Synthesis S. E. Pearson et al. Paper

Synthesis of Indole-Dihydroisoquinoline Sulfonyl Ureas via Three-Component Reactions

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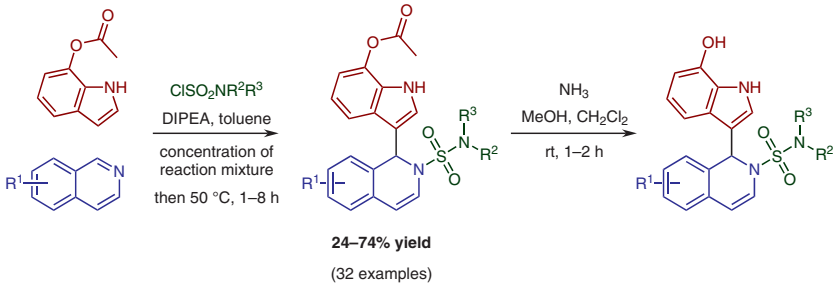

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Abstract Isoquinolines activated with sulfamoyl chlorides were reacted with indoles in a 3-component reaction to generate a library of dihydroisoquinoline derivatives. Using a differential protecting group strategy, products could be further derivatised. Synthesis of isoquinoline starting materials using several different methods is also described.

Key words multicomponent reaction, combinatorial chemistry, isoquinolines, indoles, sulfonamides

Isoquinolines and their semi-saturated derivatives feature in a vast number of natural products and pharmaceuticals, for example, the opium alkaloid antispasmodic papaverine[1] and the anticolinergic solifenacin[2] used in the treatment of urinary incontinence (Figure 1).

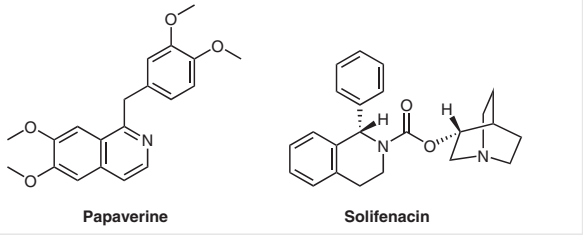


Figure 1 Examples of isoquinoline-containing substances

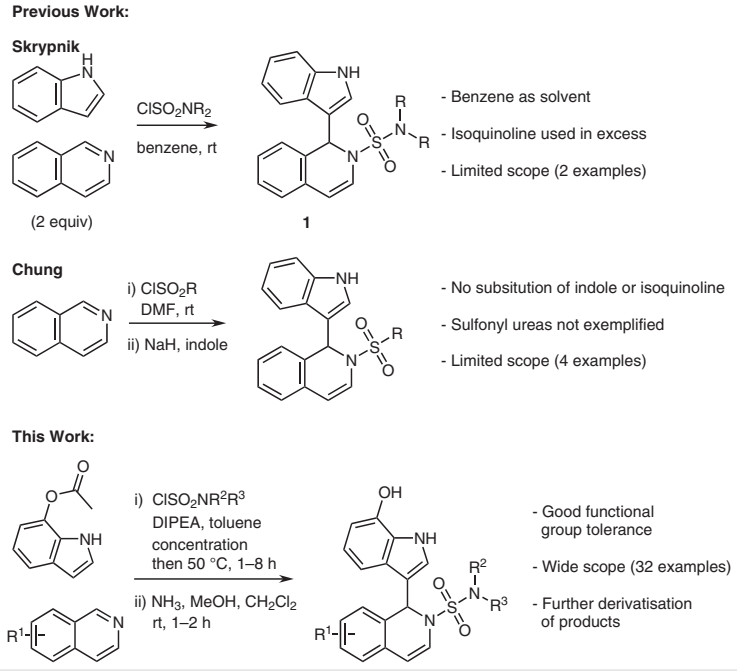
Multi-component reactions (MCRs) offer a convergent and efficient route to semi-saturated isoquinoline derivatives and have been the basis of many previously reported synthetic approaches to them. Isoquinolines can be activated towards nucleophilic attack at the 1-position by quaternisation with electrophiles such as acid chlorides,[3a] alkyl chlorophosphates,[3b] isocyanides[3c] and acetylene dicarboxylates.[3d] Electron-rich compounds such as indoles are then able to couple with the activated species, giving dihydroisoquinoline derivatives in a three-component reaction (Scheme 1). Other suitable nucleophiles include furans,[4a] siloxyfurans,[4b] pyrroles[4c] and isocyanides (in an Ugi-type reaction).[4d] Catalytic processes have also been described, such as the palladium-catalysed addition of malonates to dihydroisoquinolines by Sodeoka.[5a]

It is possible to generate these systems stereoselectively; Jacobsen has reported enantioselective acyl-Mannich reactions at the 1-position of isoquinolines, catalysed by a chiral thiourea.[5b] Also, using a chiral counteranion strategy, Zhang was able to make enantioenriched 1-indole-3-phenyl-1,2-dihydroisoquinoline derivatives.[5c]

A program to expand the chemical diversity of our corporate compound collection led us to consider compounds with an indole-isoquinoline skeleton **1** capped with a sulfonyl urea.

Skrypnik and co-workers reported a three-component reaction using sulfonyl chlorides as the activating species.[6] Their procedure used two equivalents of isoquinoline, the second equivalent acting as a base. For library synthesis, this is undesirable as it wastes potentially valuable starting materials and complicates purification. Only a limited number of isoquinolines are commercially available and many of those listed are expensive or difficult to source. Also, benzene was used as the solvent, which we wished to avoid due to its toxicity. A later paper from Skrypnik[7] reported two compounds containing our desired motif **1**, using sulfamoyl chlorides as the activating species. The scope was limited, however, with no substitution on the isoquinoline or indole and only Me and Et sulfamoyl chlorides.

Recently, Chung and co-workers described libraries of indole-dihydroisoquinoline amides, ureas and sulfonamides (although not sulfonyl ureas).[8] However, the sulfonamides were not well explored (only 4 examples) and only unsubstituted isoquinoline was used. Also, their procedure



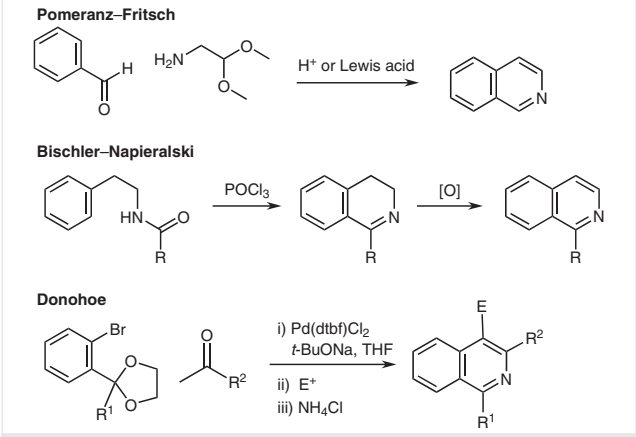
Scheme 1 3-Component reaction of isoquinolines and sulfonyl chlorides with electron-rich rings

involved using the sodium anion of indole as the attacking species. This method would be likely to have limited functional group tolerance and was therefore undesirable for a library synthesis. Given the limitations of published approaches, we decided this chemistry warranted further investigation and optimisation.

We required a diverse set of isoquinoline building blocks as substrates for the three-component reaction, including some which could not be easily accessed. Traditional isoquinoline syntheses such as the Pomeranz–Fritsch[9a–c] or the Bischler–Napieralski[9d] use harsh reagents such as $POCl_3$, $AlCl_3$ or $TiCl_4$, with low yields and troublesome workups involving the removal of gelatinous $Al(OH)_3$ or TiO_2. The Bischler–Napieralski reaction generates dihydroisoquinolines and therefore requires an additional oxidation step. We utilised the classical Pomeranz–Fritsch reaction for the synthesis of **23**, but investigated alternative routes for the reasons outlined above.

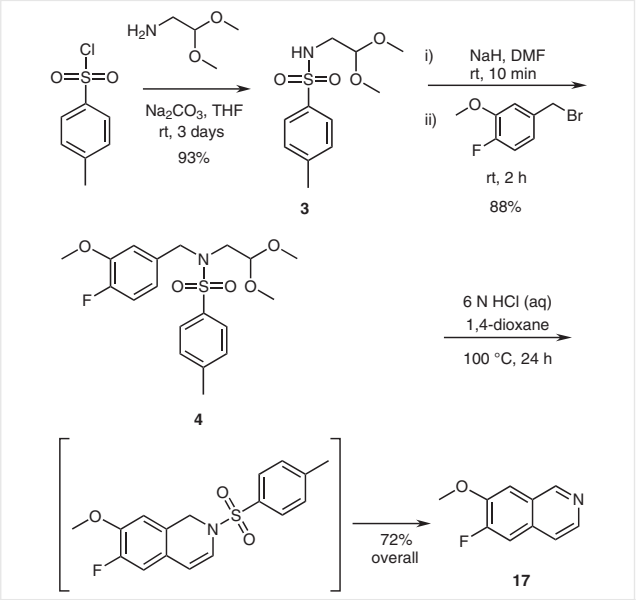
A number of novel approaches to isoquinolines have been recently described in the literature, such as the method of Donohoe and co-workers (Scheme 2),[10a] using Pd-catalysed enolate arylation to generate a variety of 3,4-substituted isoquinolines. Ohno[10b] used a copper-catalysed domino four-component cyclisation to make 3-(aminomethyl)isoquinolines from 2-ethynylbenzaldehydes.

A variation of the Pomeranz–Fritsch reaction first described by Birch[11] was used for the preparation of **17**, **18**, and **19** (Scheme 3, Method A). Alkylation of sulfonamide **3** with benzyl halides gave intermediates such as **4**, analogous to those found in the classical Pomeranz–Fritsch reaction. Heating under acidic conditions resulted in cyclisation onto the aromatic ring with good regioselectivity. Elimination of the sulfinic acid group under the reaction conditions yielded the desired isoquinolines.

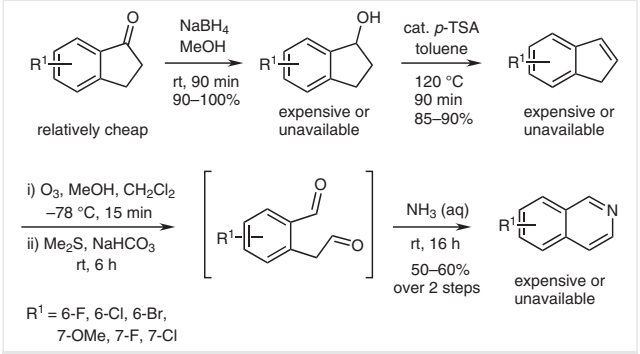


Scheme 2 Classical and modern isoquinoline syntheses

An alternative approach utilised the observation from Fields that indene could be ozonolysed in liquid ammonia to give isoquinoline.[12] This approach was subsequently improved by Miller[13] to give a more workable but rarely utilised procedure to access isoquinolines (Scheme 4). Starting from cheap and readily available indanones, borohydride reduction followed by acid-catalysed elimination produces a range of indenes, generally difficult to source commer-



Scheme 3 Method A: Isoquinoline synthesis via sulfonamide **4**



Scheme 4 Method B: Miller synthesis of isoquinolines

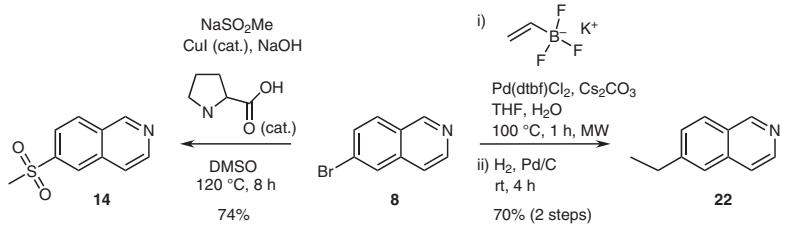
cially. The indenes can be ring-opened by low-temperature ozonolysis with a reductive workup. Subsequent addition of ammonia gives ring closure to the corresponding isoquinolines. The method is tolerant of halogen, alkoxy and nitro functional groups, can be carried out on multigram scale and usually requires no chromatography. This versatile method (Scheme 4, Method B) was used to prepare examples **6** to **11**. A related procedure described by Valdes[14] generates similar 1,5-dicarbonyl compounds via the Pd-catalysed cross-coupling of tosylhydrazones with nonaflates; these products are then cyclised with ammonia to give a range of 4-substituted isoquinolines.

Other functionalised isoquinolines were accessed by functional group interconversions. For example, copper-catalysed coupling of 6-bromoisoquinoline (**8**) to sodium methanesulfinate gave sulfone **14**. Suzuki coupling of **8** to a vinyl trifluoroborate salt followed by hydrogenation of the resulting alkene gave **22** (Scheme 5). This chemistry was also used to access regioisomeric **21**.

We found that the Mitsunobu reaction of hydroxyisoquinolines gave selective alkylation on oxygen; this was used to prepare **12** and **26** to **29**. Acylation using acetic anhydride gave **32**. Cinnamyl derivative **31** was synthesised by Horner–Wadsworth–Emmons reaction of commercially available aldehyde **30**. Amide **15** was formed by methylamine displacement of the corresponding ester in a sealed tube under high temperature and pressure. Amide couplings of isoquinoline-6-carboxylic acid using HATU [(dimethylamino)-*N*,*N*-dimethyl(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)methaniminium hexafluorophosphate] gave **16** and **20**. Ether **25** was made by displacement of the corresponding methyl bromide with sodium methoxide. The remaining commerically available starting materials (**5**, **13** and **24**) were purchased.

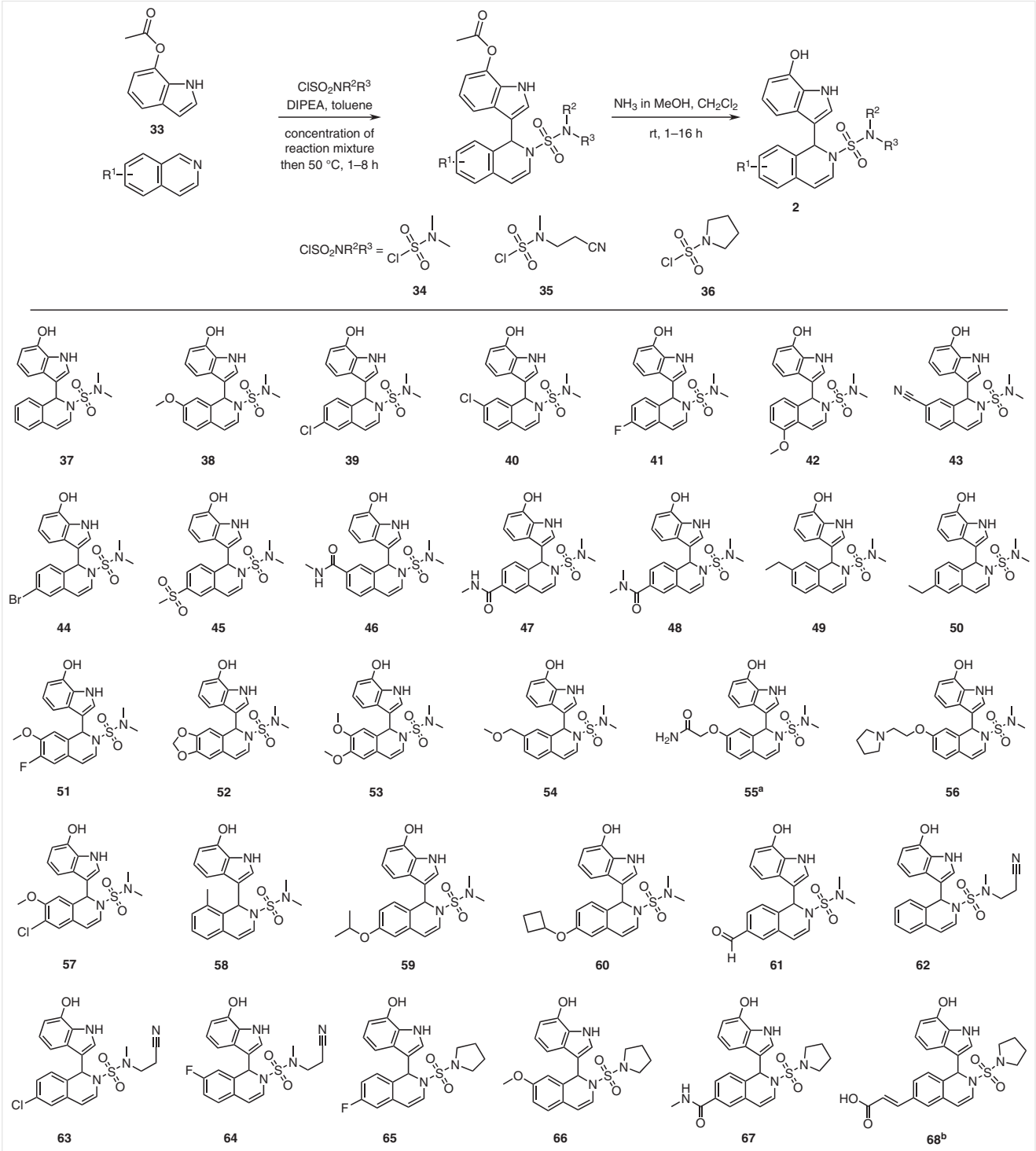
With the isoquinoline building blocks in hand (Figure 2), we examined the scope of the three-component reaction. We desired products of the general structure **2** containing a sulfonyl urea side-chain and a pendant 7-hydroxyl group on the indole ring. To avoid reaction of the hydroxyl group with the electrophile, acetyl was used as a protecting group. This remained intact during the three-component reaction and could be subsequently removed by treatment with a solution of ammonia in methanol (Scheme 6).

The reaction with sulfamoyl chlorides was significantly slower than the reaction with acid chlorides and required heating at around 40–50 °C in order to proceed. We found toluene could be used as solvent in place of benzene and the reaction rate was greatly increased by higher concentration. An effective procedure was to combine the reactants in toluene, then to concentrate the mixture under



Scheme 5 Derivatisation of 6-bromoisoquinoline

vacuum to a thick but stirrable paste. Reaction would then proceed to completion in several hours. The reaction mixtures were usually diluted with a small volume of CH_2Cl_2 and loaded directly onto silica gel columns; chromatography gave the products in 24–74% yield. The reaction tolerated a wide range of electron-donating and -withdrawing



Scheme 6 Indole-isoquinoline couplings promoted by sulfamoyl chlorides using acetyl protection of pendant OH. [a] Primary amide formed during deprotection with ammonia. [b] Cinnamic acid formed during deprotection with sodium hydroxide.

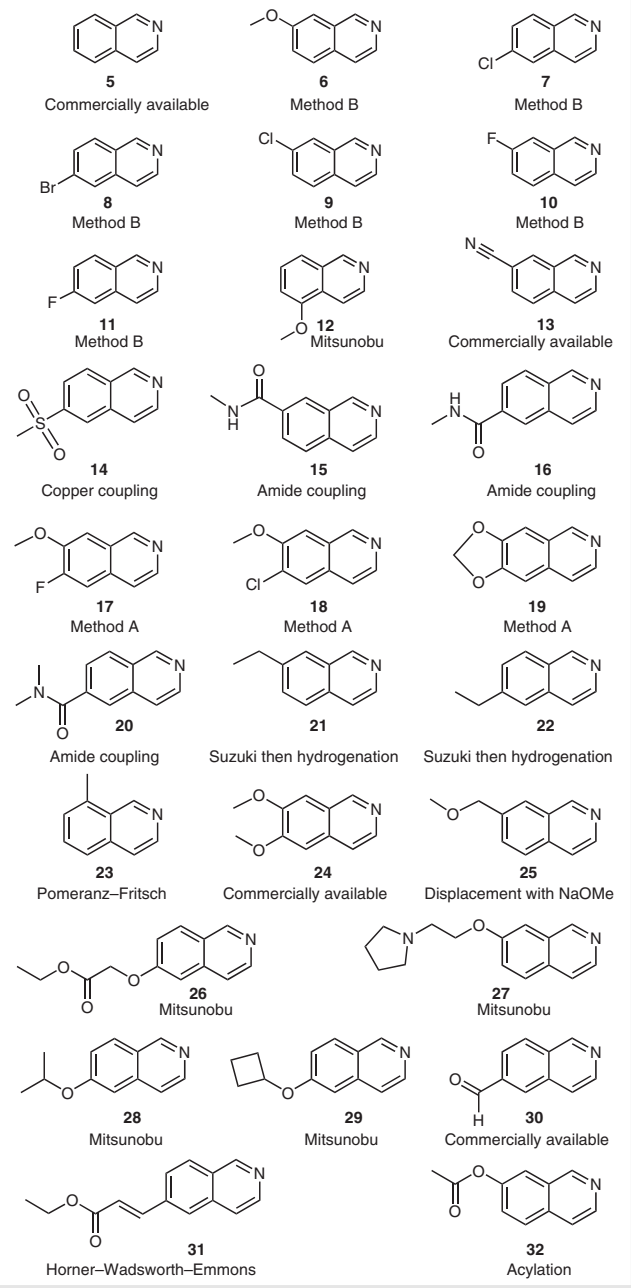


Figure 2 Substrate scope of isoquinolines used in multicomponent reactions

functional groups. Isoquinolines bearing halogens, nitriles, amides and esters could all be successfully employed in the reaction.

Following deprotection with ammonia in methanol, we were able to generate a diverse library of 7-hydroxyindole-dihydroisoquinolines (Table 1). The products were generally isolated cleanly, although in some examples the isoquinoline starting material co-eluted with the product. Trituration of these mixtures with diethyl ether gave clean final products.

Aldehyde **30** gave a low yield in the 3-component reaction; decomposition occurred on treatment with ammonia (Table 1, entry 25). In the case of **55** (entry 19), where the isoquinoline was bearing an ester group, the primary amide

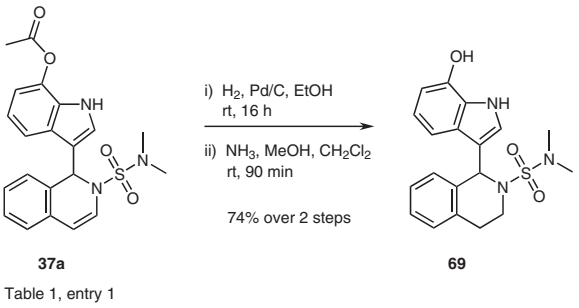
Table 1 Indole-Isoquinoline Couplings Promoted by Sulfamoyl Chlorides Using Acetyl Protection of Pendant OH

Entry	Isoquinoline	Sulfamoyl-chloride	Product	3-CR Time (h)	3-CR Yield (%)	Deprotection yield (%)
1	**5**	**34**	**37**	3	42	89
2	**6**	**34**	**38**	2	52	59
3	**7**	**34**	**39**	1	48	60
4	**9**	**34**	**40**	2	45	51
5	**11**	**34**	**41**	2	47	53
6	**12**	**34**	**42**	1	51	43
7	**13**	**34**	**43**	1	53	30
8	**8**	**34**	**44**	3	59	90
9	**14**	**34**	**45**	5	74	89
10	**15**	**34**	**46**	3	38	53
11	**16**	**34**	**47**	6	58	85
12	**20**	**34**	**48**	6	24	83
13	**21**	**34**	**49**	1	31	89
14	**22**	**34**	**50**	5	38	83
15	**17**	**34**	**51**	8	40	55
16	**19**	**34**	**52**	2	31	93
17	**24**	**34**	**53**	8	38	84
18	**25**	**34**	**54**	1	54	27
19	**26**	**34**	**55**[a]	2	31	72
20	**27**	**34**	**56**	3	32	82
21	**18**	**34**	**57**	1	37	54
22	**23**	**34**	**58**	1	37	46
23	**28**	**34**	**59**	3	52	65
24	**29**	**34**	**60**	4	22	17
25	**30**	**34**	**61**	1	35[b]	dec.
26	**5**	**35**	**62**	2	51	64
27	**7**	**35**	**63**	1	46	34
28	**10**	**35**	**64**	1	41	51
30	**11**	**36**	**65**	1	12% over 2 steps	
31	**6**	**36**	**66**	1	5% over 2 steps	
32	**16**	**36**	**67**	1	8% over 2 steps	
33	**31**	**36**	**68**[c]	1	10% over 2 steps	

[a] Primary amide formed during deprotection with ammonia.
[b] Conversion based on LCMS analysis of 3-CR reaction mixture.
[c] Cinnamic acid formed during deprotection with sodium hydroxide.

was formed under the ammonia deprotection conditions. For **68** (entry 33), use of sodium hydroxide in the acetyl deprotection led to formation of the cinnamic acid product.

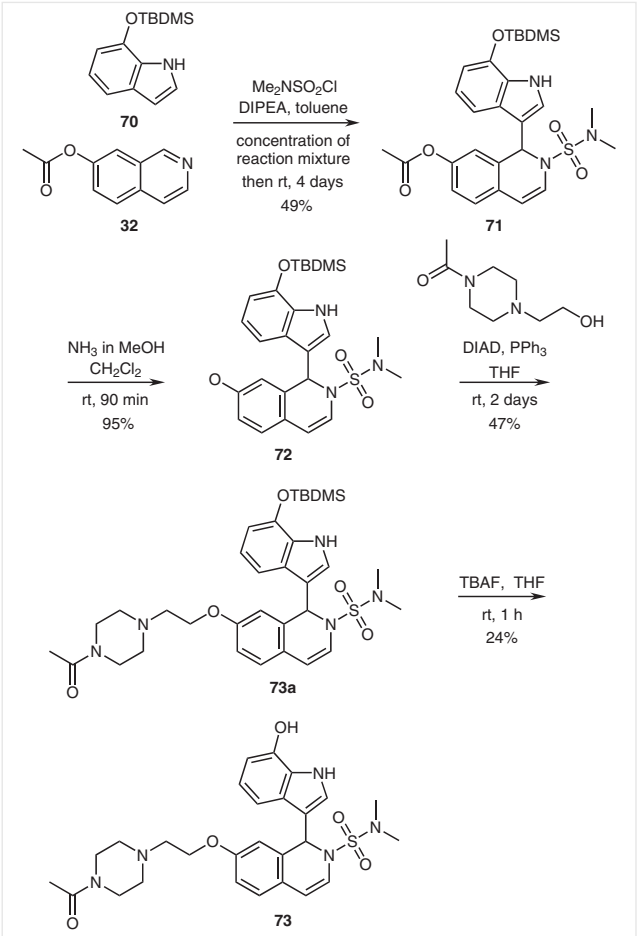
The 3,4-double bond remaining in the products after the three-component reaction could be hydrogenated to give the tetrahydroisoquinoline motif. Deprotection using the standard conditions gave analogues such as **69**, obtained from **37a** (Scheme 7).



Scheme 7 Hydrogenation to give tetrahydroisoquinoline analogues

A more divergent approach, that allowed late-stage variation of the 7-OR group, was carried out via intermediate **71** (Scheme 8). Here, the hydroxyl groups pendant to the indole and isoquinoline rings were differentially protected with TBDMS and acetyl groups respectively. After the three-component reaction, the acetyl group was selectively deprotected with methanolic ammonia, revealing phenol **72**. This could be subjected to alkylation under Mitsunobu conditions, followed by desilylation using TBAF to afford the desired hydroxyindole final product **73**.

In summary, we have used a variety of methods to access functionalised isoquinolines then utilised them in a three-component reaction to produce a diverse library of indole-dihydroisoquinoline sulfonyl ureas. We have demonstrated that the residual alkene may be saturated using hydrogenation and that, using differential protection strategies, further diversification of the products can be achieved.



Scheme 8 Differential protection strategy

Unless otherwise noted, all reagents and solvents were purchased from commercial sources and used without further purification. Non-aqueous reactions were performed under a N_2 atmosphere, unless otherwise noted. Evaporations were carried out by rotary evaporation and workup procedures were carried out after removal of residual solids by filtration. Compounds were dried under high vacuum after evaporation; small amounts of solvent residues sometimes remained after drying. Solvent residue levels were determined by ^{1}H NMR and yields are corrected for any residual solvent. Flash chromatography purifications were performed on an automated Teledyne Isco CombiFlash® Rf or Teledyne Isco CombiFlash® Companion® using prepacked RediSep Rf Gold™ Silica Columns (20–40 µm, spherical particles), GraceResolv™ Cartridges (Davisil® silica) or Silicycle cartridges (40–63 µm). Flash reverse-phase chromatography was performed using Interchim PrepaFlash C18 silica columns (30 µm). Structures of end products were confirmed by NMR spectroscopy, and NMR chemical shift values were measured on the delta scale. ^{1}H NMR spectra were recorded on a Bruker Avance 500 (500 MHz) or a Bruker Avance 400 (400 MHz) spectrometer. Measurements were taken at r.t. unless otherwise specified, and standard abbreviations are used. High-resolution mass spectrometry data were recorded on a Bruker MicrOTOF-Q II mass spectrometer. Low-resolution mass spectroscopy was carried out following liquid chromatography (LCMS or UPLC) performed in the following manner: UPLC was carried out using a Waters UPLC fitted with a Waters SQ mass spectrometer (column temp 40 °C, UV: 220–300 nm, Mass Spec: ESI with positive/negative switching) at a flow rate of 1 mL/min using a solvent system of 97% A/3% B to 3% A/97% B over 1.50 min (total run time with equilibration back to starting conditions: 1.70 min), where A = 0.1% formic acid in H_2O (for acid work) or 0.1% ammonia in H_2O (for base work) and B = MeCN. For acid analysis the column used was a Waters Acquity HSS T3 1.8 µm 2.1 × 50 mm, for base analysis the column used was a Waters Acquity BEH 1.7 µm 2.1 × 50 mm. The reported molecular ion corresponds to the $[M + H]^+$ (protonated molecule) or $[M - H]^-$ (deprotonated molecule). For molecules with multiple isotopic patterns (Br, Cl, etc.), the reported value is the one obtained for the lowest isotope mass, unless otherwise specified.

8-Methylisoquinoline (23) via Classical Pomeranz–Fritsch Reaction

[CAS Reg. No. 62882-00-2]

2,2-Dimethoxyethanamine (21.8 mL, 200 mmol) was added in one portion to 2-methylbenzaldehyde (23.1 mL, 200 mmol) in toluene (200 mL) at r.t. The resulting solution was heated at 125 °C for 3 h under Dean–Stark conditions. The mixture was cooled to r.t. and concentrated under reduced pressure. The resulting orange oil was dissolved in THF (120 mL) and cooled to –5 °C. Ethyl chloroformate (19.1 mL, 200 mmol) was added portionwise under N_2 to this solution at –5 °C. The mixture was allowed to warm to r.t. and stirred at r.t. for a further 1 h. An orange suspension was obtained. Trimethyl phosphite (29.5 mL, 250 mmol) was added portionwise to this suspension and the mixture stirred at r.t. for 16 h. The mixture was cooled in an ice bath, then poured onto a mixture of ice (200 g) and concentrated aq ammonia (100 mL). After stirring for 30 min, the mixture was filtered; the residue was carefully extracted with CH_2Cl_2 (5 × with mechanical stirring) and the combined organic layers were extracted with aq 1 N HCl (2 × 50 mL). The combined aqueous extracts were washed with CH_2Cl_2 (50 mL). Concentrated aq ammonia (10 mL) was added to the aqueous layer; this was extracted with CH_2Cl_2 (2 × 50 mL). These combined organic extracts were dried (Na_2SO_4) and concentrated under vacuum to give the title compound **23** (14.1 g, 49%) as a colourless oil, which later solidified on standing.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.47 (d, *J* = 0.9 Hz, 1 H), 8.54 (d, *J* = 5.5 Hz, 1 H), 7.82 (dd, *J* = 5.5, 0.9 Hz, 1 H), 7.80 (d, *J* = 8.2 Hz, 1 H), 7.66 (dd, *J* = 8.2, 7.0 Hz, 1 H), 7.49 (d, *J* = 7.0 Hz, 1 H), 2.77 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.7, 143.2, 136.0, 135.7, 130.8, 128.5, 127.6, 125.2, 121.1, 18.5.

MS (ES+): *m*/*z* = 144 $[M + H]^+$.

Method A: Isoquinoline Synthesis via Acetal Cyclisation

***N*-(2,2-Dimethoxyethyl)-4-methylbenzenesulfonamide (3)**

[CAS Reg. No. 58754-95-3]

2,2-Dimethoxyethanamine (5.45 mL, 50.0 mmol) was added dropwise to a stirred suspension of 4-methylbenzene-1-sulfonyl chloride (11.4 g, 60.0 mmol) and Na_2CO_3 (106 g, 1.00 mol) in THF (395 mL) at r.t. The reaction mixture was stirred at r.t. for 3 days. The mixture was filtered and the solid was washed with CH_2Cl_2 (200 mL). The combined filtrates were washed with H_2O (100 mL) and sat. brine (100 mL), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica gel chromatography (eluent: gradient 0 to 60% Et_2O in heptane). Pure fractions were evaporated to dryness to afford the title compound **3** (12.1 g, 93%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 4.66 (t, *J* = 6.2 Hz, 1 H), 4.33 (t, *J* = 5.6 Hz, 1 H), 3.33 (s, 6 H), 3.03 (dd, *J* = 6.2, 5.6 Hz, 2 H), 2.43 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.6, 136.8, 129.8, 127.1, 102.6, 54.7, 44.6, 21.5.

MS (ES+): *m*/*z* = 258 $[M + H]^+$.

***N*-(2,2-Dimethoxyethyl)-*N*-(4-fluoro-3-methoxybenzyl)-4-methylbenzenesulfonamide (4)**

A solution of **3** (870 mg, 3.36 mmol) in DMF (8 mL) was treated with 60% NaH dispersion in mineral oil (134 mg, 3.36 mmol) under N_2. The mixture was stirred at r.t. for 10 min, then 4-(bromomethyl)-1-fluoro-2-methoxybenzene (700 mg, 3.20 mmol) was added. The resulting mixture was stirred at 20 °C under N_2 for 2 h. The mixture was diluted with H_2O (80 mL) and extracted with EtOAc (80 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica gel chromatography (eluent: gradient 20 to 25% EtOAc in heptane). Pure fractions were evaporated to dryness and dried under high vacuum to afford the title compound **4**, containing 32 mol% EtOAc (1.20 g, 88%, allowing for solvent residues) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 6.96 (dd, *J* = 11.1, 8.2 Hz, 1 H), 6.82 (dd, *J* = 8.2, 2.1 Hz, 1 H), 6.71 (ddd, *J* = 8.2, 4.2, 2.1 Hz, 1 H), 4.42 (s, 2 H), 4.36 (t, *J* = 5.3 Hz, 1 H), 3.78 (s, 3 H), 3.26 (s, 6 H), 3.21 (d, *J* = 5.3 Hz, 2 H), 2.43 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.9 (*J* = 245.6 Hz), 147.7 (*J* = 11.0 Hz), 143.4, 137.5, 132.6 (*J* = 3.7 Hz), 129.7, 127.2, 120.9 (*J* = 6.8 Hz), 115.7 (*J* = 18.5 Hz), 113.4 (*J* = 1.7 Hz), 104.0, 56.1, 54.7, 52.3, 48.8, 21.5.

MS (ES+): *m*/*z* = 334 $[M + H – 2 MeOH]^+$.

6-Fluoro-7-methoxyisoquinoline (17)

[CAS Reg. No. 1036711-00-8]

A solution of **4** (1.18 g, 2.96 mmol) in 1,4-dioxane (12 mL) was treated with 6 N aq HCl (3.94 mL, 23.7 mmol) under N_2. The resulting mixture was stirred under vigourous reflux for 24 h. The mixture was evaporated and the residue partitioned between EtOAc (50 mL) and 0.1 M aq $NaHCO_3$ (70 mL). The aqueous layer was extracted with EtOAc (70 mL) and the extracts combined with the organic layer. The combined organic extracts were washed with sat. brine (50 mL), dried (Na_2SO_4), filtered and evaporated. The crude product was purified by flash silica gel chromatography (eluent: gradient 20 to 50% EtOAc in heptane). Pure fractions were evaporated to dryness to afford the title compound **17** (376 mg, 72%) as a beige solid; mp 129–131 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.13 (s, 1 H), 8.44 (d, *J* = 5.7 Hz, 1 H), 7.54 (d, *J* = 5.7 Hz, 1 H), 7.45 (d, *J* = 11.2 Hz, 1 H), 7.32 (d, *J* = 8.3 Hz, 1 H), 4.04 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.3 (*J* = 256.5 Hz), 150.5 (*J* = 1.3 Hz), 148.9 (*J* = 13.6 Hz), 142.2, 131.5 (*J* = 9.9 Hz), 126.4, 119.7 (*J* = 5.4 Hz), 111.0 (*J* = 18.5 Hz), 107.5 (*J* = 3.3 Hz), 56.2.

MS (ES+): *m*/*z* = 178 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_8FNO$: 178.0668; found: 178.0666

6-Chloro-7-methoxyisoquinoline (18)

[CAS Reg. No. 1187791-51-0]

Synthesised by a method analogous to that used for **17**, starting from 4-(bromomethyl)-1-chloro-2-methoxybenzene (1.01 g, 4.28 mmol) and **3** (1.17 g, 4.49 mmol). The title compound **18** was obtained as a pale yellow gum (116 mg, 14% over 2 steps).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.24 (s, 1 H), 8.41 (d, *J* = 5.7 Hz, 1 H), 8.16 (s, 1 H), 7.73 (d, *J* = 5.7 Hz, 1 H), 7.71 (s, 1 H), 4.01 (s, 3 H).

MS (ES+): *m*/*z* = 194 $[M + H]^+$.

6,7-Methylenedioxyisoquinoline (19)

[CAS Reg. No. 269-44-3]

Synthesised by a method analogous to that used for **17**, starting from 3,4-methylenedioxybenzyl bromide (321 mg, 1.49 mmol) and **3** (406 mg, 1.57 mmol). The title compound **19** was obtained as a white solid (145 mg, 56% over 2 steps).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.01 (s, 1 H), 8.30 (d, *J* = 8.6 Hz, 1 H), 7.63 (d, *J* = 8.6 Hz, 1 H), 7.46 (s, 1 H), 7.33 (s, 1 H), 6.20 (s, 2 H).

MS (ES+): m/z = 174 $[M + H]^+$.

Method B: Isoquinoline Synthesis via Ozonolysis

7-Methoxyisoquinoline (6)

[CAS Reg. No. 39989-39-4]

$NaBH_4$ (1.49 g, 39.3 mmol) was added to a solution of 6-methoxyindan-1-one (5.50 g, 33.9 mmol) in MeOH (100 mL) and stirred for 90 min at r.t. The reaction was quenched with H_2O (400 mL) and the mixture stirred for 15 min. The resulting mixture was extracted with Et_2O (3 × 150 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated to afford 6-methoxyindan-1-ol (5.82 g, quantitative yield) as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, J = 8.3 Hz, 1 H), 6.96 (d, J = 2.4 Hz, 1 H), 6.82 (dd, J = 8.3, 2.4 Hz, 1 H), 5.20 (br m, 1 H), 3.80 (s, 3 H), 2.97 (ddd, J = 15.5, 8.5, 4.5 Hz, 1 H), 2.74 (ddd, J = 15.5, 8.2, 6.8 Hz, 1 H), 2.50 (dddd, J = 13.1, 8.2, 6.9, 4.5 Hz, 1 H), 1.94 (dddd, J = 13.1, 8.5, 6.8, 5.5 Hz, 1 H), 1.80 (br d, J = 6.2 Hz, 1 H).

MS (EI+): m/z = 164 $[M]^+$.

HRMS: m/z $[M]^+$ calcd for $C_{10}H_{12}O_2$: 164.0837; found: 164.0841.

p-TsOH·H_2O (544 mg, 2.86 mmol) was added to a solution of the above 6-methoxyindan-1-ol (4.70 g, 28.6 mmol) in toluene (125 mL). The mixture was heated to 120 °C under Dean–Stark conditions for 90 min. The mixture was cooled to r.t., washed with H_2O (2 × 125 mL) and sat. brine (75 mL), dried (Na_2SO_4) and evaporated to dryness to afford 5-methoxy-1*H*-indene (3.55 g, 85%) as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, J = 8.1 Hz, 1 H), 6.97 (d, J = 2.4 Hz, 1 H), 6.83 (dtd, J = 5.5, 1.9, 1.9, 0.6 Hz, 1 H), 6.76 (dd, J = 8.1, 2.4 Hz, 1 H), 6.57 (dt, J = 5.5, 1.9, 1.9 Hz, 1 H), 3.83 (s, 3 H), 3.34 (ddd, J = 1.9, 1.0, 1.0 Hz, 2 H).

MS (EI+): m/z = 146 $[M]^+$.

HRMS: m/z $[M]^+$ calcd for $C_{10}H_{10}O$: 146.0732; found: 146.0731.

A solution of 5-methoxy-1*H*-indene (2.40 g, 16.4 mmol) in MeOH (20 mL) and CH_2Cl_2 (50 mL) was cooled to –78 °C under N_2. O_3 (with O_2 carrier gas) was bubbled through the solution for 30 min. An exotherm to –65 °C occurred while the reaction was in progress; this subsided at the end of the reaction and a blue colouration of dissolved ozone was seen. Unreacted ozone was removed by flushing the reaction vessel with N_2. $NaHCO_3$ (1.75 g, 20.9 mmol) and Me_2S (3.28 mL, 44.3 mmol) were added. The cooling bath was removed and the mixture was stirred for 16 h at r.t.. Concd (28–30%) aq ammonia (20 mL) was added and the mixture stirred for a further 24 h. The mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic phases were extracted with 5% aq HCl (2 × 100 mL). The combined aqueous phases were washed with CH_2Cl_2 (100 mL) and basified with Na_2CO_3 to pH 10 with stirring. An oil precipitated from solution; the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with sat. brine (50 mL), dried ($MgSO_4$) and evaporated to afford the title compound **6** (1.27 g, 49%) as a brown oil, which was used without further purification.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.16 (s, 1 H), 8.41 (d, J = 5.7 Hz, 1 H), 7.73 (d, J = 9.0 Hz, 1 H), 7.58 (d, J = 5.7 Hz, 1 H), 7.35 (dd, J = 9.0, 2.5 Hz, 1 H), 7.22 (d, J = 2.5 Hz, 1 H), 3.96 (s, 3 H).

MS (ES+): m/z = 160 $[M + H]^+$.

6-Chloroisoquinoline (7)

[CAS Reg. No. 62882-02-4]

Synthesised by a method analogous to that used for **6**, starting from 5-chloroindan-1-one (6.13 g, 36.8 mmol). The title compound **7** (2.74 g, 46% over 3 steps) was obtained as beige needles; mp 37–39 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.23 (s, 1 H), 8.55 (d, J = 5.8 Hz, 1 H), 7.92 (d, J = 8.7 Hz, 1 H), 7.82 (d, J = 1.9 Hz, 1 H), 7.58 (d, J = 5.8 Hz, 1 H), 7.56 (dd, J = 8.7, 1.9 Hz, 1 H).

MS (ES+): m/z = 164 $[M + H]^+$.

6-Bromoisoquinoline (8)

[CAS Reg. No. 34784-05-9]

Synthesised by a method analogous to that used for **6**, starting from 5-bromoindan-1-one (10.0 g, 47.4 mmol). The title compound **8** (4.80 g, 48% over 3 steps) was obtained as a tan solid; mp 43–46 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.23 (s, 1 H), 8.55 (d, J = 5.8 Hz, 1 H), 8.00 (s, 1 H), 7.84 (d, J = 8.7 Hz, 1 H), 7.69 (dd, J = 1.6, 8.7 Hz, 1 H), 7.56 (d, J = 5.8 Hz, 1 H).

MS (ES+): m/z = 208 $[M + H]^+$.

7-Chloroisoquinoline (9)

[CAS Reg. No. 34784-06-0]

Synthesised by a method analogous to that used for **6**, starting from 6-chloroindan-1-one (2.88 g, 17.3 mmol). The title compound **9** (1.74 g, 62% over 3 steps) was obtained as a beige crystalline solid; mp 43–45 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.19 (s, 1 H), 8.55 (d, J = 5.7 Hz, 1 H), 7.96 (d, J = 2.0 Hz, 1 H), 7.78 (d, J = 8.8 Hz, 1 H), 7.66–7.61 (m, 2 H).

MS (ES+): m/z = 164 $[M + H]^+$.

7-Fluoroisoquinoline (10)

[CAS Reg. No. 1075-12-3]

Synthesised by a method analogous to that used for **6**, starting from 6-fluoroindan-1-one (3.44 g, 22.9 mmol). The title compound **10** (1.39 g, 42% over 3 steps) was obtained as a beige waxy solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.22 (s, 1 H), 8.52 (d, J = 5.7 Hz, 1 H), 7.84 (dd, J = 8.9, 5.2 Hz, 1 H), 7.65 (d, J = 5.7 Hz, 1 H), 7.58 (dd, J = 8.8, 2.5 Hz, 1 H), 7.48 (ddd, J = 8.9, 8.9, 2.5 Hz, 1 H).

MS (EI+): m/z = 147 $[M]^+$.

HRMS: m/z $[M]^+$ calcd for C_9H_6FN: 147.0484; found: 147.0481.

6-Fluoroisoquinoline (11)

[CAS Reg. No. 1075-11-2]

Synthesised by a method analogous to that used for **6**, starting from 5-fluoroindan-1-one (6.19 g, 41.2 mmol). The title compound **11** (655 mg, 11% over 3 steps) was obtained as a beige crystalline solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.23 (s, 1 H), 8.53 (d, J = 5.8 Hz, 1 H), 7.99 (dd, J = 8.9, 5.5 Hz, 1 H), 7.61 (d, J = 5.8 Hz, 1 H), 7.43 (dd, J = 9.3, 2.4 Hz, 1 H), 7.38 (ddd, J = 8.9, 8.9, 2.4 Hz, 1 H).

MS (EI+): m/z = 147 $[M]^+$.

HRMS: m/z $[M]^+$ calcd for C_9H_6FN: 147.0484; found: 147.0486.

6-(Methylsulfonyl)isoquinoline (14)

[CAS Reg. No. 2140306-43-8]

DMSO (4 mL) was added to 6-bromoisoquinoline (**8**; 377 mg, 1.81 mmol), $NaSO_2Me$ (277 mg, 2.72 mmol), CuI (35 mg, 0.18 mmol), (*S*)-pyrrolidine-2-carboxylic acid (42 mg, 0.36 mmol) and NaOH (15 mg, 0.36 mmol) at r.t. N_2 was bubbled through the reaction mixture for 5

min and the resulting solution was stirred at 115 °C for 2 h. Additional $NaSO_2Me$ (139 mg, 1.36 mmol), CuI (17 mg, 0.09 mmol), (*S*)-pyrrolidine-2-carboxylic acid (21 mg, 0.18 mmol) and NaOH (7 mg, 0.18 mmol) were added and heating continued at 120 °C for a further 3 h. The crude product was purified by flash reverse-phase chromatography [eluent: gradient 10 to 30% MeCN in H_2O (containing 1% NH_4OH as modifier)]. Pure fractions were evaporated to dryness to afford the title compound **14** (280 mg, 74%) as a beige solid; mp 124–126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.43 (br s, 1 H), 8.74 (br s, 1 H), 8.53 (s, 1 H), 8.20 (d, *J* = 8.6 Hz, 1 H), 8.06 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.83 (d, *J* = 5.6 Hz, 1 H), 3.15 (s, 3 H).

MS (ES+): *m*/*z* = 208 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{10}H_9NO_2S$: 208.0432; found: 208.0441

6-Ethylisoquinoline (22)

[CAS Reg. No. 679433-92-2]

6-Bromoisoquinoline (**8**, 469 mg, 2.25 mmol), potassium trifluoro(vinyl)borate (755 mg, 5.64 mmol), Cs_2CO_3 (2.20 g, 6.76 mmol) and dichloro[1,1′-bis(di-*tert*-butylphosphino)ferrocene]palladium(II) (30 mg, 0.05 mmol) were suspended in THF (9 mL) and H_2O (1 mL). N_2 was bubbled through the slurry for 5 min, which was then sealed into a microwave tube. The reaction mixture was heated to 100 °C for 1 h in a microwave reactor and cooled to r.t. The mixture was filtered; the filtrate was diluted with CH_2Cl_2 (10 mL) and washed sequentially with H_2O (10 mL) and sat. brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to give a brown oil. The crude product was purified by flash silica gel chromatography (eluent: gradient 5 to 30% EtOAc in heptane). Pure fractions were evaporated to dryness to afford 6-vinylisoquinoline (282 mg, 81%) as a pale yellow liquid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.28 (s, 1 H), 8.50 (d, *J* = 5.7 Hz, 1 H), 8.10 (d, *J* = 8.5 Hz, 1 H), 7.95 (s, 1 H), 7.92 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.80 (d, *J* = 5.7 Hz, 1 H), 6.96 (dd, *J* = 17.7, 11.2 Hz, 1 H), 6.12 (d, *J* = 17.7 Hz, 1 H), 5.51 (d, *J* = 11.2 Hz, 1 H).

MS (ES+): *m*/*z* = 156 $[M + H]^+$.

6-Vinylisoquinoline (245 mg, 1.58 mmol) was dissolved in EtOH (25 mL) and the solution was degassed and purged with N_2. Pd/C (5%; 34 mg, 0.02 mmol) was added and the solution was degassed and purged with H_2. The mixture was stirred under a balloon of H_2 at r.t. for 4 h. The mixture was purged with N_2, filtered and evaporated to dryness. The residue was purified by flash silica gel chromatography (eluent: gradient 0 to 30% EtOAc in heptane). Pure fractions were evaporated to dryness to afford the title compound **22** (215 mg, 87%) as an orange liquid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.25 (s, 1 H), 8.46 (d, *J* = 5.8 Hz, 1 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 7.76 (s, 1 H), 7.75 (d, *J* = 5.7 Hz, 1 H), 7.58 (dd, *J* = 8.4, 1.6 Hz, 1 H), 2.83 (q, *J* = 7.6 Hz, 2 H), 1.29 (t, *J* = 7.6 Hz, 3 H).

MS (ES+): *m*/*z* = 158 $[M + H]^+$.

7-Ethylisoquinoline (21)

[CAS Reg. No. 1507307-72-3]

Synthesised by a method analogous to that used for **22**, starting from 7-bromoisoquinoline (208 mg, 1.00 mmol). The title compound **21** (140 mg, 89%) was obtained as a pale yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.24 (s, 1 H), 8.48 (d, *J* = 5.7 Hz, 1 H), 7.85–7.74 (m, 2 H), 7.67 (d, *J* = 5.7 Hz, 1 H), 7.62 (dd, *J* = 8.5, 1.4 Hz, 1 H), 2.88 (q, *J* = 7.6 Hz, 2 H), 1.36 (t, *J* = 7.6 Hz, 3 H).

MS (ES+): *m*/*z* = 158 $[M + H]^+$.

5-Methoxyisoquinoline (12)

[CAS Reg. No. 90806-58-9]

Diisopropyl azodicarboxylate (DIAD; 2.98 mL, 15.2 mmol) was added to a suspension of isoquinolin-5-ol (2.00 g, 13.8 mmol), MeOH (0.780 mL, 19.3 mmol) and PPh_3 (3.98 g, 15.2 mmol) in anhyd THF (65 mL) at 0 °C under N_2. The resulting mixture was allowed to warm to r.t. and stirred for 18 h. The mixture was diluted with EtOAc (100 mL) and washed with sat. brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated onto silica gel. The crude product was purified by flash silica gel chromatography (eluent: gradient 0 to 40% EtOAc in heptane). Fractions containing the desired product were evaporated and the residue was further purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7 N NH_3 in MeOH and pure fractions were evaporated to dryness to afford the title compound **12** (670 mg, 31%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.21 (d, *J* = 0.8 Hz, 1 H), 8.54 (d, *J* = 5.8 Hz, 1 H), 8.01 (dd, *J* = 5.8 Hz, 1 H), 7.58–7.47 (m, 2 H), 7.01 (dd, *J* = 7.0, 1.6 Hz, 1 H), 4.02 (s, 3 H).

MS (ES+): *m*/*z* = 161 $[M + H]^+$.

Ethyl 2-(Isoquinolin-7-yloxy)acetate (26)

DIAD (0.326 mL, 1.65 mmol) was added to a mixture of ethyl 2-hydroxyacetate (0.155 mL, 1.65 mmol), isoquinolin-7-ol (200 mg, 1.38 mmol) and PPh_3 (434 mg, 1.65 mmol) in anhyd THF (10 mL) at r.t. The mixture was stirred at r.t. for 2 h. Additional PPh_3 (434 mg, 1.65 mmol) and DIAD (0.326 mL, 1.65 mmol) were added and stirring continued for a further 16 h. The mixture was evaporated and the residue was purified by flash silica gel chromatography (eluent: 50% EtOAc in heptane). Fractions containing the desired product were evaporated and the residue crystallised from EtOAc/heptane. The resulting solid (PPh_3O) was removed by filtration and discarded. The filtrate was evaporated to dryness and the residue partitioned between 0.5 M aq HCl (50 mL) and Et_2O (50 mL). The aqueous layer was basified to pH 9 with 2 M aq Na_2CO_3 and extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were filtered through phase-separating filter paper, dried (Na_2SO_4) and evaporated to dryness to afford **26** (148 mg, 46%) as a colourless gum.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.14 (s, 1 H), 8.44 (d, *J* = 5.6 Hz, 1 H), 7.78 (d, *J* = 9.0 Hz, 1 H), 7.60 (d, *J* = 5.6 Hz, 1 H), 7.46 (dd, *J* = 9.0, 2.6 Hz, 1 H), 7.16 (d, *J* = 2.6 Hz, 1 H), 4.78 (s, 2 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 1.33 (t, *J* = 7.2 Hz, 3 H).

MS (ES+): *m*/*z* = 232 $[M + H]^+$.

7-[2-(Pyrrolidin-1-yl)ethoxy]isoquinoline (27)

DIAD (0.651 mL, 3.31 mmol) was added to a mixture of 2-(pyrrolidin-1-yl)ethanol (0.387 mL, 3.31 mmol), isoquinolin-7-ol (400 mg, 2.76 mmol) and PPh_3 (867 mg, 3.31 mmol) in anhyd THF (20 mL) at r.t. The mixture was stirred at r.t. for 2 h. Additional PPh_3 (867 mg, 3.31 mmol) and DIAD (0.651 mL, 3.31 mmol) were added and stirring continued for a further 16 h. The reaction was quenched with H_2O (0.5 mL) and the mixture was diluted with MeOH (20 mL). The solution was loaded onto an SCX column; the column was first eluted with 1:1 CH_2Cl_2/MeOH to remove by-products, then with 2 N ammonia in MeOH. Fractions containing the desired product were evaporated to dryness. The crude product was purified by flash silica gel chromatography [eluent: gradient 2 to 7% (10:1 MeOH/concd aq NH_3) in CH_2Cl_2]. Pure fractions were evaporated to dryness to afford the title compound **27** (235 mg, 35%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.13 (s, 1 H), 8.41 (d, *J* = 5.6 Hz, 1 H), 7.72 (d, *J* = 9.0 Hz, 1 H), 7.57 (d, *J* = 5.6 Hz, 1 H), 7.39 (dd, *J* = 9.0, 2.5 Hz, 1 H), 7.23 (d, *J* = 2.5 Hz, 1 H), 4.26 (t, *J* = 5.9 Hz, 2 H), 2.99 (t, *J* = 5.9 Hz, 2 H), 2.62–2.73 (m, 4 H), 1.81–1.85 (m, 4 H).

MS (ES+): *m*/*z* = 243 $[M + H]^+$.

6-Isopropoxyisoquinoline (28)

[CAS Reg. No. 1394988-58-9]

DIAD (1.22 mL, 6.20 mmol) was added to a mixture of isoquinolin-6-ol (600 mg, 4.13 mmol), propan-2-ol (0.316 mL, 4.13 mmol) and PPh_3 (1.63 g, 6.20 mmol) in anhyd THF (5 mL) at r.t. The mixture was stirred at r.t. for 16 h. The mixture was loaded onto an SCX column; the column was first eluted with MeOH to remove by-products, then with 7 N ammonia in MeOH. Fractions containing the desired product were evaporated to afford the title compound **28** (622 mg, 80%) as a brown oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.12 (s, 1 H), 8.38 (d, *J* = 5.8 Hz, 1 H), 8.00 (d, *J* = 9.0 Hz, 1 H), 7.68 (d, *J* = 5.8 Hz, 1 H), 7.33 (d, *J* = 2.4 Hz, 1 H), 7.24 (dd, *J* = 9.0, 2.4 Hz, 1 H), 4.84 (hept, *J* = 6.0 Hz, 1 H), 1.36 (d, *J* = 6.0 Hz, 6 H).

MS (ES+): *m*/*z* = 188 $[M + H]^+$.

6-Cyclobutoxyisoquinoline (29)

[CAS Reg. No. 1822782-90-0]

DIAD (1.22 mL, 6.20 mmol) was added to a mixture of isoquinolin-6-ol (600 mg, 4.13 mmol), cyclobutanol (0.324 mL, 4.13 mmol) and PPh_3 (1.63 g, 6.20 mmol) in anhyd THF (5 mL) at r.t. for 16 h. Additional PPh_3 (1.63 g, 6.20 mmol) and DIAD (1.22 mL, 6.20 mmol) were added and the suspension was stirred at r.t. for a further 5 h. The mixture was loaded onto an SCX column; the column was first eluted with MeOH to remove by-products, then with 7 N ammonia in MeOH. Fractions containing the desired product were evaporated onto silica gel. The crude product was purified by flash silica gel chromatography (eluent: gradient 0 to 10% MeOH in CH_2Cl_2). Fractions containing the desired product were combined and evaporated to dryness to afford the title compound **29** (800 mg, 97%) as a yellow oil.

MS (ES+): *m*/*z* = 200 $[M + H]^+$.

Isoquinolin-7-yl Acetate (32)

[CAS Reg. No. 53758-13-5]

Isoquinolin-7-ol (2.00 g, 13.8 mmol) was treated with Ac_2O (26.0 mL, 276 mmol) and the mixture stirred at r.t. for 16 h. The mixture was concentrated and the residue was treated with Et_2O (100 mL). A dark precipitate formed, which was removed by filtration and discarded. The filtrate was diluted with Et_2O (200 mL) and washed with H_2O (3 × 200 mL), sat. brine (50 mL), dried ($MgSO_4$) and evaporated to afford the title compound **32**, 80% pure (1.38 g, 42%, allowing for impurities) as a pale pink solid, used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.23 (s, 1 H), 8.53 (d, *J* = 5.8 Hz, 1 H), 7.85 (d, *J* = 8.9 Hz, 1 H), 7.71 (d, *J* = 2.3 Hz, 1 H), 7.65 (d, *J* = 5.8 Hz, 1 H), 7.46 (dd, *J* = 8.9, 2.3 Hz, 1 H), 2.37 (s, 3 H).

MS (ES+): *m*/*z* = 188 $[M + H]^+$.

Ethyl (*E*)-3-(Isoquinolin-6-yl)acrylate (31)

[CAS Reg. No. 2159082-49-0]

Ethyl 2-(diethoxyphosphoryl)acetate (0.606 mL, 3.05 mmol) was added dropwise to a suspension of 60% NaH dispersion in mineral oil (112 mg, 2.80 mmol) in THF (10 mL) and cooled to 0 °C. The resulting mixture was stirred at 20 °C for 1 h. A solution of isoquinoline-6-carbaldehyde (**30**; 400 mg, 2.55 mmol) in THF (4 mL) was added slowly to the mixture, which was stirred at r.t. for a further 1 h. The reaction mixture was quenched with sat. aq NH_4Cl (25 mL) and extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The crude residue was triturated with Et_2O; the resulting precipitate was collected by filtration and dried under vacuum to afford the title compound **31** (239 mg, 41%) as a cream-coloured solid; mp 93–95 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.33 (s, 1 H), 8.55 (d, *J* = 5.8 Hz, 1 H), 8.27 (s, 1 H), 8.15 (d, *J* = 8.6 Hz, 1 H), 8.07 (dd, *J* = 8.6, 1.6 Hz, 1 H), 7.83 (d, *J* = 16.0 Hz, 1 H), 7.83 (d, *J* = 5.8 Hz, 1 H), 6.87 (d, *J* = 16.0 Hz, 1 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

MS (ES+): *m*/*z* = 228 $[M + H]^+$.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{13}NO_2$: 228.1025; found: 228.1032

***N*-Methylisoquinoline-7-carboxamide (15)**

[CAS Reg. No. 1158755-24-8]

Diisopropylethylamine (DIPEA; 0.419 mL, 2.40 mmol) was added to a mixture of isoquinoline-7-carboxylic acid (173 mg, 1.00 mmol), $MeNH_2$ solution (2 M in THF, 0.550 mL, 1.10 mmol) and HATU (418 mg, 1.10 mmol) in DMA (4 mL) at r.t. The reaction mixture was stirred at r.t. for 16 h. Additional $MeNH_2$ solution (2 M in THF, 0.550 mL, 1.10 mmol) and HATU (418 mg, 1.10 mmol) were added and the solution was stirred at r.t. for a further 2 h. The mixture was diluted with CH_2Cl_2 (50 mL), and washed sequentially with sat. aq $NaHCO_3$ (20 mL) and sat. brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7 N NH_3 in MeOH and pure fractions were evaporated to dryness to afford the title compound **15** (186 mg, quantitative yield) as a pale yellow oil, which solidified under vacuum.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.54 (s, 1 H), 8.75 (q, *J* = 4.5 Hz, 1 H), 8.73 (s, 1 H), 8.62 (d, *J* = 5.9 Hz, 1 H), 8.26 (dd, *J* = 8.6, 1.7 Hz, 1 H), 8.12 (d, *J* = 8.6 Hz, 1 H), 8.04 (d, *J* = 5.9 Hz, 1 H), 2.87 (d, *J* = 4.5 Hz, 3 H).

MS (ES+): *m*/*z* = 187 $[M + H]^+$.

***N*-Methylisoquinoline-6-carboxamide (16)**

[CAS Reg. No. 1158754-96-1]

Methyl isoquinoline-6-carboxylate (140 mg, 0.75 mmol) and $MeNH_2$ (33% in absolute EtOH, 0.931 mL, 7.48 mmol) were suspended in MeCN (1 mL) and sealed into a microwave tube. The reaction mixture was heated to 120 °C for 30 min in a microwave reactor and cooled to r.t.. Additional $MeNH_2$ solution (33% in absolute EtOH, 0.931 mL, 7.48 mmol) was added and heated to 140 °C in a microwave reactor for a further 60 min, then cooled to r.t. The mixture was evaporated and purified by flash reverse-phase chromatography [eluent: gradient 10 to 30% MeCN in H_2O (containing 1% NH_4OH as modifier)]. Pure fractions were evaporated to dryness to afford the title compound **16** (90 mg, 65%) as a cream-coloured solid; mp 130–134 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.39 (s, 1 H), 8.76 (br q, *J* = 4.2 Hz, 1 H), 8.58 (d, *J* = 5.7 Hz, 1 H), 8.44 (s, 1 H), 8.21 (d, *J* = 8.6 Hz, 1 H), 8.06 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.93 (d, *J* = 5.7 Hz, 1 H), 2.86 (d, *J* = 4.2 Hz, 3 H).

MS (ES+): *m*/*z* = 187 $[M + H]^+$.

***N*,*N*-Dimethylisoquinoline-6-carboxamide (20)**

[CAS Reg. No. 1789232-36-5]

$MeNH_2$·HCl (96 mg, 1.18 mmol) was added to a mixture of isoquinoline-6-carboxylic acid (170 mg, 0.98 mmol), HATU (448 mg, 1.18 mmol) and DIPEA (0.256 mL, 1.47 mmol) in DMF (4 mL) at 0 °C. The resulting solution was stirred at r.t. for 16 h. The mixture was purified by flash reverse-phase chromatography [eluent: gradient 10 to 30% MeCN in H_2O (containing 1% NH_4OH as modifier)]. Pure fractions were evaporated to dryness to afford the title compound **20** (112 mg, 57%) as a pale beige solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.37 (s, 1 H), 8.56 (d, *J* = 5.7 Hz, 1 H), 8.19 (d, *J* = 8.4 Hz, 1 H), 8.02 (s, 1 H), 7.89 (d, *J* = 5.7 Hz, 1 H), 7.67 (dd, *J* = 8.4, 1.6 Hz, 1 H), 3.06 (s, 3 H), 2.94 (s, 3 H).

MS (ES+): *m*/*z* = 201 $[M + H]^+$.

7-(Methoxymethyl)isoquinoline (25)

NaOMe (97 mg, 1.80 mmol) was added to a solution of 7-(bromomethyl)isoquinoline (200 mg, 0.90 mmol) in THF (5 mL). The resulting suspension was stirred at r.t. for 2 h. Additional NaOMe (97 mg, 1.80 mmol) was added and stirring continued at r.t. for 16 h. The reaction mixture was neutralised with sat. aq NH_4Cl and extracted with EtOAc (20 mL). The organic layer was washed sequentially with H_2O (20 mL) and sat. brine (20 mL), dried ($MgSO_4$), filtered and evaporated to afford the title compound **25** (101 mg, 64%) as a brown liquid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.31 (s, 1 H), 8.50 (d, *J* = 5.7 Hz, 1 H), 8.05 (s, 1 H), 7.96 (d, *J* = 8.5 Hz, 1 H), 7.82 (d, *J* = 5.7 Hz, 1 H), 7.72 (dd, *J* = 8.5, 1.7 Hz, 1 H), 4.63 (s, 2 H), 3.38 (s, 3 H).

MS (ES+): *m*/*z* = 174 $[M + H]^+$.

1*H*-Indol-7-yl Acetate (33)

[CAS Reg. No. 5526-13-6]

Et_3N (2.08 mL, 15.0 mmol) was added dropwise to a suspension of 1*H*-indol-7-ol (995 mg, 7.47 mmol) and Ac_2O (0.807 mL, 8.59 mmol) in CH_2Cl_2 (80 mL). The mixture was stirred at r.t. for 16 h. The mixture was washed with H_2O (4 × 25 mL) and sat. brine (10 mL), dried (Na_2SO_4), filtered and evaporated to afford the title compound **33** (1.31 g, quantitative yield) as a dark purple oil, which later crystallised; mp 50–52 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.29 (s, 1 H), 7.44 (d, *J* = 7.9 Hz, 1 H), 7.38 (t, *J* = 2.7 Hz, 1 H), 6.98 (t, *J* = 7.8 Hz, 1 H), 6.83 (dd, *J* = 7.6, 0.7 Hz, 1 H), 6.50 (dd, *J* = 3.0, 2.0 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.4, 136.7, 130.8, 128.9, 126.3, 119.3, 118.3, 113.8, 102.1, 21.4.

MS (ES–): *m*/*z* = 174 $[M - H]^-$.

Modified Method for Indole-Isoquinoline 3-Component Reactions

3-[2-(*N*,*N*-Dimethylsulfamoyl)-1,2-dihydroisoquinolin-1-yl]-1*H*-indol-7-yl Acetate (37a)

Dimethylsulfamoyl chloride (**34**; 0.144 mL, 1.34 mmol) was added to a solution of isoquinoline (**5**; 157 mg, 1.22 mmol) and 1*H*-indol-7-yl acetate (**33**; 213 mg, 1.22 mmol) in toluene (4 mL) at r.t. The mixture was concentrated to a thick but stirrable paste (1.5 mL), which was stirred at 50 °C for 3 h. TLC and LCMS showed reaction was largely complete by this time. The mixture was diluted with EtOAc (40 mL), washed with H_2O (40 mL) and sat. brine (20 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified by flash silica gel chromatography (loading in CH_2Cl_2) (eluent: gradient 20 to 50% EtOAc in heptane). Fractions containing the desired product were evaporated to afford the title compound **37a** (208 mg, 42%) as a white solid; mp 172–175 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.14 (s, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.40 (d, *J* = 7.3 Hz, 1 H), 7.23–7.34 (m, 3 H), 6.99 (t, *J* = 7.8 Hz, 1 H), 6.83 (dd, *J* = 7.7, 0.6 Hz, 1 H), 6.71 (d, *J* = 2.4 Hz, 1 H), 6.63 (dd, *J* = 7.4, 1.2 Hz, 1 H), 6.51 (s, 1 H), 6.24 (d, *J* = 7.4 Hz, 1 H), 2.56 (s, 6 H), 2.32 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.4, 136.6, 131.9, 130.3, 129.3, 128.3, 128.1, 128.0, 126.9, 126.3, 125.3, 125.2, 119.5, 117.8, 116.7, 114.3, 111.7, 54.6, 38.2, 21.4.

MS (ES–): *m*/*z* = 410 $[M - H]^-$.

1-(7-Hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (37)

A 7 N ammonia solution in MeOH (5.94 mL, 41.6 mmol) was added to a solution of **37a** (190 mg, 0.46 mmol) in CH_2Cl_2 (5 mL) and the mixture stirred at r.t. for 2 h. TLC and LCMS showed completion of the reaction. The mixture was evaporated to dryness and the residue partitioned between EtOAc (20 mL) and H_2O (15 mL). The organic layer was washed with H_2O (15 mL) and sat. brine (15 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash silica gel chromatography [eluent: gradient 0 to 1% (10:1 MeOH/concd aq NH_3) in CH_2Cl_2]. Pure fractions were evaporated to dryness to afford the title compound **37** (169 mg, 89%) as a white foam.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.75 (s, 1 H), 9.51 (s, 1 H), 7.37 (d, *J* = 7.3 Hz, 1 H), 7.22–7.33 (m, 4 H), 6.80 (t, *J* = 7.8 Hz, 1 H), 6.62 (dd, *J* = 7.4, 1.3 Hz, 1 H), 6.56 (d, *J* = 2.5 Hz, 1 H), 6.50 (d, *J* = 7.4 Hz, 1 H), 6.45 (s, 1 H), 6.22 (d, *J* = 7.4 Hz, 1 H), 2.55 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ =143.9, 132.2, 130.3, 128.1, 127.9, 127.4, 126.9, 126.8, 126.3, 125.1, 124.2, 120.0, 116.3, 111.5, 111.1, 106.0, 54.9, 38.2.

MS (ES–): *m*/*z* = 368 $[M - H]^-$.

HRMS: *m*/*z* $[M - H]^-$ calcd for $C_{19}H_{19}N_3O_3S$: 368.1069; found: 368.1082.

1-(7-Hydroxy-1*H*-indol-3-yl)-7-methoxy-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (38)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.123 mL, 1.14 mmol), 7-methoxyisoquinoline (**6**; 182 mg, 1.14 mmol), DIPEA (0.199 mL, 1.14 mmol) and 1*H*-indol-7-yl acetate (**33**; 200 mg, 1.14 mmol). The 3-component coupling took place in 52% yield, after concentrating the mixture and stirring at 45 °C for 2 h. The deprotection was carried out in 59% yield to afford the title compound **38** (138 mg) as a white foam.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.73 (s, 1 H), 9.49 (s, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.21 (d, *J* = 8.4 Hz, 1 H), 6.99 (d, *J* = 2.5 Hz, 1 H), 6.88 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.79 (t, *J* = 7.8 Hz, 1 H), 6.53 (d, *J* = 2.5 Hz, 1 H), 6.47–6.51 (m, 1 H), 6.44 (dd, *J* = 7.3, 1.3 Hz, 1 H), 6.41 (s, 1 H), 6.18 (d, *J* = 7.3 Hz, 1 H), 3.73 (s, 3 H), 2.55 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 59.3, 143.9, 134.0, 127.5, 126.8, 126.5, 124.3, 123.9, 123.4, 120.0, 115.9, 113.6, 112.5, 112.0, 111.2, 106.0, 55.7, 54.8, 38.2.

MS (ES–): *m*/*z* = 398 $[M - H]^-$.

HRMS: *m*/*z* $[M - H]^-$ calcd for $C_{20}H_{21}N_3O_4S$: 398.1175; found: 398.1169.

6-Chloro-1-(7-hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (39)

Synthesised by a method analogous to that used for **36**, starting from dimethylsulfamoyl chloride (**34**; 0.058 mL, 0.54 mmol), 6-chloroisoquinoline (**7**; 80 mg, 0.49 mmol), DIPEA (0.094 mL, 0.54 mmol) and 1*H*-indol-7-yl acetate (**33**; 86 mg, 0.49 mmol). The 3-component coupling took place in 48% yield, after concentrating the mixture and stirring at 50 °C for 1 h. The deprotection was carried out in 60% yield to afford the title compound **39** (67 mg) as a white crystalline solid; mp 113–117 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.80 (d, *J* = 1.9 Hz, 1 H), 9.51 (s, 1 H), 7.41 (d, *J* = 8.2 Hz, 1 H), 7.36 (d, *J* = 2.2 Hz, 1 H), 7.29 (d, *J* = 8.1 Hz, 1 H), 7.27 (dd, *J* = 8.1, 2.2 Hz, 1 H), 6.79 (t, *J* = 7.8 Hz, 1 H), 6.72 (dd, *J* = 7.5, 1.2 Hz, 1 H), 6.62 (d, *J* = 2.5 Hz, 1 H), 6.49 (dd, *J*= 7.5, 0.5 Hz, 1 H), 6.48 (s, 1 H), 6.20 (d, *J* = 7.5 Hz, 1 H), 2.55 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 144.0, 132.5, 132.3, 130.8, 128.7, 127.7, 127.4, 127.2, 126.9, 124.5, 124.2, 120.1, 116.1, 111.1, 109.8, 106.1, 54.4, 38.2.

MS (ES–): *m*/*z* = 402, 404 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{19}H_{18}ClN_3O_3S$: 402.0679; found: 402.0666.

7-Chloro-1-(7-hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (40)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.061 mL, 0.57 mmol), 7-chloroisoquinoline (**9**; 84 mg, 0.51 mmol), DIPEA (0.098 mL, 0.57 mmol) and 1*H*-indol-7-yl acetate **33** (90 mg, 0.51 mmol). The 3-component coupling took place in 45% yield, after concentrating the mixture and stirring at 50 °C for 2 h. The deprotection was carried out in 51% yield to afford the title compound **40** (104 mg) as a pale pink foam.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.81 (br d, *J* = 1.8 Hz, 1 H), 9.54 (s, 1 H), 7.52 (d, *J* = 2.0 Hz, 1 H), 7.34 (dd, *J* = 8.2, 2.0 Hz, 1 H), 7.30 (d, *J* = 7.8 Hz, 1 H), 7.28 (d, *J* = 8.2 Hz, 1 H), 6.80 (t, *J* = 7.8 Hz, 1 H), 6.69 (dd, *J* = 7.4, 1.2 Hz, 1 H), 6.66 (d, *J* = 2.6 Hz, 1 H), 6.48–6.53 (m, 2 H), 6.23 (d, *J* = 7.4 Hz, 1 H), 2.57 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 144.0, 134.1, 131.7, 129.2, 128.0, 127.2, 127.0, 126.8, 126.7, 126.6, 124.2, 120.1, 116.1, 111.1, 110.0, 106.1, 54.3, 38.2.

MS (ES–): *m*/*z* = 402 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{19}H_{17}ClN_3O_3S$: 402.0679; found: 402.0666

6-Fluoro-1-(7-hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (41)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.064 mL, 0.60 mmol), 6-fluoroisoquinoline (**11**; 80 mg, 0.54 mmol), DIPEA (0.104 mL, 0.60 mmol) and 1*H*-indol-7-yl acetate (**33**; 95 mg, 0.54 mmol). The 3-component coupling took place in 47% yield, after concentrating the mixture and stirring at 50 °C for 2 h. The deprotection was carried out in 53% yield to afford the title compound **41** (61 mg) as a white crystalline solid; mp 107–111 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.76 (s, 1 H), 9.50 (s, 1 H), 7.42 (dd, *J* = 8.5, 5.7 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.13 (dd, *J* = 9.7, 2.6 Hz, 1 H), 7.05 (ddd, *J* = 8.5, 8.5, 2.7 Hz, 1 H), 6.79 (t, *J* = 7.8 Hz, 1 H), 6.70 (d, *J* = 7.5 Hz, 1 H), 6.59 (d, *J* = 2.5 Hz, 1 H), 6.49 (s, 1 H), 6.46–6.48 (m, 1 H), 6.20 (d, *J* = 7.5 Hz, 1 H), 2.55 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 162.0 (d, *J* = 242.4 Hz), 143.9, 132.5 (d, *J* = 8.9 Hz), 128.8 (d, *J* = 8.4 Hz), 128.3, 127.5, 127.3, 126.9, 124.2, 120.1, 116.3, 114.3 (d, *J* = 21.9 Hz), 111.3 (d, *J* = 22.4 Hz), 111.1, 110.4, 106.0, 54.4, 38.1.

MS (ES–): *m*/*z* = 386 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{19}H_{18}FN_3O_3S$: 386.0975; found: 386.0987.

1-(7-Hydroxy-1*H*-indol-3-yl)-5-methoxy-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (42)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.118 mL, 1.10 mmol), 5-methoxyisoquinoline (**12**; 159 mg, 1.00 mmol), DIPEA (0.192 mL, 1.10 mmol) and 1*H*-indol-7-yl acetate (**33**; 175 mg, 1.00 mmol). The 3-component coupling took place in 51% yield, after concentrating the mixture and stirring at 50 °C for 1 h. The deprotection was carried out in 43% yield to afford the title compound **42** (89 mg) as a brown foam.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.72 (br s, 1 H), 9.49 (s, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.21 (dd, *J* = 8.3, 7.5 Hz, 1 H), 6.95 (d, *J* = 7.5 Hz, 1 H), 6.93 (d, *J* = 8.3 Hz, 1 H), 6.79 (t, *J* = 7.8 Hz, 1 H), 6.58 (dd, *J* = 7.6, 1.3 Hz, 1 H), 6.56 (d, *J* = 2.6 Hz, 1 H), 6.48 (dd, *J* = 7.5, 0.7 Hz, 1 H), 6.35–6.41 (m, 2 H), 3.85 (s, 3 H), 2.55 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 38.21, 54.73, 55.98, 105.99, 106.00, 110.17, 111.11, 115.90, 118.99, 119.14, 120.03, 124.27, 125.50, 126.79, 127.41, 128.81, 133.37, 143.91, 153.91.

MS (ES–): *m*/*z* = 398 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{20}H_{21}N_3O_4S$: 398.1175; found: 398.1169.

7-Cyano-1-(7-hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (43)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.132 mL, 1.22 mmol), 7-cyanoisoquinoline (**13**; 172 mg, 1.11 mmol), DIPEA (0.214 mL, 1.22 mmol) and 1*H*-indol-7-yl acetate (**33**; 195 mg, 1.11 mmol). The 3-component coupling took place in 53% yield, after concentrating the mixture and stirring at 50 °C for 1 h. The deprotection was carried out in 30% yield to afford the title compound **43** (73 mg) as a white solid; mp 196–199 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.85 (br s, 1 H), 9.55 (s, 1 H), 7.90 (d, *J* = 1.2 Hz, 1 H), 7.70 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 6.89 (dd, *J* = 7.5, 1.3 Hz, 1 H), 6.80 (t, *J* = 7.8 Hz, 1 H), 6.72 (d, *J* = 2.6 Hz, 1 H), 6.57 (s, 1 H), 6.50 (dd, *J* = 7.5, 0.6 Hz, 1 H), 6.26 (d, *J* = 7.5 Hz, 1 H), 2.55 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 144.0, 134.8, 132.6, 132.0, 130.7, 130.0, 127.0, 126.9, 125.7, 124.2, 120.3, 119.5, 116.1, 111.0, 109.4, 108.9, 106.2, 54.3, 38.1.

MS (ES–): *m*/*z* = 393 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{20}H_{18}N_4O_3S$: 393.1021; found: 393.1014.

6-Bromo-1-(7-hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (44)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.061 mL, 0.57 mmol), 6-bromoisoquinoline (**8**; 107 mg, 0.51 mmol), DIPEA (0.104 mL, 0.60 mmol) and 1*H*-indol-7-yl acetate (**33**; 90 mg, 0.51 mmol). The 3-component coupling took place in 59% yield, after concentrating the mixture and

stirring at 50 °C for 3 h. The deprotection was carried out in 90% yield to afford the title compound **44** (65 mg) as a white solid; mp 127–129 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.84 (d, *J* = 2.1 Hz, 1 H), 9.56 (s, 1 H), 7.55 (d, *J* = 2.0 Hz, 1 H), 7.45 (dd, *J* = 8.1, 2.0 Hz, 1 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 6.84 (dd, *J* = 8.0, 7.5 Hz, 1 H), 6.76 (dd, *J* = 7.5, 1.2 Hz, 1 H), 6.68 (d, *J* = 2.5 Hz, 1 H), 6.54 (dd, *J* = 7.5, 0.7 Hz, 1 H), 6.51 (s, 1 H), 6.24 (d, *J* = 7.5 Hz, 1 H), 2.60 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 144.0, 132.7, 131.2, 130.2, 129.0, 127.7, 127.4, 127.2, 126.9, 124.2, 121.0, 120.1, 116.0, 111.1, 109.7, 106.1, 54.5, 38.2.

MS (ES–): *m*/*z* = 446 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{19}H_{18}BrN_3O_3S$: 446.0174; found: 446.0176.

1-(7-Hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethyl-6-(methylsulfonyl)isoquinoline-2(1*H*)-sulfonamide (45)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.063 mL, 0.59 mmol), 6-(methylsulfonyl)isoquinoline (**14**, 111 mg, 0.54 mmol), DIPEA (0.103 mL, 0.59 mmol) and 1*H*-indol-7-yl acetate (**33**; 94 mg, 0.54 mmol). The 3-component coupling took place in 74% yield, after concentrating the mixture and stirring at 55 °C for 5 h. The deprotection was carried out in 89% yield to afford the title compound **45** (159 mg) as a cream-coloured solid; mp 152–154 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.86 (d, *J* = 1.9 Hz, 1 H), 9.55 (s, 1 H), 7.82 (d, *J* = 1.8 Hz, 1 H), 7.74 (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 6.84 (dd, *J* = 7.5, 1.1 Hz, 1 H), 6.81 (t, *J* = 7.8 Hz, 1 H), 6.76 (d, *J* = 2.5 Hz, 1 H), 6.59 (s, 1 H), 6.50 (d, *J* = 7.3 Hz, 1 H), 6.34 (d, *J* = 7.5 Hz, 1 H), 3.22 (s, 3 H), 2.55 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 144.0, 140.7, 136.9, 131.1, 128.5, 127.9, 127.0, 126.8, 125.9, 124.1, 123.3, 120.3, 115.9, 111.0, 109.1, 106.1, 54.6, 43.9, 38.1.

MS (ES–): *m*/*z* = 446 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{20}H_{21}N_3O_5S_2$: 446.0844; found: 446.0825.

2-(*N*,*N*-Dimethylsulfamoyl)-1-(7-hydroxy-1*H*-indol-3-yl)-*N*-methyl-1,2-dihydroisoquinoline-7-carboxamide (46)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.118 mL, 1.10 mmol), *N*-methylisoquinoline-7-carboxamide (**15**; 186 mg, 1.00 mmol), DIPEA (0.191 mL, 1.10 mmol) and 1*H*-indol-7-yl acetate (**33**; 175 mg, 1.00 mmol). The 3-component coupling took place in 38% yield, after concentrating the mixture and stirring at 50 °C for 1 h. The deprotection was carried out in 53% yield to afford the title compound **46** (88 mg) as a beige solid; mp 199–201 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.81 (d, *J* = 2.2 Hz, 1 H), 9.53 (s, 1 H), 8.34 (q, *J* = 4.4 Hz, 1 H), 7.79 (d, *J* = 1.3 Hz, 1 H), 7.75 (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 6.79 (t, *J* = 7.8 Hz, 1 H), 6.73 (dd, *J* = 7.5, 1.3 Hz, 1 H), 6.62 (d, *J* = 2.6 Hz, 1 H), 6.49 (dd, *J* = 7.5, 0.7 Hz, 1 H), 6.46 (s, 1 H), 6.26 (d, *J* = 7.4 Hz, 1 H), 2.75 (d, *J* = 4.6 Hz, 3 H), 2.55 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.5, 144.0, 133.6, 132.7, 131.9, 127.9, 127.3, 126.9, 126.8, 125.7, 124.9, 124.4, 120.2, 116.2, 111.1, 110.3, 106.1, 55.0, 38.2, 26.7.

MS (ES–): *m*/*z* = 425 [M – H]$^-$.

2-(*N*,*N*-Dimethylsulfamoyl)-1-(7-hydroxy-1*H*-indol-3-yl)-*N*-methyl-1,2-dihydroisoquinoline-6-carboxamide (47)

Dimethylsulfamoyl chloride (**34**; 0.052 mL, 0.48 mmol) was added to a solution of *N*-methylisoquinoline-6-carboxamide (**16**; 81 mg, 0.44 mmol) and DIPEA (0.084 mL, 0.48 mmol) in toluene (1 mL) at r.t. A solution of 1*H*-indol-7-yl acetate (**33**, 76 mg, 0.44 mmol) in toluene (1 mL) was added and the mixture concentrated to a thick but stirrable paste (0.7 mL). The residue was stirred at 50 °C for 3 h. Additional **34** (0.026 mL, 0.24 mmol) and DIPEA (0.042 mL, 0.22 mmol) were added and heating continued for a further 3 h at 50 °C. The crude product was purified by flash silica chromatography (eluent: gradient 0 to 10% MeOH in CH_2Cl_2). Pure fractions were evaporated to dryness to afford 3-[2-(*N*,*N*-dimethylsulfamoyl)-6-(methylcarbamoyl)-1,2-dihydroisoquinolin-1-yl]-1*H*-indol-7-yl acetate (**47a**; 119 mg, 58%) as a cream-coloured solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.20 (s, 1 H), 8.43 (q, *J* = 4.5 Hz, 1 H), 7.75 (d, *J* = 7.9 Hz, 1 H), 7.73 (d, *J* = 1.6 Hz, 1 H), 7.68 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.49 (d, *J* = 7.9 Hz, 1 H), 7.00 (t, *J* = 7.9 Hz, 1 H), 6.83 (d, *J* = 7.5 Hz, 1 H), 6.74 (d, *J* = 2.4 Hz, 1 H), 6.70 (dd, *J* = 7.5, 1.1 Hz, 1 H), 6.58 (s, 1 H), 6.29 (d, *J* = 7.5 Hz, 1 H), 2.78 (d, *J* = 4.5 Hz, 3 H), 2.56 (s, 6 H), 2.32 (s, 3 H).

MS (ES–): *m*/*z* = 469 [M + H]$^+$.

A 7 N ammonia solution in MeOH (0.970 mL, 6.79 mmol) was added to a solution of **47a** (106 mg, 0.23 mmol) in CH_2Cl_2 (15 mL) and the mixture stirred at r.t. for 2 h. TLC and LCMS showed completion of the reaction. The reaction mixture was evaporated and the crude product was purified by flash reverse-phase chromatography [eluent: gradient 25 to 50% MeCN in H_2O (containing 1% NH_4OH as modifier)]. Pure fractions were evaporated to dryness to afford the title compound **47** (82 mg, 85%) as a cream-coloured solid; mp 179–181 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.79 (d, *J* = 2.2 Hz, 1 H), 9.51 (s, 1 H), 8.41 (q, *J* = 4.5 Hz, 1 H), 7.71 (d, *J* = 1.7 Hz, 1 H), 7.67 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.45 (d, *J* = 7.9 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 6.79 (t, *J* = 8.0 Hz, 1 H), 6.69 (dd, *J* = 7.5, 1.2 Hz, 1 H), 6.61 (d, *J* = 2.6 Hz, 1 H), 6.46–6.52 (m, 2 H), 6.26 (d, *J* = 7.5 Hz, 1 H), 2.78 (d, *J* = 4.5 Hz, 3 H), 2.54 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.9, 144.0, 134.7, 134.6, 130.2, 127.3, 127.1, 126.9, 126.8, 126.4, 124.3, 123.9, 120.1, 116.0, 111.1, 110.8, 106.1, 54.7, 38.2, 26.7.

MS (ES–): *m*/*z* = 425 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{21}H_{22}N_4O_4S$: 425.1284; found: 425.1266.

2-(*N*,*N*-Dimethylsulfamoyl)-1-(7-hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethyl-1,2-dihydroisoquinoline-6-carboxamide (48)

Synthesised by a method analogous to that used for **47**, starting from dimethylsulfamoyl chloride (**34**; 0.052 mL, 0.48 mmol), *N*,*N*-dimethylisoquinoline-6-carboxamide (**20**; 88 mg, 0.44 mmol), DIPEA (0.084 mL, 0.44 mmol) and 1*H*-indol-7-yl acetate (**33**; 77 mg, 0.44 mmol). For the 3-component coupling, the mixture was concentrated and heated to 50 °C for 3 h. Additional **34** (0.026 mL, 0.24 mmol) and DIPEA (0.042 mL, 0.22 mmol) were added and heating continued for a further 3 h at 50 °C, giving the acetyl ester intermediate in 24% isolated yield. After deprotection, purification was carried out by flash reverse-phase chromatography [eluent: gradient 15 to 50% MeCN in H_2O (containing 1% NH_4OH as modifier)]. The title compound **48** (38 mg) was obtained in 83% yield as a cream-coloured solid; mp 173–176 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.80 (br s, 1 H), 9.54 (s, 1 H), 7.42 (d, *J* = 7.8 Hz, 1 H), 7.27–7.33 (m, 2 H), 7.24 (dd, *J* = 7.8, 1.7 Hz, 1 H), 6.80 (t, *J* = 7.8 Hz, 1 H), 6.69 (dd, *J* = 7.4, 1.3 Hz, 1 H), 6.65 (d, *J* = 2.4 Hz, 1 H), 6.46–6.51 (m, 2 H), 6.24 (d, *J* = 7.4 Hz, 1 H), 2.98 (s, 3 H), 2.92 (s, 3 H), 2.55 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.3, 144.0, 136.3, 133.0, 130.2, 127.3, 127.1, 126.8, 126.7, 126.3, 124.2, 123.6, 120.1, 116.1, 111.1, 110.6, 106.1, 54.7, 39.2, 38.2, 35.5.

MS (ES–): *m*/*z* = 439 [M – H]$^-$.

7-Ethyl-1-(7-hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (49)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.105 mL, 0.98 mmol), 7-ethylisoquinoline (**21**; 140 mg, 0.89 mmol), DIPEA (0.171 mL, 0.98 mmol) and 1*H*-indol-7-yl acetate (**33**; 156 mg, 0.89 mmol). The 3-component coupling took place in 31% yield, after concentrating the mixture and stirring at 50 °C for 1 h. The deprotection was carried out in 89% yield to afford the title compound **49** (116 mg) as a beige foam.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.72 (br s, 1 H), 9.49 (s, 1 H), 7.30 (d, *J* = 8.1 Hz, 1 H), 7.14–7.19 (m, 2 H), 7.12 (dd, *J* = 7.8, 1.6 Hz, 1 H), 6.78 (t, *J* = 7.8 Hz, 1 H), 6.56 (d, *J* = 2.4 Hz, 1 H), 6.53 (dd, *J* = 7.4, 1.3 Hz, 1 H), 6.48 (dd, *J* = 7.50, 0.6 Hz, 1 H), 6.38 (s, 1 H), 6.18 (d, *J* = 7.4 Hz, 1 H), 2.53 (s, 6 H), 2.52 (q, *J* = 7.6 Hz, 2 H), 1.14 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 143.9, 143.7, 132.4, 127.9, 127.5, 127.4, 126.8, 126.1, 125.4, 125.1, 124.2, 120.0, 116.3, 111.6, 111.1, 106.0, 55.0, 38.2, 28.4, 15.9.

MS (ES–): *m*/*z* = 396 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{21}H_{23}N_3O_3S$: 396.1382; found: 396.1370.

6-Ethyl-1-(7-hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (50)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.063 mL, 0.58 mmol), 6-ethylisoquinoline (**22**; 83 mg, 0.53 mmol), DIPEA (0.102 mL, 0.58 mmol) and 1*H*-indol-7-yl acetate (**33**; 93 mg, 0.53 mmol). The 3-component coupling took place in 38% yield, after concentrating the mixture and stirring at 50 °C for 5 h. After deprotection, purification was carried out first by flash silica gel chromatography, eluting with 5 to 70% EtOAc in heptane, then by flash reverse-phase chromatography [eluent: gradient 35 to 60% MeCN in H_2O (containing 1% NH_4OH as modifier)]. The title compound **50** (58 mg) was obtained in 83% yield as a cream-coloured solid; mp 144–148 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.71 (br s, 1 H), 9.49 (s, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.25 (d, *J* = 7.6 Hz, 1 H), 7.08–7.11 (m, 2 H), 6.76–6.81 (m, 1 H), 6.60 (dd, *J* = 7.4, 1.3 Hz, 1 H), 6.56 (d, *J* = 2.4 Hz, 1 H), 6.47–6.50 (m, 1 H), 6.39 (s, 1 H), 6.17 (d, *J* = 7.4 Hz, 1 H), 2.60 (q, *J* = 7.6 Hz, 2 H), 2.54 (s, 6 H), 1.19 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 143.9, 143.5, 130.1, 129.8, 127.4, 127.3, 126.8, 126.7, 126.2, 124.4, 124.1, 120.0, 116.6, 111.5, 111.2, 106.0, 54.8, 38.2, 28.3, 15.9.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{21}H_{23}N_3O_3S$: 396.1382; found: 396.1370.

6-Fluoro-1-(7-hydroxy-1*H*-indol-3-yl)-7-methoxy-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (51)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.079 mL, 0.73 mmol), 6-fluoro-7-methoxyisoquinoline (**17**; 100 mg, 0.56 mmol), DIPEA (0.128 mL, 0.73 mmol) and 1*H*-indol-7-yl acetate (**33**; 99 mg, 0.56 mmol). The 3-component coupling took place in 40% yield, after concentrating the mixture and stirring at 50 °C for 8 h. The deprotection was carried out in 55% yield to afford the title compound **51** (52 mg) as a white solid; mp 178–179 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.75 (d, *J* = 1.9 Hz, 1 H), 9.50 (s, 1 H), 7.35 (d, *J* = 7.9 Hz, 1 H), 7.27 (d, *J* = 8.5 Hz, 1 H), 7.18 (d, *J* = 11.9 Hz, 1 H), 6.80 (t, *J* = 7.9 Hz, 1 H), 6.53 (d, *J* = 2.4 Hz, 1 H), 6.48–6.52 (m, 2 H), 6.46 (s, 1 H), 6.15 (d, *J* = 7.4 Hz, 1 H), 3.79 (s, 3 H), 2.56 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 152.1 (*J* = 242.7 Hz), 146.9 (*J* = 11.1 Hz), 143.9, 128.7 (*J* = 2.9 Hz), 127.5, 126.9, 125.0, 124.5, 123.7 (*J* = 7.8 Hz), 120.1, 115.7, 112.7, 112.5, 112.4, 111.2, 106.0, 56.6, 54.4, 38.2.

MS (ES–): *m*/*z* = 416 [M – H]$^-$.

5-(7-Hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethyl-[1,3]dioxolo[4,5-*g*]isoquinoline-6(5*H*)-sulfonamide (52)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.099 mL, 0.92 mmol), 6,7-methylenedioxyisoquinoline (**19**; 145 mg, 0.92 mmol), DIPEA (0.160 mL, 0.92 mmol) and 1*H*-indol-7-yl acetate (**33**; 161 mg, 0.92 mmol). The 3-component coupling took place in 31% yield, after concentrating the mixture and stirring at 50 °C for 2 h. The deprotection was carried out in 93% yield to afford the title compound **52** (101 mg) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 1 H), 7.54 (d, *J* = 8.1 Hz, 1 H), 6.94 (dd, *J* = 8.1, 7.5 Hz, 1 H), 6.67 (s, 2 H), 6.62 (s, 1 H), 6.55 (d, *J* = 7.5 Hz, 1 H), 6.46 (dd, *J* = 7.3, 1.1 Hz, 1 H), 6.39 (s, 1 H), 5.99 (d, *J* = 7.3 Hz, 1 H), 5.96 (d, *J* = 1.3 Hz, 1 H), 5.93 (d, *J* = 1.3 Hz, 1 H), 2.63 (s, 6 H).

MS (ES–): *m*/*z* = 412 [M – H]$^-$.

1-(7-Hydroxy-1*H*-indol-3-yl)-6,7-dimethoxy-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (53)

Synthesised by a method analogous to that used for **47**, starting from dimethylsulfamoyl chloride (**34**; 0.072 mL, 0.67 mmol), 6,7-dimethoxyisoquinoline (**24**; 115 mg, 0.61 mmol), DIPEA (0.116 mL, 0.67 mmol) and 1*H*-indol-7-yl acetate (**33**; 106 mg, 0.61 mmol). For the 3-component coupling, the mixture was concentrated and heated to 50 °C for 5 h. Additional **34** (0.036 mL, 0.33 mmol) and DIPEA (0.058 mL, 0.33 mmol) were added and heating continued for a further 3 h at 50 °C, giving the acetyl ester intermediate in 38% isolated yield. After deprotection, purification was carried out by flash reverse-phase chromatography [eluent: gradient 30 to 60% MeCN in H_2O (containing 1% NH_4OH as modifier)]. The title compound **53** (76 mg) was obtained in 84% yield as a cream-coloured solid; mp 187–190 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.70 (d, *J* = 2.1 Hz, 1 H), 9.48 (s, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.02 (s, 1 H), 6.92 (s, 1 H), 6.79 (t, *J* = 7.9 Hz, 1 H), 6.45–6.51 (m, 2 H), 6.42 (dd, *J* = 7.3, 1.2 Hz, 1 H), 6.38 (s, 1 H), 6.17 (d, *J* = 7.3 Hz, 1 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 2.56 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 148.8, 148.5, 143.9, 127.6, 126.9, 124.8, 124.5, 124.0, 123.3, 119.9, 116.1, 112.5, 111.3, 110.7, 108.8, 106.0, 56.1, 56.0, 54.5, 38.3.

MS (ES–): *m*/*z* = 428 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{21}H_{23}N_3O_5S$: 428.1280; found: 428.1264.

1-(7-Hydroxy-1*H*-indol-3-yl)-7-(methoxymethyl)-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (54)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.069 mL, 0.64 mmol), 7-(methoxymethyl)isoquinoline (**25**; 101 mg, 0.58 mmol), DIPEA (0.112 mL, 0.64 mmol) and 1*H*-indol-7-yl acetate (**33**; 102 mg, 0.58 mmol). The 3-component coupling took place in 54% yield, after concentrating the mixture and stirring at 40 °C for 1 h. The deprotection was carried out in 27% yield to afford the title compound **54** (36 mg) as a brown solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.78 (br s, 1 H), 9.51 (s, 1 H), 7.26–7.31 (m, 2 H), 7.22–7.25 (m, 2 H), 6.78 (t, *J* = 7.8 Hz, 1 H), 6.61 (dd, *J* = 5.3, 1.3 Hz, 1 H), 6.58 (s, 1 H), 6.49 (dd, *J* = 7.4, 0.7 Hz, 1 H), 6.42 (s, 1 H), 6.21 (d, *J* = 7.4 Hz, 1 H), 4.36 (s, 2 H), 3.25 (s, 3 H), 2.54 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 143.9, 138.1, 132.2, 129.5, 127.4, 127.3, 126.8, 126.2, 126.0, 125.0, 124.3, 120.1, 116.4, 111.2, 111.1, 106.0, 73.9, 58.0, 54.9, 38.2

MS (ES–): *m*/*z* = 412 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{21}H_{23}N_3O_4S$: 412.1331; found: 412.1345.

2-[2-(*N*,*N*-Dimethylsulfamoyl)-1-(7-hydroxy-1*H*-indol-3-yl)-1,2-dihydroisoquinolin-7-yloxy]acetamide (55)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.074 mL, 0.69 mmol), ethyl 2-(isoquinolin-7-yloxy)acetate (**26**; 145 mg, 0.63 mmol), DIPEA (0.120 mL, 0.69 mmol) and 1*H*-indol-7-yl acetate (**33**; 110 mg, 0.63 mmol). The 3-component coupling took place in 31% yield, after concentrating the mixture and stirring at 50 °C for 2 h. The deprotection and subsequent primary amide formation was carried out in 72% yield to afford the title compound **55** (61 mg) as a beige crystalline solid; mp 184–187 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.76 (d, *J* = 2.2 Hz, 1 H), 9.52 (s, 1 H), 7.51 (s, 1 H), 7.37 (s, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.22 (d, *J* = 8.4 Hz, 1 H), 7.00 (d, *J* = 2.5 Hz, 1 H), 6.89 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.79 (t, *J* = 7.8 Hz, 1 H), 6.53 (d, *J* = 2.4 Hz, 1 H), 6.48 (d, *J* = 7.2 Hz, 1 H), 6.45 (dd, *J* = 7.4, 1.2 Hz, 1 H), 6.38 (s, 1 H), 6.19 (d, *J* = 7.4 Hz, 1 H), 4.33–4.45 (m, 2 H), 2.55 (s, 6 H).

MS (ES–): *m*/*z* = 441 [M – H]$^-$.

1-(7-Hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethyl-7-[2-(pyrrolidin-1-yl)ethoxy]isoquinoline-2(1*H*)-sulfonamide (56)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.068 mL, 0.64 mmol), 7-[2-(pyrrolidin-1-yl)ethoxy]isoquinoline (**27**; 140 mg, 0.58 mmol), DIPEA (0.111 mL, 0.64 mmol) and 1*H*-indol-7-yl acetate (**33**; 101 mg, 0.58 mmol). The 3-component coupling took place after concentrating the mixture and stirring at 50 °C for 3 h. Purification was by flash silica gel chromatography [eluent: gradient 0 to 3% (10:1 MeOH/concd aq NH_3) in CH_2Cl_2], giving the intermediate acetyl ester in 32% yield. The deprotection was carried out in 82% yield to afford the title compound **56** (71 mg) as a beige crystalline solid; mp 181–185 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.73 (d, *J* = 2.2 Hz, 1 H), 9.51 (s, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.19 (d, *J* = 8.4 Hz, 1 H), 7.00 (d, *J* = 2.5 Hz, 1 H), 6.87 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.79 (t, *J* = 7.8 Hz, 1 H), 6.54 (d, *J* = 2.5 Hz, 1 H), 6.47–6.51 (m, 1 H), 6.44 (dd, *J* = 7.3, 1.2 Hz, 1 H), 6.40 (s, 1 H), 6.17 (d, *J* = 7.3 Hz, 1 H), 3.96–4.10 (m, 2 H), 2.77 (t, *J* = 5.8 Hz, 2 H), 2.55 (s, 6 H), 2.47–2.53 (m, 4 H), 1.62–1.71 (m, 4 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 158.6, 143.9, 134.1, 127.5, 126.8, 126.5, 124.2, 123.9, 123.3, 120.0, 116.0, 114.1, 113.0, 111.9, 111.2, 106.0, 67.2, 54.8, 54.7, 54.5, 38.2, 23.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{30}N_4O_4S$: 483.2066; found: 483.2076.

6-Chloro-1-(7-hydroxy-1*H*-indol-3-yl)-7-methoxy-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (57)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.025 mL, 0.23 mmol), 6-chloro-7-methoxyisoquinoline (**18**; 34 mg, 0.18 mmol), DIPEA (0.040 mL, 0.23 mmol) and 1*H*-indol-7-yl acetate (**33**; 31 mg, 0.18 mmol). The 3-component coupling took place in 37% yield, after concentrating the mixture and stirring at 50 °C for 1 h. Following deprotection with ammonia in MeOH, purification was via flash silica gel chromatography (loading in CH_2Cl_2) (eluent: gradient 20 to 50% EtOAc in heptane), followed by trituration with Et_2O. The title compound **57** (15 mg, deprotection step yield 54%) was obtained as a white solid; mp 152–155 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.75 (s, 1 H), 9.48 (s, 1 H), 7.40 (s, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.26 (s, 1 H), 6.80 (dd, *J* = 8.0 Hz, 1 H), 6.56 (d, *J* = 2.4 Hz, 1 H), 6.46–6.53 (m, 3 H), 6.18 (d, *J* = 7.3 Hz, 1 H), 3.81 (s, 3 H), 2.56 (s, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 154.3, 143.9, 132.5, 127.4, 126.9, 126.3, 125.0, 124.5, 124.3, 120.5, 120.1, 115.4, 111.6, 111.1, 110.8, 106.1, 56.8, 54.5, 38.3.

MS (ES–): *m*/*z* = 432 [M – H]$^-$.

1-(7-Hydroxy-1*H*-indol-3-yl)-*N*,*N*,8-trimethylisoquinoline-2(1*H*)-sulfonamide (58)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.101 mL, 0.94 mmol), 8-methylisoquinoline (**23**; 123 mg, 0.86 mmol), DIPEA (0.164 mL, 0.94 mmol) and 1*H*-indol-7-yl acetate (**33**; 150 mg, 0.86 mmol). The 3-component coupling took place in 37% yield, after concentrating the mixture and stirring at 50 °C for 1 h. The deprotection was carried out in 46% yield to afford the title compound **58** (22 mg) as a grey solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.75 (s, 1 H), 9.52 (s, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.5 Hz, 1 H), 7.13–7.20 (m, 2 H), 6.81 (t, *J* = 7.8 Hz, 1 H), 6.49–6.52 (m, 2 H), 6.47 (dd, *J* = 7.3, 1.1 Hz, 1 H), 6.32 (d, *J* = 2.5 Hz, 1 H), 6.27 (d, *J* = 7.3 Hz, 1 H), 2.54 (s, 6 H), 2.15 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 144.0, 133.6, 130.9, 130.6, 130.0, 128.0, 127.9, 126.8, 125.4, 125.3, 123.3, 120.2, 113.9, 113.4, 110.9, 106.1, 51.7, 38.1, 18.3.

MS (ES–): *m*/*z* = 382 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{20}H_{21}N_3O_3S$: 382.1225; found: 382.1242.

1-(7-Hydroxy-1*H*-indol-3-yl)-6-isopropoxy-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (59)

Synthesised by a method analogous to that used for **37**, starting from dimethylsulfamoyl chloride (**34**; 0.392 mL, 3.65 mmol), 6-isopropoxyisoquinoline (**28**; 622 mg, 3.32 mmol), DIPEA (0.636 mL, 3.65 mmol) and 1*H*-indol-7-yl acetate (**33**; 582 mg, 3.32 mmol). The 3-component coupling took place in 52% yield, after concentrating the mixture and stirring at 50 °C for 3 h. Purification was by flash silica gel chromatography (eluent: 0 to 10% MeOH in CH_2Cl_2). The deprotection was carried out in 65% yield; purification of the final product

was by flash silica chromatography (eluent: 0 to 40% EtOAc in CH_2Cl_2 to afford the title compound **59** (489 mg) as a cream-coloured solid; mp 173–176 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.71 (d, *J* = 2.0 Hz, 1 H), 9.48 (s, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.24 (d, *J* = 8.3 Hz, 1 H), 6.82 (d, *J* = 2.5 Hz, 1 H), 6.77 (m, 2 H), 6.59 (dd, *J* = 7.4, 1.1 Hz, 1 H), 6.55 (d, *J* = 2.5 Hz, 1 H), 6.48 (d, *J* = 7.1 Hz, 1 H), 6.36 (s, 1 H), 6.15 (d, *J* = 7.4 Hz, 1 H), 4.60 (hept, *J* = 6.0 Hz, 1 H), 2.55 (s, 6 H), 1.27 (dd, *J* = 6.0, 2.0 Hz, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.3, 143.9, 131.5, 127.9, 127.4, 126.9, 126.4, 124.5, 124.2, 120.0, 116.7, 115.0, 111.7, 111.6, 111.2 106.0, 69.7, 54.5, 38.2, 22.4, 22.3.

MS (ES–): *m*/*z* = 426 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{22}H_{25}N_3O_4S$: 426.1488; found: 426.1494.

6-Cyclobutoxy-1-(7-hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (60)

Synthesised by a method analogous to that used for **47**, starting from dimethylsulfamoyl chloride (**34**; 0.133 mL, 1.24 mmol), 6-cyclobutoxyisoquinoline (**29**; 223 mg, 1.12 mmol), DIPEA (0.215 mL, 1.24 mmol) and 1*H*-indol-7-yl acetate (**33**; 197 mg, 1.12 mmol). For the 3-component coupling, the mixture was concentrated and heated to 50 °C for 3 h. Additional **34** (0.133 mL, 1.24 mmol), DIPEA (0.215 mL, 1.24 mmol) and **33** (197 mg, 1.12 mmol) were added and heating continued for a further 1 h at 50 °C. Purification was carried out by flash silica gel chromatography (eluent: 0 to 5% MeOH in CH_2Cl_2), giving the acetyl ester intermediate in 22% isolated yield. After deprotection, purification was carried out by flash silica gel chromatography (eluent: 0 to 40% EtOAc in CH_2Cl_2), followed by flash reverse-phase chromatography [eluent: gradient 30 to 60% MeCN in H_2O (containing 1% NH_4OH as modifier)]. The title compound **60** (19 mg) was obtained in 17% yield as a brown solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.71 (d, *J* = 2.0 Hz, 1 H), 9.48 (s, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.24 (d, *J* = 8.3 Hz, 1 H), 6.77 (t, *J* = 7.8 Hz, 1 H), 6.73 (d, *J* = 2.5 Hz, 1 H), 6.70 (dd, *J* = 8.2, 2.5 Hz, 1 H), 6.60 (dd, *J* = 7.5, 1.1 Hz, 1 H), 6.55 (d, *J* = 2.5 Hz, 1 H), 6.48 (dd, *J* = 7.5, 0.4 Hz, 1 H), 6.36 (s, 1 H), 6.15 (d, *J* = 7.5 Hz, 1 H), 4.68 (pent, *J* = 7.2 Hz, 1 H), 2.54 (s, 6 H), 2.37–2.47 (m, 2 H), 1.98–2.09 (m, 2 H), 1.74–1.82 (m, 1 H), 1.59–1.68 (m, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 157.0, 143.9, 131.5, 127.9, 127.4, 126.8, 126.5, 124.7, 124.1, 120.0, 116.8, 114.2, 111.4, 111.2, 110.9, 106.0, 71.2, 54.5, 38.2, 30.7, 30.7, 13.3.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{23}H_{25}N_3O_4S$: 438.1488; found: 438.1489.

Attempted Synthesis of 6-Formyl-1-(7-hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (61)

Dimethylsulfamoyl chloride (**34**; 0.113 mL, 1.05 mmol) was added to isoquinoline-6-carbaldehyde (**30**; 150 mg, 0.95 mmol), 1*H*-indol-7-yl acetate (**33**; 167 mg, 0.95 mmol) and DIPEA (0.183 mL, 1.05 mmol) in toluene (5 mL). The resulting suspension was concentrated to 0.7 mL volume and stirred at 40 °C for 1 h. LCMS showed formation of the acetyl-protected intermediate.

MS (ES–): *m*/*z* = 438 [M – H]$^-$.

Treatment of this mixture with a solution of 7 N ammonia in MeOH (3 mL) led to decomposition of the product.

N-(2-Cyanoethyl)-1-(7-hydroxy-1*H*-indol-3-yl)-*N*-methylisoquinoline-2(1*H*)-sulfonamide (62)

Synthesised by a method analogous to that used for **37**, starting from 2-cyanoethyl(methyl)sulfamoyl chloride (**35**; 156 mg, 0.85 mmol), isoquinoline (**5**; 100 mg, 0.77 mmol), DIPEA (0.148 mL, 0.85 mmol) and 1*H*-indol-7-yl acetate (**33**; 136 mg, 0.77 mmol). The 3-component coupling took place in 51% yield, after concentrating the mixture and stirring at 45 °C for 2 h. The deprotection was carried out in 64% yield; purification was carried out by flash reverse-phase chromatography [eluent: gradient 30 to 60% MeCN in H_2O (containing 1% NH_4OH as modifier] to afford the title compound **62** (105 mg) as a white solid; mp 112–115 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.76 (d, *J* = 2.1 Hz, 1 H), 9.50 (s, 1 H), 7.34 (d, *J* = 7.3 Hz, 1 H), 7.21–7.32 (m, 4 H), 6.79 (t, *J* = 7.8 Hz, 1 H), 6.59–6.63 (m, 2 H), 6.46–6.51 (m, 2 H), 6.25 (d, *J* = 7.4 Hz, 1 H), 3.22–3.29 (m, 1 H), 3.10–3.17 (m, 1 H), 2.67 (t, *J* = 6.6 Hz, 2 H), 2.54 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 144.0, 132.3, 130.0, 128.2, 128.0, 127.3, 126.9, 126.8, 125.9, 125.2, 124.2, 120.1, 119.1, 116.3, 112.0, 111.1, 106.0, 54.8, 46.6, 35.2, 17.0.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{21}H_{20}N_4O_3S$: 407.1178; found: 407.1180.

6-Chloro-*N*-(2-cyanoethyl)-1-(7-hydroxy-1*H*-indol-3-yl)-*N*-methylisoquinoline-2(1*H*)-sulfonamide (63)

Synthesised by a method analogous to that used for **37**, starting from 2-cyanoethyl(methyl)sulfamoyl chloride (**35**; 156 mg, 0.85 mmol), 6-chloroisoquinoline (**7**; 126 mg, 0.77 mmol), DIPEA (0.148 mL, 0.85 mmol) and 1*H*-indol-7-yl acetate (**33**; 136 mg, 0.77 mmol). The 3-component coupling took place in 46% yield, after concentrating the mixture and stirring at 45 °C for 1 h. The deprotection was carried out in 34% yield; purification was carried out by flash reverse-phase chromatography [eluent: gradient 30 to 60% MeCN in H_2O (containing 1% NH_4OH as modifier] to afford the title compound **63**, (60 mg) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.79 (d, *J* = 2.2 Hz, 1 H), 9.50 (s, 1 H), 7.39 (d, *J* = 8.2 Hz, 1 H), 7.36 (d, *J* = 2.2 Hz, 1 H), 7.25–7.30 (m, 2 H), 6.79 (dd, *J* = 7.8 Hz, 1 H), 6.72 (dd, *J* = 7.5, 1.2 Hz, 1 H), 6.68 (d, *J* = 2.2 Hz, 1 H), 6.52 (s, 1 H), 6.50 (dd, *J* = 7.5, 0.7 Hz, 1 H), 6.24 (d, *J* = 7.5 Hz, 1 H), 3.22–3.29 (m, 1 H), 3.11–3.18 (m, 1 H), 2.69 (t, *J* = 6.6 Hz, 2 H), 2.56 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 144.0, 132.5, 132.1, 130.9, 128.8, 127.5, 127.4, 127.2, 126.9, 124.6, 124.2, 120.2, 119.1, 116.1, 111.0, 110.3, 106.1, 54.3, 46.6, 35.2, 17.0.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{21}H_{19}ClN_4O_3S$: 441.0788; found: 441.0780.

N-(2-Cyanoethyl)-7-fluoro-1-(7-hydroxy-1*H*-indol-3-yl)-*N*-methylisoquinoline-2(1*H*)-sulfonamide (64)

Synthesised by a method analogous to that used for **37**, starting from 2-cyanoethyl(methyl)sulfamoyl chloride (**35**; 164 mg, 0.90 mmol), 7-fluoroisoquinoline (**10**; 120 mg, 0.82 mmol), DIPEA (0.156 mL, 0.90 mmol) and 1*H*-indol-7-yl acetate (**33**; 143 mg, 0.82 mmol). The 3-component coupling took place in 41% yield, after concentrating the mixture and stirring at 45 °C for 1 h. The deprotection was carried out in 51% yield; purification was carried out by flash reverse-phase chromatography [eluent: gradient 30 to 60% MeCN in water (containing 1% NH_4OH as modifier)] to afford the title compound **64** (75 mg) as a tan foam.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.80 (d, *J* = 2.1 Hz, 1 H), 9.53 (s, 1 H), 7.26–7.35 (m, 3 H), 7.12 (ddd, *J* = 8.7, 8.6, 2.7 Hz, 1 H), 6.80 (t, *J* = 7.8 Hz, 1 H), 6.62 (d, *J* = 2.5 Hz, 1 H), 6.58 (dd, *J* = 7.5, 1.2 Hz, 1 H), 6.53 (s, 1 H), 6.50 (dd, *J* = 7.5, 0.7 Hz, 1 H), 6.27 (d, *J* = 7.5 Hz, 1 H), 3.26 (dt, *J* = 13.6, 6.6 Hz, 1 H), 3.12–3.19 (m, 1 H), 2.69 (t, *J* = 6.6 Hz, 2 H), 2.56 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 161.9 (*J* = 244.1), 144.0, 134.5 (*J* = 7.4), 127.3, 127.1 (*J* = 8.3), 126.9, 126.7, 125.4, 124.2, 120.2, 119.1, 115.7, 115.0 (*J* = 21.8), 113.9 (*J* = 22.7), 111.3, 111.1, 106.1, 54.3, 46.6, 35.2, 17.0.

MS (ES–): *m*/*z* = 425 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{21}H_{19}FN_4O_3S$: 425.1084; found: 425.1097.

3-[6-Fluoro-2-(pyrrolidin-1-ylsulfonyl)-1,2-dihydroisoquinolin-1-yl]-1*H*-indol-7-ol (65)

Synthesised by a method analogous to that used for **37**, starting from pyrrolidine-1-sulfonyl chloride (**36**; 128 mg, 0.75 mmol), 6-fluoroisoquinoline (**11**; 101 mg, 0.68 mmol), DIPEA (0.131 mL, 0.75 mmol) and 1*H*-indol-7-yl acetate (**33**; 120 mg, 0.68 mmol). The 3-component coupling took place after concentrating the mixture and stirring at 50 °C for 1 h. After deprotection with methanolic ammonia, purification was carried out by flash C_{18} reverse-phase silica gel chromatography [eluent: gradient 30 to 60% MeCN in H_2O (containing 1% NH_4OH as modifier)] to afford the title compound **65** (35 mg, 12% overall) as a beige solid; mp 108–112 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.74 (s, 1 H), 9.47 (s, 1 H), 7.42 (dd, *J* = 8.4, 5.7 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.11 (dd, *J* = 9.7, 2.7 Hz, 1 H), 7.04 (td, *J* = 8.7, 2.7 Hz, 1 H), 6.80 (t, *J* = 7.8 Hz, 1 H), 6.75 (d, *J* = 7.5 Hz, 1 H), 6.66 (d, *J* = 2.5 Hz, 1 H), 6.53 (s, 1 H), 6.50 (d, *J* = 7.0 Hz, 1 H), 6.18 (d, *J* = 7.5 Hz, 1 H), 2.97–3.12 (m, 4 H), 1.40–1.50 (m, 4 H).

MS (ES–): *m*/*z* = 412 [M – H]$^-$.

3-[7-Methoxy-2-(pyrrolidin-1-ylsulfonyl)-1,2-dihydroisoquinolin-1-yl]-1*H*-indol-7-ol (66)

Synthesised by a method analogous to that used for **37**, starting from pyrrolidine-1-sulfonyl chloride (**36**; 128 mg, 0.75 mmol), 7-methoxyisoquinoline (**6**; 152 mg, 0.96 mmol), DIPEA (0.131 mL, 0.75 mmol) and 1*H*-indol-7-yl acetate (**33**; 120 mg, 0.68 mmol). The 3-component coupling took place after concentrating the mixture and stirring at 50 °C for 1 h. After deprotection with methanolic ammonia, purification was carried out by flash C_{18} reverse-phase silica gel chromatography [eluent: gradient 30 to 60% MeCN in H_2O (containing 1% NH_4OH as modifier)]. Fractions containing the desired compound were concentrated to a volume such that the MeCN had been removed. The resulting suspension was extracted with EtOAc; the organic extractions were evaporated to dryness to afford the title compound **66**, containing 10 mol% EtOAc (30 mg, 5% overall) as a beige solid; mp 183–188 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.70 (s, 1 H), 9.46 (s, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.20 (d, *J* = 8.4 Hz, 1 H), 6.98 (d, *J* = 2.5 Hz, 1 H), 6.87 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.80 (t, *J* = 7.8 Hz, 1 H), 6.59 (d, *J* = 2.3 Hz, 1 H), 6.44–6.52 (m, 3 H), 6.17 (d, *J* = 7.3 Hz, 1 H), 3.73 (s, 3 H), 2.99–3.13 (m, 4 H), 1.40–1.52 (m, 4 H).

MS (ES–): *m*/*z* = 424 [M – H]$^-$.

1-(7-Hydroxy-1*H*-indol-3-yl)-*N*-methyl-2-(pyrrolidin-1-ylsulfonyl)-1,2-dihydroisoquinoline-6-carboxamide (67)

Synthesised by a method analogous to that used for **37**, starting from pyrrolidine-1-sulfonyl chloride (**36**; 85 mg, 0.50 mmol), *N*-methylisoquinoline-6-carboxamide (**16**; 85 mg, 0.45 mmol), DIPEA (0.88 mL, 0.50 mmol) and 1*H*-indol-7-yl acetate (**33**; 80 mg, 0.45 mmol). The 3-component coupling took place after concentrating the mixture and stirring at 50 °C for 1 h. After deprotection with methanolic ammonia, purification was carried out by flash C_{18} reverse-phase silica gel chromatography [eluent: gradient 15 to 50% MeCN in H_2O (containing 1% NH_4OH as modifier)] to afford the title compound **67** (35 mg, 8% overall) as a beige solid; mp 137–140 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.82 (s, 1 H), 9.54 (s, 1 H), 8.44 (q, *J* = 4.5 Hz, 1 H), 7.73 (d, *J* = 1.7 Hz, 1 H), 7.70 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.48 (d, *J* = 7.9 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 6.84 (t, *J* = 7.8 Hz, 1 H), 6.77 (dd, *J* = 7.4, 1.1 Hz, 1 H), 6.71 (d, *J* = 2.3 Hz, 1 H), 6.59 (s, 1 H), 6.54 (d, *J* = 7.4 Hz, 1 H), 6.28 (d, *J* = 7.5 Hz, 1 H), 3.04–3.14 (m, 4 H), 2.83 (d, *J* = 4.5 Hz, 3 H), 1.43–1.53 (m, 4 H).

MS (ES+): *m*/*z* = 453 [M + H]$^+$.

(*E*)-3-[1-(7-Hydroxy-1*H*-indol-3-yl)-2-(pyrrolidin-1-ylsulfonyl)-1,2-dihydroisoquinolin-6-yl]acrylic Acid (68)

Pyrrolidine-1-sulfonyl chloride (**36**; 85 mg, 0.50 mmol) was added to a solution of ethyl (*E*)-3-(isoquinolin-6-yl)acrylate (**31**; 104 mg, 0.46 mmol) and DIPEA (0.087 mL, 0.50 mmol) in toluene (4 mL) at r.t. A solution of 1*H*-indol-7-yl acetate (**33**; 80 mg, 0.46 mmol) in toluene (4 mL) was added. The mixture was concentrated to 2 mL volume and the resulting solution stirred at 50 °C for 1 h. The mixture was evaporated to dryness and the residue was purified by flash silica chromatography (loading in CH_2Cl_2) (eluent: 50% EtOAc in heptane). Pure fractions were evaporated to dryness to give the coupled acetyl ester intermediate. The residue was dissolved in MeOH (8 mL) and treated with NaOH (37 mg, 0.91 mmol) in H_2O (5 mL). The mixture was stirred for 30 min at r.t., then evaporated to dryness. The crude product was purified by preparative HPLC (Waters XBridge Prep C_{18} OBD column, 5 µ silica gel, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of H_2O (containing 1% NH_4OH as modifier) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness and the residue triturated with Et_2O to afford the title compound **68**, containing 12 mol% Et_2O (25 mg, 10% overall, allowing for solvent residues) as a beige solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.24 (br s, 1 H), 10.81 (s, 1 H), 9.54 (s, 1 H), 7.48–7.60 (m, 3 H), 7.39 (d, *J* = 7.8 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 6.78 (t, *J* = 7.8 Hz, 1 H), 6.73 (d, *J* = 7.5 Hz, 1 H), 6.69 (d, *J* = 2.4 Hz, 1 H), 6.45–6.55 (m, 3 H), 6.18 (d, *J* = 7.5 Hz, 1 H), 2.99–3.09 (m, 4 H), 1.38–1.46 (m, 4 H).

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{24}H_{23}N_3O_5S$: 464.1280; found: 464.1294.

1-(7-Hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethyl-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide (69)

3-[2-(*N*,*N*-Dimethylsulfamoyl)-1,2-dihydroisoquinolin-1-yl)-1*H*-indol-7-yl acetate (**37a**; 135 mg, 0.33 mmol) was dissolved in EtOH (30 mL) and the solution was degassed and purged with N_2. Pd/C (10%, 52 mg, 0.050 mmol) was added and the mixture degassed and purged with H_2. The mixture was stirred under a balloon of H_2 for 16 h. The mixture was degassed and purged with N_2, filtered and evaporated to afford 1-(7-acetoxy-1*H*-indol-3-yl)-*N*,*N*-dimethyl-3,4-dihydroisoquinoline-2(1*H*)-sulfonamide (130 mg) as a colourless gum. The gum was dissolved in CH_2Cl_2 (10 mL) and 7 N ammonia in MeOH (4.70 mL,

33 mmol) was added. The mixture was stirred at r.t. for 90 min. The mixture was evaporated to dryness and the residue was purified by flash silica gel chromatography (eluent: gradient 20 to 30% EtOAc in heptane). Pure fractions were evaporated to dryness to afford the title compound **69** (94 mg, 74% overall) as a white foam.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.87 (d, *J* = 1.9 Hz, 1 H), 9.55 (s, 1 H), 7.20–7.29 (m, 2 H), 7.14 (ddd, *J* = 7.1, 6.4, 2.2 Hz, 1 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 6.76 (t, *J* = 7.8 Hz, 1 H), 6.55 (d, *J* = 2.4 Hz, 1 H), 6.50 (d, *J* = 7.8 Hz, 1 H), 6.16 (s, 1 H), 3.56 (dd, *J* = 14.3, 6.7 Hz, 1 H), 3.28–3.37 (m, 1 H), 3.00–3.13 (m, 1 H), 2.81 (dd, *J* = 16.8, 3.8 Hz, 1 H), 2.60 (s, 6 H).

MS (ES–): *m*/*z* = 370 [M – H]$^-$.

7-(*tert*-Butyldimethylsilyloxy)-1*H*-indole (70)

[CAS Reg. No. 106792-42-1]

Imidazole (16.8 g, 246 mmol) was added to a solution of 1*H*-indol-7-ol (14.9 g, 112 mmol) and *tert*-butylchlorodimethylsilane (18.6 g, 123 mmol) in DMF (560 mL) at r.t. and the resulting solution was stirred at r.t. for 16 h. Additional *tert*-butylchlorodimethylsilane (5.57 g, 37.0 mmol) and 1*H*-imidazole (2.52 g, 37.0 mmol) were added and the solution was stirred at r.t. for a further 2 h. The mixture was concentrated, diluted with H_2O (250 mL) and extracted with EtOAc (3 × 100 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash silica gel chromatography (eluent: 40% CH_2Cl_2 in heptane). Pure fractions were evaporated to dryness to afford the title compound **70** (23.1 g, 83%) as a white crystalline solid; mp 87–89 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 7.26 (d, *J* = 7.9 Hz, 1 H), 7.18 (t, *J* = 2.8 Hz, 1 H), 6.96 (t, *J* = 7.8 Hz, 1 H), 6.63 (d, *J* = 7.6 Hz, 1 H), 6.53 (dd, *J* = 3.0, 2.3 Hz, 1 H), 1.06 (s, 9 H), 0.28 (s, 6 H).

MS (ES–): *m*/*z* = 246 [M – H]$^-$.

1-[7-(*tert*-Butyldimethylsilyloxy)-1*H*-indol-3-yl]-2-(*N*,*N*-dimethylsulfamoyl)-1,2-dihydroisoquinolin-7-yl Acetate (71)

Dimethylsulfamoyl chloride (**34**; 0.631 mL, 5.88 mmol) was added to a solution of isoquinolin-7-yl acetate (**32**; 1.00 g, 5.34 mmol) and DIPEA (1.02 mL, 5.88 mmol) in toluene (10 mL) at r.t. A solution of 7-(*tert*-butyldimethylsilyloxy)-1*H*-indole (**70**; 1.32 g, 5.34 mmol) in toluene (10 mL) was added and the mixture concentrated to a thick paste. The residue was stirred at r.t. for 4 days, by which time reaction was complete. The mixture was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (100 mL) and the extracts combined with the organic layer. The combined extracts were filtered through phase-separating paper and evaporated. The crude product was purified by flash silica chromatography (loading in CH_2Cl_2) (eluent: gradient 15% to 30% EtOAc in heptane). Pure fractions were evaporated to dryness to afford the title compound **71** (1.44 g, 49%) as a white crystalline solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.51 (s, 1 H), 7.45 (d, *J* = 8.0 Hz, 1 H), 7.32 (d, *J* = 8.3 Hz, 1 H), 7.21 (d, *J* = 2.3 Hz, 1 H), 7.08 (dd, *J* = 8.3, 2.3 Hz, 1 H), 6.87 (t, *J* = 7.9 Hz, 1 H), 6.68 (d, *J* = 2.6 Hz, 1 H), 6.64 (dd, *J* = 7.5, 1.1 Hz, 1 H), 6.56 (d, *J* = 7.5 Hz, 1 H), 6.48 (s, 1 H), 6.25 (d, *J* = 7.5 Hz, 1 H), 2.56 (s, 6 H), 2.25 (s, 3 H), 1.00 (s, 9 H), 0.24 (s, 6 H).

MS (ES–): *m*/*z* = 540 [M – H]$^-$.

1-[7-(*tert*-Butyldimethylsilyloxy)-1*H*-indol-3-yl]-7-hydroxy-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (72)

A 7 N ammonia solution in MeOH (19.0 mL, 133 mmol) was added to a solution of **71** (1.44 g, 2.66 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at r.t. for 90 min. The mixture was evaporated to dryness and the residue was purified by flash silica chromatography (eluent: gradient 20 to 40% EtOAc in heptane). Pure fractions were evaporated to dryness to afford the title compound **72**, containing 40 mol% EtOAc (1.35 g, 95%, allowing for solvent residues) as a beige foam.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.45 (d, *J* = 1.9 Hz, 1 H), 9.52 (s, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.11 (d, *J* = 8.1 Hz, 1 H), 6.86 (t, *J* = 7.9 Hz, 1 H), 6.75 (d, *J* = 2.3 Hz, 1 H), 6.72 (dd, *J* = 8.1, 2.3 Hz, 1 H), 6.64 (d, *J* = 2.5 Hz, 1 H), 6.56 (d, *J* = 7.2 Hz, 1 H), 6.41 (dd, *J* = 7.3, 1.2 Hz, 1 H), 6.34 (s, 1 H), 6.15 (d, *J* = 7.3 Hz, 1 H), 2.56 (s, 6 H), 1.00 (s, 9 H), 0.25 (s, 6 H).

MS (ES–): *m*/*z* = 498 [M – H]$^-$.

7-[2-(4-Acetylpiperazin-1-yl)ethoxy]-1-(7-hydroxy-1*H*-indol-3-yl)-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (73)

DIAD (0.047 mL, 0.24 mmol) was added to a mixture of **72** (100 mg, 0.20 mmol) and PPh_3 (63 mg, 0.24 mmol) in anhyd THF (5 mL) at r.t. The mixture was stirred at r.t. for 3 h. Additional PPh_3 (95 mg, 0.36 mmol) and DIAD (0.071 mL, 0.36 mmol) were added and stirring continued for a further 16 h. The mixture was evaporated to dryness and the residue was purified by flash silica gel chromatography [eluent: gradient 0 to 2% (10:1 MeOH/concd aq NH_3) in EtOAc]. Pure fractions were evaporated to dryness to afford 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-1-[7-(*tert*-butyldimethylsilyloxy)-1*H*-indol-3-yl]-*N*,*N*-dimethylisoquinoline-2(1*H*)-sulfonamide (**73a**; 62 mg, 47%) as a beige gum.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.45 (s, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.22 (d, *J* = 8.4 Hz, 1 H), 7.03 (d, *J* = 2.4 Hz, 1 H), 6.90 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.87 (t, *J* = 7.8 Hz, 1 H), 6.66 (d, *J* = 2.6 Hz, 1 H), 6.56 (d, *J* = 7.5 Hz, 1 H), 6.48 (dd, *J* = 7.4, 1.0 Hz, 1 H), 6.44 (s, 1 H), 6.20 (d, *J* = 7.4 Hz, 1 H), 4.07–4.11 (m, 2 H), 3.36–3.45 (m, 4 H), 2.67–2.72 (m, 2 H), 2.57 (s, 6 H), 2.45–2.49 (m, 2 H), 2.38–2.44 (m, 2 H), 1.98 (s, 3 H), 1.00 (s, 9 H), 0.24 (s, 6 H).

MS (ES–): *m*/*z* = 652 [M – H]$^-$.

A 1 M solution of Bu_4NF in THF (1.10 mL, 1.10 mmol) was added to **73a** (60 mg, 0.09 mmol) in THF (5 mL) at r.t. The resulting yellow solution was stirred at r.t. for 1 h. The reaction mixture was diluted with EtOAc (50 mL), washed with H_2O (2 × 50 mL) and sat. brine (50 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to give a yellow gum. The crude product was purified by flash silica gel chromatography [eluent: gradient 0 to 5% (10:1 MeOH/concd aq NH_3) in CH_2Cl_2]. Pure fractions were evaporated to dryness to afford the title compound **73** (12 mg, 24%) as a beige solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.69 (d, *J* = 2.0 Hz, 1 H), 9.44 (s, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.18 (d, *J* = 8.4 Hz, 1 H), 6.98 (d, *J* = 2.4 Hz, 1 H), 6.87 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.77 (t, *J* = 7.8, Hz, 1 H), 6.56 (d, *J* = 2.6 Hz, 1 H), 6.47 (d, *J* = 7.4 Hz, 1 H), 6.44 (dd, *J* = 7.4, 1.1 Hz, 1 H), 6.38 (s, 1 H), 6.16 (d, *J* = 7.4 Hz, 1 H), 4.00 – 4.11 (m, 2 H), 3.34–3.43 (m, 4 H), 2.65–2.70 (m, 2 H), 2.55 (s, 6 H), 2.42–2.47 (m, 2 H), 2.36–2.41 (m, 2 H), 1.96 (s, 3 H).

MS (ES–): *m*/*z* = 538 [M – H]$^-$.

HRMS: *m*/*z* [M – H]$^-$ calcd for $C_{27}H_{33}N_5O_5S$: 538.2124; found: 538.2119.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610223.

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