH), 7.50 (s, 1 H, CH), 8.11 (d, *J* = 8.0 Hz, 1 H, CH), 8.19 (dt, *J* = 7.4, 1.3 Hz, 1 H, CH), 8.90 (br s, 1 H, CH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 45.4, 65.5, 94.3, 119.5, 122.8, 127.4, 134.3, 134.7, 134.9, 153.9, 157.9.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{16}N_3O_3S$: 292.11142; found: 292.11148.

5-(Piperidin-1-ylsulfonyl)isoquinolin-3-amine (10f)

Mp 225–226 °C; HPLC: t_R = 2.85 min.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.39–1.54 (m, 6 H, CH_2), 3.07–3.09 (m, 4 H, CH_2), 6.42 (s, 2 H, NH_2), 7.25 (t, *J* = 7.4 Hz, 1 H, CH), 7.29 (s, 1 H, CH), 8.03 (d, *J* = 7.4 Hz, 1 H, CH), 8.09 (d, *J* = 7.4 Hz, 1 H, CH), 8.94 (s, 1 H, CH).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.9, 24.9, 46.2, 94.5, 119.5, 122.8, 128.7, 134.1, 134.2, 134.4, 153.2, 157.8.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}N_3O_2S$: 293.10667; found: 293.10635.

5-(Piperazin-1-ylsulfonyl)isoquinolin-3-amine (11f)

Mp 134–135 °C; HPLC: t_R = 1.49 min.

^{1}H NMR (500 MHz, MeOD): δ = 2.99–3.01 (m, 4 H, CH_2), 3.27–3.29 (m, 4 H, CH_2), 7.29 (t, *J* = 8.0 Hz, 1 H, CH), 7.47 (s, 1 H, CH), 8.09 (d, *J* = 8.0 Hz, 1 H, CH), 8.19 (dd, *J* = 8.0, 1.2 Hz, 1 H, CH), 8.89 (s, 1 H, CH).

^{13}C NMR (125 MHz, MeOD): δ = 45.3, 45.7, 97.3, 121.5, 124.9, 129.7, 136.2, 136.3, 136.8, 154.2, 158.8.

HRMS-TOF: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}N_4O_2S$: 293.10667; found: 293.10358.

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