A New Focused Microwave Approach to the Synthesis of Amino-Substituted Pyrroloisoquinolines and Pyrroloquinolines via a Sequential Multi-Component Coupling Process

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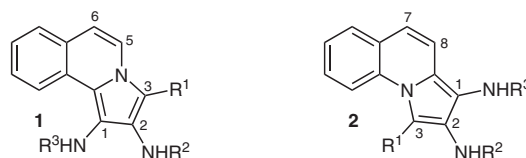Fax +44(1223)336442; E-mail: svl1000@cam.ac.uk
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Abstract: A multi-component reaction has been developed allowing direct access to pyrroloisoquinolines and pyrroloquinolines with new, electron-rich substitution patterns. The synthesised amino-substituted heterocyclic compounds and intermediates involved in their formation represent novel compounds. Focused microwave irradiation was used extensively to allow simple access to a wide temperature range using low boiling point solvents.

Key words: focused microwave irradiation, fused-ring systems, heterocycles, multi-component reactions, pyrroloisoquinolines, solid-supported reagents

Figure 1 Structure of pyrroloisoquinolines **1** and pyrroloquinolines **2**

Heterocyclic rings based on the indolizine structure have received significant attention due to their extensive biological diversity and the richness of the target therapeutic classes they represent. Although not widely found in nature, indolizines comprise an important class of pharmaceutical compounds that exhibit and regulate many different biological functions. Compounds based on these core templates have been shown to act as powerful antimycobacterial agents,[1] and inhibit a range of targets such as 15-lipoxygenase,[2,3] secretory phospholipase A2[4] and testosterone 5α-reductase,[5] as well as enzymes involved in cancers,[6] and autoimmune disorders.[7] In addition, they have also demonstrated effectiveness in the treatment of several CNS disorders,[8,9] cardiovascular complaints,[10] respiratory diseases[11] and have shown analgesic and anti-inflammatory activity.[12] These same motifs have also found a niche as antagonists of calcium channels[13] and both 5-HT$_4$[14] and histamine H$_3$ receptors.[15] Finally, their application as antioxidants,[16] dyes[17] and spectral sensitisers[18] has also been recognised. Obviously the broad utility of these indolizine compounds have made them prime synthetic candidates resulting in the development of many synthetic routes which are well reviewed in the literature.[19]

Nevertheless, in spite of all this synthetic effort, routes to structures possessing electron-rich arrangements around the indolizine have been very few.[20] This is especially true of those with functional attachments at the 1 and 2 positions of the pyrrole-type ring system (Figure 1).

Our research group has long been interested in the synthesis of heterocyclic compounds utilising focused microwave irradiation, both in batch and flow-mode.[21] Herein, we report on a new route to pyrroloisoquinolines **1** and pyrroloquinolines **2** using microwave techniques enabling the introduction of a more diverse and electron-rich pattern of functionality at the 1–3 positions.

Our synthetic strategy was based upon the sequential condensation of a quinolinium or isoquinolinium salt with readily available isothiocyanates and isocyanides followed by intramolecular rearrangement to yield the desired extended pyrrole structure.

Preparation of Isoquinolinium Salts

The reaction of 2,4′-dibromoacetophenone with isoquinoline led to the isoquinolinium salt **3** (Scheme 1). Subsequent addition of triethylamine (1.1 equiv) and an isothiocyanate (1 equiv) in CH$_2$Cl$_2$ gave the corresponding betaine **4** (Table 1). Microwave irradiation (60 min, 100 °C) was found to accelerate the reaction but did not increase the isolated yield. Further optimisation of these basic reactions was not attempted at this stage. Furthermore, no product arising from the secondary addition of the sulfur anion into the aromatic pyridinium ring, as has been suggested in previous studies, was observed.[22]

Addition of Isocyanide Components

Isocyanides are well-established, versatile synthetic reagents used in many multi-component reactions as a result of their unique reactivity.[23] Unfortunately, they are not as readily available as may always be desired. In this respect we have previously shown the viability of generating these reagents through the use of solid-supported reagents
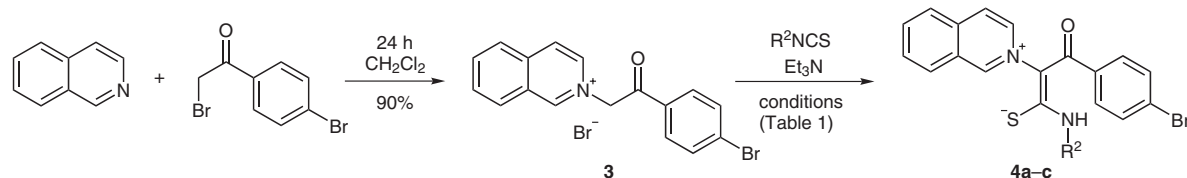
Scheme 1 Formation of zwitterion intermediates **4a–c**

Table 1 Compounds **4a–c**

| Entry	R²	4	Conditions[a]	Yield (%)[b]
1	(4-nitrophenyl, O₂N)	**4a**	A	85
2			B	83
3	(4-methoxyphenyl, MeO)	**4b**	A	72
4			B	54
5	(3-trifluoromethylphenyl, F₃C)	**4c**	B	90

[a] Conditions A: stirred overnight, ambient temperature. Conditions B: 1 h, microwave irradiation at 100 °C.
[b] Yield of isolated product.

in conjunction with focused microwave irradiation[24] giving us ready access to a variety of components.

In our current synthetic sequence we proposed that the addition of an isocyanide to the zwitterion **4** would result in nucleophilic attack upon the isoquinolinium ring (Scheme 2). Indeed additions of this type to pyridinium species by isocyanides are well precedented.[25] Furthermore, in our case the presence of a second fused aromatic ring should help to reduce the degree of aromatic character lost upon initial attack making the attack more favoured. The resulting addition product is then capable of undergoing a favoured 6-*exo-dig* intramolecular cyclisation[26] followed by proton transfer to form the intermediate **7** with an anti-aromatic structure. Next, an intramolecular rearrangement driven by the thermodynamic sink of regaining aromaticity could occur via a postulated strained 6,5,3-tricyclic fused ring system that is likely to ring open to yield **9**. The addition of a thiophile, for example, a phosphine would then induce elimination of the sulfur leading to the desired aromatic indolizine **10**. An alternative mechanistic sequence, albeit leading to the same product, can be envisaged and involves the isocyanide initially behaving as an electrophile by attack of the thiolate of **4**. This would then be followed by intramolecular cyclisation onto the pyridinium ring intercepting the same intermediate compound **6**.

The postulated reaction sequence was initially tested and validated using the 4-nitrophenyl-substituted betaine **4a**. This substrate was selected as it was the most insoluble betaine of those synthesised. Consequently it was hoped that a general set of conditions for all other substrates could be derived from its more difficult optimisation.
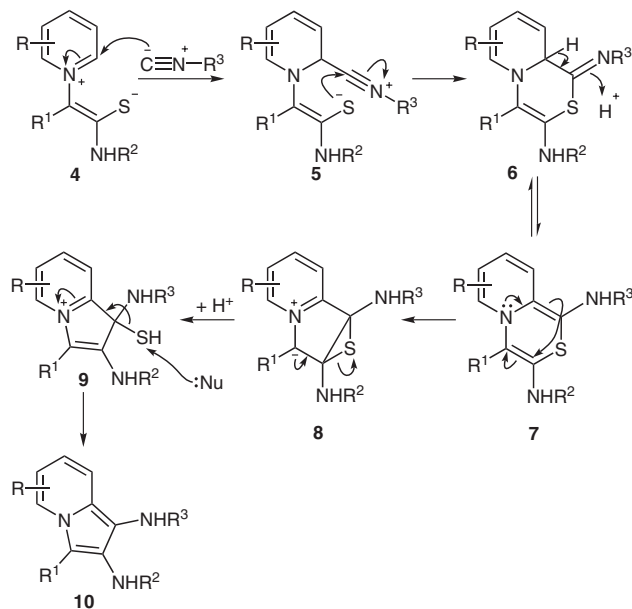
Scheme 2 Proposed mechanism for the formation of indolizines

A solution of 4-chlorophenyl isocyanide (1 equiv) was added to betaine **4a** and the reaction heated (microwave irradiation, 80 °C) in the following solvents: acetone, MeCN, CHCl₃, CH₂Cl₂, 1,4-dioxane, DMF, EtOH, and THF, respectively. After 26 hours, HPLC-MS analysis showed that the reactions performed in CHCl₃ and CH₂Cl₂ no longer contained **4a** but comprised a new compound, **6a** (Figure 2), with a mass corresponding to the addition adduct. The other solvents screened produced many more by-products and issues of decreased solubility were also encountered. Ultimately, CH₂Cl₂ was chosen as the solvent for all further reactions in preference to CHCl₃ as it had already been used in previous steps. It was therefore hoped that this would eventually allow starting materials from previous stages to be used without the need for workup or solvent change, ultimately enabling a one-pot preparation of the desired compounds. NMR experiments on a sample of **6a** isolated by column chromatography (22% yield[27]) from a CH₂Cl₂ solution suggested that the aromaticity of the isoquinoline ring had been lost due to the lowering of the chemical shift of the characteristic doublets [positions 14 and 13 (Figure 2); d = 6.30 and 5.54]. The ¹H NMR spectrum also contained a distinctive singlet (d = 5.83) shown by COSY experimentation to possess a weak coupling to the isoquinoline proton 14 (Figure 2).
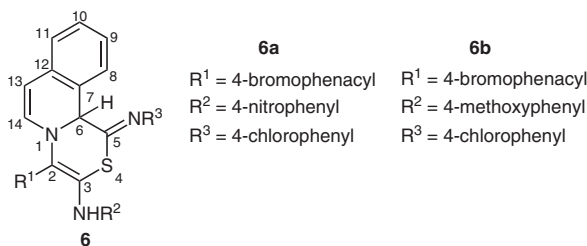
Figure 2   Compounds **6a** and **6b**

This suggested the structure of **6a** to be that shown in Scheme 2 (**6**), thus avoiding the alternative anti-aromatic structure **7**. Intermediate **6b** (Figure 2), also isolated by column chromatography (11% yield), exhibited a similar NMR spectrum suggesting it also adopted structure **6**. An HMQC experiment revealed that proton 6 (d = 5.27) was connected to an sp^3 hybridised carbon (d = 64.21), further supporting the proposed structure. Unfortunately, attempted crystallisation of both compounds **6a** and **6b** failed to produce crystals suitable for X-ray analysis making absolute determination of these new structures difficult.

Upon increasing the stoichiometry of the 4-chlorophenyl isocyanide, the reaction rate increased as expected. Employing a two equivalent excess reduced the reaction time to 11 hours as determined by depletion of **4a** monitored by HPLC-MS. The time to completion also followed a standard Arrhenius trend when the reaction temperature was increased (90 °C, 6 h; 100 °C, 3 h). However, higher temperatures (>100 °C) could not be used as these led to significant decomposition of the starting materials (i.e., retro-addition of the isothiocyanate to the pyridinium salts).

Interestingly, the HPLC-MS spectrum of the reaction mixture run at 100 °C was found to contain two additional component signals compared to the reaction heated at only 80 °C. One of these peaks had a mass corresponding to the loss of a sulfur atom from **6a** indicating that conversion into the indolizine product **10aa** had occurred. The second signal corresponded to that of 4-chlorophenyl isothiocyanate (authenticated against the known material) suggesting that the excess 4-chlorophenyl isocyanide could remove the sulfur from **6a** forming the corresponding isothiocyanate (Path A, Scheme 3). To test this mechanism, only one equivalent of 4-chlorophenyl isocyanide was added to **4a** and the reaction then heated at 100 °C until all of **4a** had reacted. The proposed formation of **10aa** would not be expected since all of the isocyanide should have coupled to **4a**; however, the major product was still **10aa** suggesting an alternative reductive mechanism was taking place at the elevated temperature. This could be explained by the direct extrusion of sulfur[28] (Path B, Scheme 3). It is hard to discount either potential mechanistic pathway, indeed both may be acting. It has been shown that isocyanides can also be converted into isothiocyanates by heating with molecular sulfur, which could be the source of this by-product in our reactions.[29] It is inter-
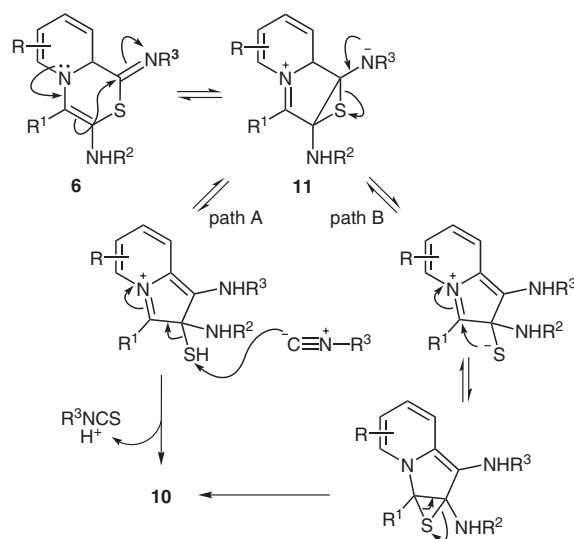
Scheme 3   Possible mechanisms for sulfur extrusion

esting to note that the reaction only proceeds to the intermediate structure **6a** at lower temperatures (80 °C), but can be forced to the final product **10aa** without the addition of further reagents at higher temperatures. This may be as a result of the large thermodynamic barrier associated with the five-membered ring formation of **11**. From the reactions conducted at higher temperatures, the pyrroloisoquinoline **10aa** could be isolated as a bright yellow amorphous solid (35% yield) by standard column chromatography. NMR analysis was entirely consistent with the expected product structure, however, repeated attempts at crystallisation in order to attain X-ray structural confirmation were not successful.

Table 2   Compounds **10**[a]

Entry	**4**	R^3	Time (h)	Temp (°C)	Product **10**	Isolated yield (%)
1	**4a**	Cl	6	100	**10aa**	35
2	**4a**	OMe	6	80	**10ab**	22
3	**4b**	Cl	15	100	**10ba**	33
4	**4b**	OMe	9	80	**10bb**	27
5	**4c**	Cl	6	100	**10ca**	34
6	**4c**	OMe	6	80	**10cb**	23

[a] Reaction conditions: **4** (1 equiv) and an isocyanide (1 equiv) in CH$_2$Cl$_2$ were heated (microwave irradiation) until no more compound **4** could be detected by HPLC-MS. Compounds were purified by column chromatography on silica gel.

Next, to demonstrate the generality of the reaction, other betaine precursors **4** were investigated along with 4-methoxyphenyl isocyanide (Table 2). The more electron-rich methoxy-substituted isocyanide did not show the same high temperature requirement as previously determined to induce sulfur elimination to yield the indolizine **10**. The lower temperature of 80 °C was sufficient to promote both

the initial isocyanide addition and subsequent rearrangement.

One-Pot Reaction

In an effort to reduce decomposition of the reaction components and maximise yields of both **6** and **10**, we aimed to find a method by which intermediate **6** was formed initially using lower temperatures and then converted into the pyrroloisoquinoline **10** by addition of a thiophile (such as a phosphine) without prolonged heating. In addition, in order to reduce the number of workup steps required during the synthesis, a one-pot reaction was envisaged where reaction mixtures were telescoped to the next step without purification. This seemed feasible as CH_2Cl_2 had been used successfully as a solvent in all the previous steps. Also, in an attempt to gain compounds more suitable for crystallisation and hence X-ray analysis, the problematic nitro group introduced via 4-nitrophenyl isothiocyanate was replaced by the corresponding cyano variant. It was hoped that this would offer better solubility whilst retaining the electron-withdrawing nature. To this end, 4-cyanophenyl isothiocyanate (1 equiv) was stirred for 48 hours with isoquinolinium salt **3** and diethylaminomethyl polystyrene[30] (PS-NEt$_2$, 1.1 equiv) resulting in complete conversion into the corresponding betaine **4d**. The use of a solid-supported base permitted the product to be separated by simple filtration without the need for further workup. Experiments performed on **4d** in CH_2Cl_2 showed that significant decomposition began to occur under microwave irradiation at temperatures of 100 °C and greater. With this in mind, 4-chlorophenyl isocyanide (1.5 equiv) was added to the crude solution of **4d** and heated (microwave irradiation, 90 °C, 6 h) until no betaine remained. Reaction monitoring by HPLC-MS showed the gradual generation of a signal with a mass corresponding to that of the intermediate **6**. This product was isolated and purified by column chromatography and crystallised[31] as red needle like crystals (32% yield). NMR and X-ray analysis of the crystals confirmed the proposed structure **6d** (Figure 3). Comparison of the data obtained previously for compounds **6a** and **6b** suggested that they similarly adopt this same 6,6,6-tricyclic fused heterocyclic core. This core structure with both the imine and amine substituents is quite unique, representing a new and previously unprecedented heterocyclic system. Whilst the isolated yield of **6d** was relatively poor, HPLC-MS and analysis of the crude ^{1}H NMR spectrum suggested that the conversion was significantly higher (>80%). This loss of yield was attributed to the noticeably poor stability (2D TLC analysis) of **6d** on chromatography over both silica gel and alumina.

In an attempt to convert **6d** into **10da** under mild conditions, **6d** was heated (microwave irradiation, 90 °C) with PPh$_3$ (1 equiv) in CH_2Cl_2. After one hour, only minimal amounts of **10da** were observed, likely due to the background thermal transformation as previously observed
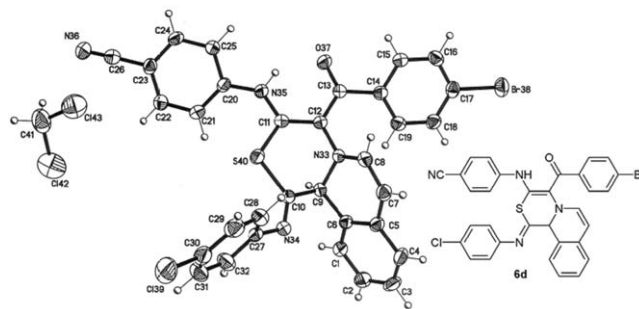

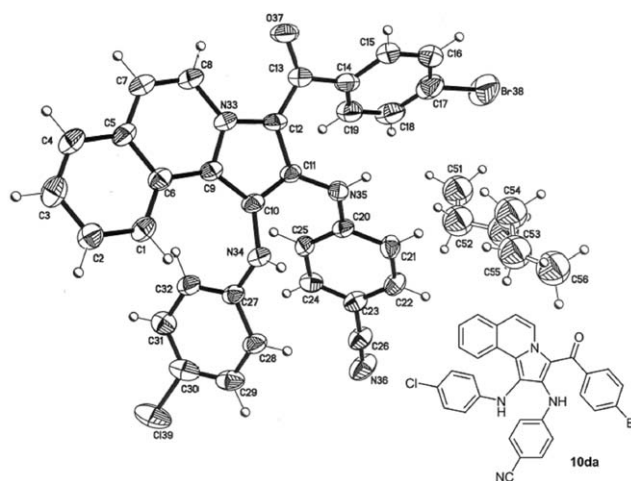**Figure 3**   Crystal structure of intermediate **6d**

Figure 4   Crystal structure of product **10da**

rather than the action of PPh$_3$. An identical outcome was also obtained when PPh$_3$ was substituted for the more electron-rich P(OEt)$_3$.

On further consideration of the mechanism, the intramolecular attack into the imine to form the five-membered core was considered to represent the highest energy transition and therefore would determine the reaction rate. Consequently the reaction should be promoted by acid catalysis. The reaction of **6d** to **10da** was therefore repeated under the same conditions (microwave irradiation, 90 °C), but in the presence of TFA (2 equiv). HPLC-MS analysis after only 10 minutes indicated no remaining intermediate **6d**; however, a new signal with a mass corresponding to that of the pyrroloisoquinoline **10da** was present. It has been shown previously that indolizines form salts with strong acids,[32] hence the TFA was removed with a base rather than by evaporation. After removing the TFA by addition of macroporous polymer-supported carbonate (PS-CO$_3$), crude **10da** was purified by column chromatography and crystallised[31] as yellow crystals (47% yield). X-ray and NMR analysis confirmed the proposed structure **10da** (Figure 4). It was found that catalytic amounts of TFA (0.2 equiv) also effected the transformation under the same conditions, but resulted in a longer reaction time (45 min). The similar isolated yield (45%) suggests that the reaction is indeed catalytic in acid.
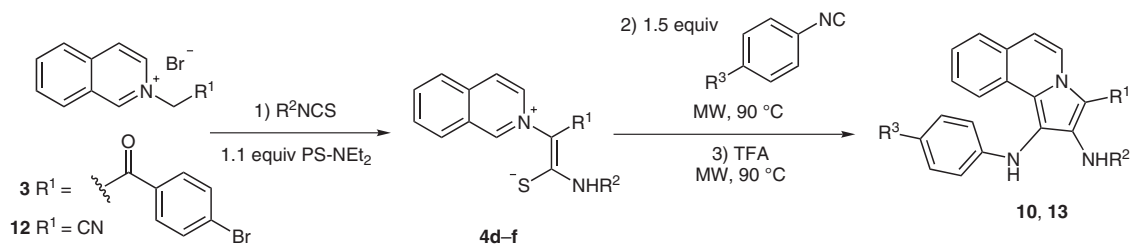
Scheme 4 One-pot reaction sequence for the generation of compounds **10** and **13**

The NMR spectra of the six synthesised pyrroloisoquinolines (Table 2) contained similar key characteristics to that of the fully characterised compound **10da** supporting their structural assignments.

The reaction was also attempted using a macroporous polymer-supported sulfonic acid[33] (PS-SO$_3$H) thus enabling the acid component to be simply removed by filtration at the end of the reaction. This approach was somewhat successful although a longer reaction time was required (1 h, 90 °C), presumably as a result of slow diffusion of reagents into the polymer matrix and the weaker nature of the acid moiety. It was also noted that some of the product was captured by the polymer resin; however, this was not a selective process with other impurities also being sequestered. This meant that a 'catch and release' purification protocol[34] would not be appropriate in this instance.

To further investigate the effect of acidity on the reaction, a weaker acid namely AcOH (2 equiv) was also evaluated. In these reactions only trace amounts of the rearranged product **10da** were observed after heating (microwave irradiation, 90 °C, 70 min) suggesting that a relatively strong acid source is required for the transformation.

To determine whether any nonthermal or specific microwave effects[35] were involved, the reaction utilising TFA (0.2 equiv) was repeated using conventional heating methods. The temperature and pressure conditions achieved in the microwave heating experiments were simulated by submerging a sealed microwave tube into a preheated oil bath and, at the end of the heating period, the sample was rapidly cooled by submersion in cold water. The isolated yield of **10da** (45%) was identical to that obtained previously, suggesting that a purely thermal process was in operation.

Having explored the reaction conditions and devised an optimised procedure, a small collection of compounds were prepared using a series of different isothiocyanates and isocyanides (Scheme 4, Table 3). Similar isolated yields were obtained when 3,5-bis(trifluoromethyl)phenyl isothiocyanate was used, however, when the reaction with benzyl isothiocyanate was attempted, a complex mixture was produced. Upon lowering the stoichiometry of TFA to 0.2 equivalents and increasing the heating time, the reactions with both 4-chlorophenyl isocyanide and 4-methoxyphenyl isocyanide gave better conversions to **10fa** and **10fb**, respectively. Unfortunately, isolation of **10fa** in acceptable purity was not possible due to a co-eluting impu-
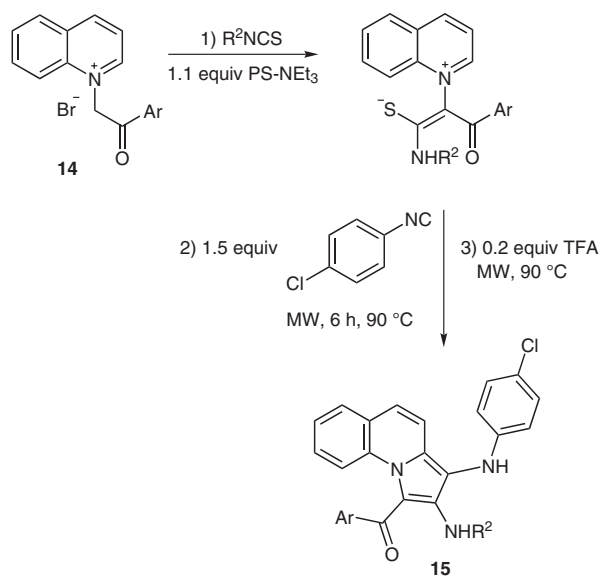
Scheme 5 Formation of quinoline derived pyrroloquinolines **15**

rity, although analysis of the crude reaction mixture indicated a similar conversion and product profile.

Mechanistically the R^1 substituent is required to be electron-withdrawing in order to stabilise the ylide formed by deprotonation of the isoquinolinium salt; hitherto, the 4-bromophenacyl group had been used. To demonstrate that an alternative functionality could be used, the isoquinolinium salt **12** was prepared. Compound **12** was then subjected to the one-pot reaction conditions as applied previously (Table 3). In all cases, the use of 2 equivalents of TFA resulted in the formation of complex mixtures, but better results were obtained when only 0.2 equivalents were used. The lower isolated yields of compound **13** can be partially attributed to the difficulty in isolation of the compound as a result of a closely-eluting impurity during chromatographic purification.

Since isoquinolinium salts had been used successfully throughout this research, it seemed likely that the method could also be applied to the analogous quinolinium salts. Consequently, salt **14** was formed in high yield (83%) in a similar procedure as used to form **3**. The standard one-pot procedure was then employed using 4-chlorophenyl isocyanide and resulted in the isolation of the expected product **15** in relatively good yield (Scheme 5, Table 4).

In summary, a new multi-component reaction has been developed that allows access to pyrroloisoquinolines and

Table 3 Compounds **10** and **13**

Entry	R[1]	R[2]	R[3]	Heating time		TFA (equiv)[a]	Yield (%)[b]	Product
				Step 2 (h)	Step 3 (min)			
1	(4-bromobenzoyl)	(4-cyanophenyl)	Cl	6	10	2	47	**10da**
2			OMe	6	10	2	38	**10db**
3		(3,5-bis(trifluoromethyl)phenyl)	Cl	6	10	2	48	**10ea**
4			OMe	7	10	2	40	**10eb**
5[c]		(benzyl)	Cl	8	60	0.2	—[d]	**10fa**
6[c]			OMe	8	40	0.2	31	**10fb**
7	(CN)	(4-cyanophenyl)	Cl	6	60	0.2	17	**13da**
8			OMe	6	60	0.2	21	**13db**
9		(3,5-bis(trifluoromethyl)phenyl)	Cl	6	60	0.2	23	**13ea**
10			OMe	6	60	0.2	29	**13eb**

[a] Only 0.2 equiv of TFA was used for entries 5–10 since 2 equiv resulted in the generation of complex mixtures.
[b] Yield of isolated products, purified by column chromatography.
[c] In addition to stirring overnight, the reaction was microwave irradiated at 90 °C for 30 min in order to form betaine **4f**.
[d] No **10fa** could be isolated due to a co-eluting impurity.

Table 4 Compounds **15**

Entry	R[2]	Heating time Step 3 (min)	Isolated yield (%)	**15**
1	(4-cyanophenyl)	50	35	**15da**
2	(3,5-bis(trifluoromethyl)phenyl)	30	46	**15ea**

pyrroloquinolines with novel substitution patterns. The multi-component nature of the reaction allows a large degree of molecular diversity to be introduced into the heterocyclic products by simply selecting alternative starting materials. A variety of amine substituents can be introduced bearing both electron-poor and electron-rich aryls, in addition to benzylic systems. The reaction utilised focused microwave irradiation as a heating protocol, enabling simple and safe access to temperatures above the standard boiling point of the solvent (CH_2Cl_2). The isolated yields from the one-pot protocol are reasonable considering the sequence of transformations involved. Further work is underway to determine alternative purification procedures and to expand the range of substrates.

^{1}H NMR spectra were recorded on a Bruker Avance DPX-400, DRX-500 or DRX-600 spectrometer with residual DMSO or $CHCl_3$
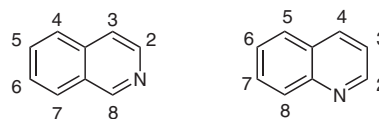
Figure 5 Ring numbering system for NMR assignments of quinoline and isoquinoline units.

as the internal reference (DMSO $\delta_H = 2.50$ and $CHCl_3$ $\delta_H = 7.26$). COSY and HMQC experiments were used to aid in the assignment of signals in the ^{1}H and ^{13}C NMR spectra. ^{13}C NMR spectra were recorded on the same spectrometers with the central peak of DMSO-d_6 or $CDCl_3$ as the internal reference (DMSO-d_6 $\delta_C = 39.5$ and $CDCl_3$ $\delta_C = 77.2$). DEPT 135 experiments were used to aid in the assignment of signals in the ^{13}C NMR spectra. Coupling constants (J) are quoted in Hz and recorded to the nearest 0.1 Hz. ^{1}H NMR assignments were made using the numbering system as specified in Figure 5 for the parent quinoline and isoquinoline systems respectively. Phenyl protons were labelled according to their IUPAC priority ring position (Figure 5).

IR spectra were recorded neat as a thin film on a PerkinElmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Letters next to the IR absorptions refer to the relative absorbency of the peak; w = weak, less than 40% of the main peak; m = medium, ca. 41–74% of the main peak; s = strong, greater than 75% of the most intense peak.

High-resolution mass spectrometry (HRMS) within ± 5 ppm was carried out on a Waters Micromass LCT Premier spectrometer using time of flight with positive and negative electrospray ionisation. HPLC-MS analysis was performed via two methods; A: an Agilent HP 1100 series chromatograph [Mercury Luna 3μ C18 (2) column] attached to a Waters ZQ2000 mass spectrometer with ESCi ionisation source in ESI mode. Elution was carried out at a flow rate of 0.6

Table 5 HPLC-MS Solvent Gradients

Gradient A		Gradient B	
Time (min)	MeCN (%)	Time (min)	MeCN (%)
0.0	5	0.0	5
1.0	5	3.0	5
4.0	95	5.0	95
5.0	95	5.5	5
7.0	5	8.0	5
8.0	5		

mL/min using a reverse phase gradient of MeCN and H_2O containing 0.1% formic acid; and B: an Agilent HP 1100 chromatograph (Luna Max RP column) attached to an HPLC/MSD mass spectrometer. Elution was carried out at a flow rate of 1 mL/min using a reverse phase gradient of MeCN–H_2O with both solvents containing 0.1% trifluoroacetic acid. The gradient runs for both methods are described in Table 5.

Retention time (t_R) is in minutes and the *m/z* value is reported. Unless otherwise specified, reagents were obtained from commercial sources and used without further purification. Laboratory reagent grade CH_2Cl_2, Et_2O, EtOAc, and PE (petroleum ether used refers to the fraction boiling in the range 40–60 °C) were obtained from Fischer Scientific. The CH_2Cl_2, EtOAc, and PE were distilled before use. All heating was carried out by microwave irradiation using a Biotage Emrys Synthesiser or Biotage Emrys Optimiser[36] unless otherwise specified. The removal of solvent under reduced pressure was carried out on a Biotage V-10 evaporator[36] or a standard rotary evaporator. TLC was performed on Merck 60 F254 silica gel plates and were visualised using short wave ultraviolet light. Melting points were performed on a Reichert hot stage apparatus and are uncorrected.

2-[2-(4-Bromophenyl)-2-oxoethyl]isoquinolinium Bromide (3)
2,4′-Dibromoacetophenone (18.00 g, 64.76 mmol) was dissolved in a minimum amount of CH_2Cl_2 (50 mL). Isoquinoline (7.56 mL, 64.34 mmol) was added dropwise to the solution and the mixture was stirred overnight at r.t. The solvent was removed in vacuo, and the crude solid product triturated with Et_2O. The sample was filtered and the solid dried in vacuo to yield the title compound as a cream solid; yield: 24.0 g (90%).

IR: 2982.9 (w), 2814.7 (w), 2340.1 (w), 1692.8 (m), 1636.8 (w), 1605.0 (w), 1584.4 (m), 1509.2 (w), 1485.7 (w), 1465.1 (w), 1396.6 (w), 1386.1 (m), 1360.5 (w), 1340.0 (w), 1287.2 (w), 1242.3 (w), 1224.4 (w), 1173.9 (m), 1071.4 (w), 996.0 (m), 980.9 (m), 893.9 (w), 850.4 (w), 816.3 (s), 775.4 (m), 744.2 (m), 706.5 (w), 688.05 (w) cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.02 (s, 1 H, 8H-isoquin), 8.73 (d, *J* = 6.8 Hz, 1 H, 2H-isoquin), 8.69 (d, *J* = 6.8 Hz, 1 H, 3H-isoquin), 8.56 (d, *J* = 8.3 Hz, 1 H, 7H-isoquin), 8.42 (d, *J* = 8.3 Hz, 1 H, 4H-isoquin), 8.35–8.32 (m, 1 H, 5H-isoquin), 8.14–8.11 (m, 1 H, 6H-isoquin), 8.05 (d, *J* = 8.6 Hz, 2 H, 2H-PhBr), 7.92 (d, *J* = 8.6 Hz, 2 H, 3H-PhBr), 6.63 (s, 2 H, CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 190.45 (C), 151.80 (CH), 137.63 (CH), 137.37 (C), 136.43 (CH), 132.76 (C), 132.41 (CH), 131.53 (CH), 130.75 (CH), 130.35 (CH), 129.02 (C), 127.53 (CH), 126.96 (C), 125.60 (CH), 65.01 (CH_2).

HPLC-MS (A): t_R = 2.66; *m/z* = 328.0 [M – Br]$^+$.

HRMS: *m/z* calcd for $C_{17}H_{13}BrNO$ [M – Br]$^+$: 328.0160; found: 328.0170.

Formation of Betaines 4; General Procedure A
Method A1: An isothiocyanate (6.14 mmol) was added to a suspension of compound **3** (2.50 g, 6.14 mmol) in CH_2Cl_2 (25 mL) followed by the dropwise addition of Et_3N (0.95 mL, 6.82 mmol). The mixture was stirred overnight at r.t. and Et_2O added to effect precipitation of product. The solid was filtered, washed with Et_2O, and dried in vacuo.

Method A2: An isothiocyanate (12.3 mmol) was added to a suspension of a compound **3** (5.00 g, 12.3 mmol) in CH_2Cl_2 (20 mL) and Et_3N (1.70 mL, 13.5 mmol). The mixture was heated (microwave irradiation, 100 °C, 1 h) then filtered, washed with Et_2O, and dried in vacuo.

(Z)-3-(4-Bromophenyl)-2-(isoquinolinium-2-yl)-1-(4-nitrophenylamino)-3-oxoprop-1-ene-1-thiolate (4a)
Prepared according to the general procedure A using 4-nitrophenyl isothiocyanate to yield the title compound as a bright orange powder. No Et_2O was added to effect precipitation in Method 1; yield (Method A1): 2.62 g (85%); (Method A2): 5.18 g (83%).

IR: 3049.8 (w), 1637.7 (w), 1608.2 (w), 1571.8 (m), 1501.1 (m), 1418.0 (w), 1392.0 (m), 1366.8 (m), 1324.1 (s), 1298.1 (m), 1258.1 (m), 1200.7 (m), 1157.9 (s), 1107.4 (s), 1059.6 (m), 1002.9 (m), 909.5 (w), 874.7 (w), 842.2 (s), 819.3 (m), 772.3 (s), 761.3 (m), 753.2 (m), 740.8 (m), 704.9 (m), 681.2 (m), 658.5 (s) cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 15.09 (s, 1 H, NH), 10.14 (s, 1 H, 8H-isoquin), 8.61 (d, *J* = 6.7 Hz, 1 H, 2H-isoquin), 8.36 (d, *J* = 8.3 Hz, 1 H, 7H-isoquin), 8.32 (d, *J* = 6.7 Hz, 1 H, 3H-isoquin), 8.27 (d, *J* = 9.2 Hz, 2 H, 3H-PhNO$_2$), 8.24 (d, *J* = 6.9 Hz, 1 H, 4H-isoquin), 8.23 (d, *J* = 9.2 Hz, 2 H, 2H-PhNO$_2$), 8.22–8.19 (m, 1 H, 5H-isoquin), 8.01–7.97 (m, 1 H, 6H-isoquin), 7.31 (d, *J* = 8.5 Hz, 2 H, 2H-PhBr), 7.19 (d, *J* = 8.5 Hz, 2 H, 3H-PhBr).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 184.52 (C), 177.57 (C), 156.31 (CH), 147.31 (C), 142.26 (C), 141.22 (CH), 139.80 (C), 137.31 (CH), 136.88 (C), 130.98 (CH), 130.85 (CH), 130.45 (CH), 128.45 (CH), 127.18 (CH), 126.98 (C), 125.65 (C), 124.65 (CH), 124.38 (CH), 121.94 (C), 121.34 (CH).

HPLC-MS (B): t_R = 3.67; *m/z* = 508.0 [M + H]$^+$.

HRMS: *m/z* calcd for $C_{24}H_{17}BrN_3O_3S$ [M + H]$^+$: 506.0174; found: 506.0192.

(Z)-3-(4-Bromophenyl)-2-(isoquinolinium-2-yl)-1-(4-methoxyphenylamino)-3-oxoprop-1-ene-1-thiolate (4b)
Prepared according to the general procedure A using 4-methoxyphenyl isothiocyanate to yield the title compound as a bright yellow powder; yield (Method A1): 2.17 g (72%); (Method A2): 3.26 g (54%).

IR: 2983.9 (w), 2124.8 (w), 1903.4 (w), 1636.2 (w), 1587.4 (w), 1536.7 (w), 1506.9 (m), 1490.3 (m), 1463.5 (m), 1414.9 (m), 1375.3 (s), 1284.5 (m), 1241.8 (s), 1202.9 (m), 1182.2 (m), 1165.4 (m), 1152.4 (m), 1106.9 (w), 1073.4 (w), 1057.7 (m), 1035.1 (m), 1009.8 (m), 953.5 (w), 867.6 (w), 836.7 (s), 822.2 (m), 790.7 (s), 757.2 (s), 738.2 (m), 679.0 (s) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 14.34 (s, 1 H, NH), 10.07 (s, 1 H, 8H-isoquin), 8.51 (d, *J* = 6.8 Hz, 1 H, 2H-isoquin), 8.31 (d, *J* = 8.3 Hz, 1 H, 7H-isoquin), 8.22 (d, *J* = 6.8 Hz, 1 H, 3H-isoquin), 8.18 (d, *J* = 7.8 Hz, 1 H, 4H-isoquin), 8.17–8.13 (m, 1 H, 5H-isoquin), 7.96–7.92 (m, 1 H, 6H-isoquin), 7.65 (d, *J* = 9.0 Hz, 2 H, 2H-*Ph*OMe), 7.26 (d, *J* = 8.6 Hz, 2 H, 2H-PhBr), 7.14 (d, *J* = 8.6 Hz, 2 H, 3H-PhBr), 6.89 (d, *J* = 9.0 Hz, 2 H, 3H-*Ph*OMe), 3.73 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 184.60 (C), 175.77 (C), 156.05 (CH), 141.53 (CH), 140.40 (C), 136.94 (CH), 136.67 (C), 133.85 (C), 130.84 (CH), 130.60 (CH), 130.34 (CH), 128.52 (CH), 127.05 (C), 126.79 (C), 126.73 (C) 124.70 (CH), 123.89 (CH), 123.79 (C), 121.42 (C), 113.59 (CH), 55.26 (CH$_3$).

HPLC-MS (B): t_R = 3.50; m/z = 491.0 [M + H]$^+$.

HRMS: m/z calcd for C$_{25}$H$_{20}$BrN$_2$O$_2$S [M + H]$^+$: 491.0429; found: 491.0433.

(Z)-3-(4-Bromophenyl)-2-(isoquinolinium-2-yl)-3-oxo-1-[3-(trifluoromethyl)phenylamino]prop-1-ene-1-thiolate (4c)
Prepared according to the general procedure A using 3-(trifluoromethyl)phenyl isothiocyanate to yield the title compound as a yellow-orange powder; yield (Method A2): 6.58 g (90%).

IR: 3042.1 (w), 1635.8 (w), 1607.9 (w), 1580.5 (w), 1567.1 (m), 1530.5 (m), 1500.9 (m), 1482.2 (m), 1401.2 (m), 1381.1 (m), 1328.7 (s), 1304.5 (m), 1293.8 (m), 1274.1 (m), 1240.4 (m), 1216.9 (m), 1199.1 (m), 1183.3 (w), 1156.2 (s), 1112.2 (s), 1091.8 (m), 1063.5 (s), 1009.3 (m), 981.8 (w), 955.1 (w), 916.9 (w), 904.6 (m), 889.4 (w), 878.5 (w), 851.4 (m), 808.0 (m), 790.0 (s), 769.6 (m), 749.3 (s), 696.1 (s), 674.0 (m), 658.9 (m) cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 14.76 (s, 1 H, NH), 10.11 (s, 1 H, 8H-isoquin), 8.57 (d, J = 6.8 Hz, 1 H, 2H-isoquin), 8.49 [s, 1 H, 2H-(CF$_3$)Ph], 8.34 (d, J = 8.3 Hz, 1 H, 7H-isoquin), 8.28 (d, J = 6.8 Hz, 1 H, 3H-isoquin), 8.22 (d, J = 8.1 Hz, 1 H, 4H-isoquin), 8.19–8.17 (m, 1 H, 5H-isoquin), 7.98–7.95 (m, 1 H, 6H-isoquin), 7.91 [d, J = 7.9 Hz, 1 H, 4H-(CF$_3$)Ph], 7.57 [t, J = 7.9 Hz, 1 H, 5H-(CF$_3$)Ph], 7.44 [d, J = 7.9 Hz, 1 H, 6H-(CF$_3$)Ph], 7.29 (d, J = 8.5 Hz, 2 H, 2H-PhBr), 7.16 (d, J = 8.5 Hz, 2 H, 3H-PhBr).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 184.86 (C), 176.89 (C), 156.32 (CH), 141.59 (C), 141.39 (CH), 140.02 (C), 137.20 (CH), 136.81 (C), 130.96 (CH), 130.79 (CH), 130.43 (CH), 129.80 (CH), 129.02 (C, q, J = 31.5 Hz), 128.50 (CH), 127.15 (CH), 126.91 (C), 126.45 (CH), 124.64 (C), 124.23 (C, q, J = 270.8 Hz), 124.16 (CH), 121.76 (C), 120.39 (CH, q, J = 3.8 Hz), 118.89 (CH, q, J = 4.0 Hz).

HPLC-MS (B): t_R = 3.74; m/z = 528.9 [M + H]$^+$.

HRMS: m/z calcd for C$_{25}$H$_{17}$BrF$_3$N$_2$OS [M + H]$^+$: 529.0197; found: 529.0211.

Indolizines and Their Intermediates; General Procedure B
A mixture of isocyanide and compound **4** in CH$_2$Cl$_2$ (4.5 mL) was heated (microwave irradiation). The solvent was removed in vacuo and the residue purified by flash column chromatography using a Varian Bond Elut SI 40 μm silica column[37] and eluting with the specified solvent system.

(4-Bromophenyl)[1-(4-chlorophenylimino)-3-(4-nitrophenylamino)-1,11b-dihydro[1,4]thiazino[3,4-a]isoquinolin-4-yl]methanone (6a)
Prepared according to the general procedure B using 4-chlorophenyl isocyanide (26 mg, 0.198 mmol), **4a** (100 mg, 0.198 mmol), heated (15 h, 80 °C), and eluted with CH$_2$Cl$_2$; yield: 23 mg (22%); red solid.

IR: 2924.7 (w), 1585.1 (m), 1490.4 (s), 1396.4 (w), 1374.9 (w), 1325.0 (s), 1303.2 (s), 1245.2 (s), 1173.6 (s), 1109.5 (s), 1090.7 (m), 1069.0 (m), 1038.9 (m), 1009.0 (s), 827.8 (s), 749.5 (s), 681.5 (m) cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.62 (s, 1 H, NH), 8.01 (d, J = 9.2 Hz, 2 H, 3H-PhNO$_2$), 7.67 (d, J = 8.6 Hz, 2 H, 2H-PhBr), 7.53 (d, J = 8.6 Hz, 2 H, 3H-PhBr), 7.36 (d, J = 8.7 Hz, 2 H, 3H-PhCl), 7.34 (d, J = 7.5 Hz, 1 H, 4H-isoquin), 7.25 (td, J = 7.5, 1.4 Hz, 1 H, 5H-isoquin), 7.19 (td, J = 7.5, 1.3 Hz, 1 H, 6H-isoquin), 7.06 (dd, J = 7.5, 1.3 Hz, 1 H, 7H-isoquin), 6.99 (d, J = 9.2 Hz, 2 H, 2H-PhNO$_2$), 6.75 (d, J = 8.7 Hz, 2 H, 2H-PhCl), 6.30 (d, J = 7.6 Hz, 1

H, 2H-isoquin), 5.83 (s, 1 H, 8H-isoquin), 5.54 (d, J = 7.6 Hz, 1 H, 3H-isoquin).

HPLC-MS (B): t_R = 4.71; m/z = 644.9 [M + H]$^+$.

(4-Bromophenyl)[3-(4-methoxyphenylamino)-1-(4-methoxyphenylimino)-1,11b-dihydro[1,4]thiazino[3,4-a]isoquinolin-4-yl]methanone (6b)
Prepared according to the general procedure B using 4-methoxyphenyl isocyanide (27 mg, 0.204 mmol), **4b** (100 mg, 0.204 mmol), heated (6 h, 80 °C), and eluted with CH$_2$Cl$_2$; yield: 21 mg (17%); red solid.

IR: 2950.9 (w), 1645.3 (w), 1604.2 (w), 1579.7 (m), 1555.7 (m), 1501.3 (s), 1457.3 (w), 1416.2 (w), 1394.9 (m), 1377.3 (m), 1326.5 (w), 1294.8 (m), 1268.8 (m), 1244.6 (s), 1169.9 (m), 1123.6 (w), 1106.1 (w), 1071.4 (m), 1034.4 (m), 1008.6 (s), 964.5 (w), 869.3 (m), 835.2 (m), 786.4 (w), 759.0 (s), 742.8 (s), 717.1 (m), 695.1 (m), 669.5 (m) cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 12.99 (s, 1 H, NH), 7.65 (d, J = 8.6 Hz, 2 H, 2H-PhBr), 7.39 (d, J = 8.6 Hz, 2 H, 3H-PhBr), 7.26–7.23 (m, 1 H, 5H-isoquin), 7.18 (d, J = 5.8 Hz, 1 H, 7H-isoquin), 7.19–7.16 (m, 1 H, 6H-isoquin), 7.11 (d, J = 8.8 Hz, 2 H, PhOMe), 7.00 (d, J = 7.5 Hz, 1 H, 4H-isoquin), 6.84 (d, J = 8.8 Hz, 2 H, PhOMe), 6.72 (d, J = 8.8 Hz, 2 H, PhOMe), 6.60 (d, J = 8.8 Hz, 2 H, PhOMe), 5.87 (d, J = 7.4 Hz, 1 H, 2H-isoquin), 5.44 (d, J = 7.4 Hz, 1 H, 3H-isoquin), 5.27 (s, 1 H, 8H-isoquin), 3.79 (s, 3 H, OCH$_3$), 3.72 (s, 3 H, OCH$_3$).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 185.32 (C), 158.41 (C), 158.40 (C), 156.89 (C), 156.67 (C), 141.29 (C), 137.69 (C), 134.58 (CH), 131.79 (C), 131.20 (CH), 130.52 (CH), 129.93 (C), 128.52 (CH), 128.40 (CH), 126.84 (CH), 125.17 (C), 125.15 (CH), 125.07 (C), 123.82 (CH), 120.64 (CH), 115.27 (C), 114.45 (CH), 114.14 (CH), 102.21 (CH), 64.21 (CH), 55.45 (CH$_3$), 55.33 (CH$_3$).

HPLC-MS (B): t_R = 4.59; m/z = 624.0 [M + H]$^+$.

(4-Bromophenyl)[1-(4-chlorophenylamino)-2-(4-nitrophenylamino)pyrrolo[2,1-a]isoquinolin-3-yl]methanone (10aa)
Prepared according to the general procedure B using 4-chlorophenyl isocyanide (27 mg, 0.198 mmol), **4a** (100 mg, 0.198 mmol), heated (6 h, 100 °C), and eluted with CH$_2$Cl$_2$; yield: 44 mg (35%); yellow solid.

IR: 3328.4 (w), 1723.7 (w), 1586.0 (m), 1530.5 (m), 1490.1 (m), 1436.0 (w), 1404.4 (m), 1374.2 (m), 1318.9 (s), 1301.9 (s), 1266.9 (m), 1171.4 (m), 1109.7 (s), 1067.1 (m), 1043.1 (s), 1008.4 (m), 937.2 (m), 836.9 (m), 819.3 (m), 795.1 (m), 749.3 (m), 692.2 (m), 660.4 (m) cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.19 (d, J = 7.6 Hz, 1 H, 2H-isoquin), 8.54 (s, 1 H, NH), 8.44 (d, J = 8.2 Hz, 1 H, 7H-isoquin), 7.84 (d, J = 7.5 Hz, 1 H, 4H-isoquin), 7.76 (d, J = 9.2 Hz, 2 H, 3H-PhNO$_2$), 7.63 (s, 1 H, NH), 7.58–7.55 (m, 1 H, 5H-isoquin), 7.52–7.49 (m, 1 H, 6H-isoquin), 7.41 (d, J = 8.6 Hz, 2 H, 2H-PhBr), 7.34 (d, J = 8.6 Hz, 2 H, 3H-PhBr), 7.31 (d, J = 7.6 Hz, 1 H, 3H-isoquin), 6.99 (d, J = 8.9 Hz, 2 H, 3-PhCl), 6.48 (d, J = 8.9 Hz, 2 H, 2H-PhBr), 6.41 (d, J = 9.2 Hz, 2 H, 2H-PhNO$_2$).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 183.90 (C), 152.27 (C), 145.71 (C), 138.29 (C), 137.49 (C), 131.58 (C), 130.94 (CH), 130.51 (CH), 129.47 (C), 128.83 (C), 128.77 (CH), 128.34 (CH), 128.03 (CH), 126.96 (CH), 125.35 (CH), 125.22 (C), 124.55 (CH), 124.08 (CH), 123.79 (C), 120.62 (C), 116.10 (C), 115.82 (C), 114.55 (CH), 113.29 (CH), 112.95 (CH).

HPLC-MS (B): t_R = 4.61; m/z = 612.9 [M + H]$^+$.

HRMS: m/z calcd for C$_{31}$H$_{21}$BrClN$_4$O$_3$ [M + H]$^+$: 611.0480; found: 611.0486.

(4-Bromophenyl)[1-(4-methoxyphenylamino)-2-(4-nitrophenylamino)pyrrolo[2,1-*a*]isoquinolin-3-yl]methanone (10ab)

Prepared according to the general procedure B using 4-methoxyphenyl isocyanate (26 mg, 0.198 mmol), **4a** (100 mg, 0.198 mmol), heated (6 h, 80 °C), and eluted with CH$_2$Cl$_2$; yield: 25 mg (20%); yellow solid.

IR: 3335.2 (w), 1588.2 (m), 1557.7 (w), 1507.2 (s), 1480.6 (m), 1437.1 (w), 1397.4 (m), 1374.4 (m), 1320.3 (s), 1303.3 (s), 1268.4 (m), 1233.2 (m), 1172.1 (m), 1110.1 (s), 1066.9 (w), 1033.7 (w), 1009.8 (m), 937.8 (m), 824.0 (m), 795.3 (m), 749.0 (m), 690.8 (w), 666.8 (w) cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.12 (d, *J* = 7.6 Hz, 1 H, 2H-isoquin), 8.62 (d, *J* = 8.2 Hz, 1 H, 7H-isoquin), 7.92 (d, *J* = 8.9 Hz, 2 H, 3H-PhNO$_2$), 7.70 (d, *J* = 8.0 Hz, 1 H, 4H-isoquin), 7.55–7.52 (m, 1 H, 5H-isoquin), 7.46–7.43 (m, 1 H, 6H-isoquin), 7.41 (d, *J* = 8.7 Hz, 2 H, 2H-PhBr), 7.39 (d, *J* = 8.7 Hz, 2 H, 3H-PhBr), 7.10 (d, *J* = 7.6 Hz, 1 H, 3H-isoquin), 6.66 (d, *J* = 8.9 Hz, 2 H, 3H-*Ph*OMe), 6.42 (d, *J* = 8.9 Hz, 4 H, 2H-PhNO$_2$ and 2H-*Ph*OMe), 5.79 (s, 1 H, NH), 4.80 (s, 1 H, NH), 3.69 (s, 3 H, OCH$_3$).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 183.89 (C), 153.29 (C), 149.89 (C), 140.19 (C), 139.09 (C), 138.56 (C), 131.50 (CH), 131.07 (C), 130.83 (C), 129.95 (CH), 129.24 (C), 128.49 (CH), 128.16 (CH), 126.68 (CH), 126.41 (C), 125.77 (CH), 124.95 (CH), 124.63 (CH), 124.26 (C), 116.63 (C), 115.88 (C), 114.93 (CH), 114.90 (CH), 113.81 (CH), 113.67 (CH), 55.63 (CH$_3$).

HPLC-MS (B): t_R = 4.30; *m/z* = 609.0 [M + H]$^+$.

HRMS: *m/z* calcd for C$_{32}$H$_{24}$BrN$_4$O$_4$ [M + H]$^+$: 607.0981; found: 607.0977.

(4-Bromophenyl)[1-(4-chlorophenylamino)-2-(4-methoxyphenylamino)pyrrolo[2,1-*a*]isoquinolin-3-yl]methanone (10ba)

Prepared according to the general procedure B using 4-chlorophenyl isocyanide (28 mg, 0.204 mmol), **4b** (100 mg, 0.204 mmol), heated (15 h, 80 °C), and eluted with 10% PE in CH$_2$Cl$_2$; yield: 40 mg (33%); yellow solid.

IR: 2924.6 (w), 1583.8 (m), 1557.6 (m), 1506.9 (s), 1488.7 (s), 1449.7 (m), 1433.6 (m), 1415.5 (m), 1396.0 (s), 1373.1 (s), 1353.5 (s), 1291.8 (s), 1232.0 (s), 1170.2 (m), 1090.3 (w), 1067.0 (m), 1033.1 (m), 1008.9 (m), 934.7 (m), 817.1 (m), 788.7 (s), 743.7 (s), 695.1 (w), 664.3 (m) cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.57 (d, *J* = 7.5 Hz, 1 H, 2H-isoquin), 8.55 (d, *J* = 8.3 Hz, 1 H, 7H-isoquin), 7.60 (d, *J* = 7.8 Hz, 1 H, 4H-isoquin), 7.50–7.48 (m, 4 H, PhBr), 7.47–7.45 (m, 1 H, 5H-isoquin), 7.37–7.34 (m, 1 H, 6H-isoquin), 6.96 (d, *J* = 8.8 Hz, 2 H, 3H-PhCl), 6.84 (d, *J* = 7.5 Hz, 1 H, 3H-isoquin), 6.67 (d, *J* = 9.0 Hz, 2 H, *Ph*OMe), 6.64 (d, *J* = 9.0 Hz, 2 H, *Ph*OMe), 6.51 (s, 1 H, NH), 6.23 (d, *J* = 8.8 Hz, 2 H, 2H-PhCl), 4.72 (s, 1 H, NH), 3.75 (s, 3 H, OCH$_3$).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 182.94 (C), 155.56 (C), 144.69 (C), 139.28 (C), 138.90 (C), 135.57 (C), 132.19 (C), 131.83 (CH), 129.95 (CH), 129.71 (C), 128.92 (CH), 128.36 (CH), 127.65 (CH), 126.52 (CH), 125.92 (C), 124.99 (CH), 124.86 (CH), 123.92 (C), 123.31 (C), 121.83 (CH), 114.85 (CH), 114.25 (CH), 113.69 (C), 111.37 (CH), 110.44 (C), 55.58 (CH$_3$).

HPLC-MS (B): t_R = 4.63; *m/z* = 598.0 [M + H]$^+$.

HRMS: *m/z* calcd for C$_{32}$H$_{24}$BrClN$_3$O$_2$ [M + H]$^+$: 596.0740; found: 596.0735.

[1,2-Bis(4-methoxyphenylamino)pyrrolo[2,1-*a*]isoquinolin-3-yl](4-bromophenyl)methanone (10bb)

Prepared according to the general procedure B using 4-methoxyphenyl isocyanide (27 mg, 0.204 mmol), **4b** (100 mg, 0.204 mmol),

heated (9 h, 80 °C), and eluted with CH$_2$Cl$_2$; yield: 34 mg (27%); yellow solid.

IR: 3330.8 (w), 2928.6 (w), 2831.0 (w), 1583.7 (m), 1557.6 (w), 1505.4 (s), 1479.6 (m), 1433.7 (m), 1415.1 (m), 1396.0 (m), 1372.8 (m), 1353.3 (s), 1288.2 (w), 1230.4 (s), 1170.5 (m), 1106.9 (w), 1066.5 (m), 1032.5 (m), 1008.5 (m), 935.2 (m), 819.3 (s), 791.0 (s), 765.3 (m), 744.4 (m), 677.2 (m) cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.73 (d, *J* = 7.5 Hz, 1 H, 2H-isoquin), 8.68 (d, *J* = 8.2 Hz, 1 H, 7H-isoquin), 7.64 (d, *J* = 8.1 Hz, 1 H, 4H-isoquin), 7.51–7.47 (m, 5 H, PhBr and 5H-isoquin), 7.41–7.38 (m, 1 H, 6H-isoquin), 6.89 (d, *J* = 7.5 Hz, 1 H, 3H-isoquin), 6.68–6.67 (m, 4 H, *Ph*OMe), 6.66 (d, *J* = 8.9 Hz, 2 H, *Ph*OMe), 6.36 (s, 1 H, NH), 6.32 (d, *J* = 8.9 Hz, 2 H, *Ph*OMe), 4.60 (s, 1 H, NH), 3.79 (s, 3 H, OCH$_3$), 3.72 (s, 3 H, OCH$_3$).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 183.09 (C), 155.27 (C), 152.89 (C), 139.94 (C), 139.03 (C), 138.86 (C), 136.23 (C), 132.12 (C), 131.70 (CH), 130.04 (CH), 129.71 (C), 128.20 (CH), 127.60 (CH), 126.40 (CH), 125.81 (C), 125.21 (CH), 125.07 (CH), 124.17 (C), 121.14 (CH), 114.80 (CH), 114.67 (CH), 114.32 (CH), 113.74 (C), 112.50 (C), 111.40 (CH), 55.67 (CH$_3$), 55.63 (CH$_3$).

HPLC-MS (B): t_R = 4.43; *m/z* = 592.0 [M + H]$^+$.

HRMS: *m/z* calcd for C$_{33}$H$_{27}$BrN$_3$O$_3$ [M + H]$^+$: 592.1236; found: 592.1235.

(4-Bromophenyl){1-(4-chlorophenylamino)-2-[3-(trifluoromethyl)phenylamino]pyrrolo[2,1-*a*]isoquinolin-3-yl}methanone (10ca)

Prepared according to the general procedure B using 4-chlorophenyl isocyanide (26 mg, 0.189 mmol), **4c** (100 mg, 0.189 mmol), heated (6 h, 100 °C) and eluted with CH$_2$Cl$_2$; yield: 43 mg (34%), yellow solid.

IR: 3306.8 (w), 1584.8 (m), 1557.8 (w), 1525.7 (m), 1488.9 (s), 1445.5 (m), 1396.0 (m), 1373.6 (s), 1356.5 (m), 1331.1 (s), 1273.2 (m), 1236.6 (m), 1214.3 (w), 1163.5 (m), 1121.8 (s), 1093.6 (m), 1066.7 (s), 1009.6 (m), 942.4 (m), 885.2 (m), 818.6 (m), 787.1 (s), 745.2 (m), 696.7 (m), 662.9 (m) cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.18 (d, *J* = 7.5 Hz, 1 H, 2H-isoquin), 8.41 (d, *J* = 8.1 Hz, 1 H, 7H-isoquin), 7.82 (d, *J* = 7.5 Hz, 1 H, 4H-isoquin), 7.73 (s, 1 H, NH), 7.64 (s, 1 H, NH), 7.57–7.54 (m, 1 H, 5H-isoquin), 7.50–7.47 (m, 1 H, 6H-isoquin), 7.33–7.32 (m, 4 H, PhBr), 7.26 (d, *J* = 7.5 Hz, 1 H, 3H-isoquin), 7.07–7.04 [m, 1 H, 5H-(CF$_3$)Ph], 7.02 (d, *J* = 8.9 Hz, 2 H, 3H-PhCl), 6.81 [d, *J* = 7.6 Hz, 1 H, 4H-(CF$_3$)Ph], 6.68 [dd, *J* = 8.2, 1.7 Hz, 1 H, 6H-(CF$_3$)phenyl], 6.54 (d, *J* = 8.9 Hz, 2 H, 2H-PhCl), 6.50 [d, *J* = 1.7 Hz, 1 H, 2H-(CF$_3$)Ph].

^{13}C NMR (125 MHz, DMSO-d_6): δ = 183.89 (C), 146.62 (C), 145.95 (C), 138.24 (C), 133.88 (C), 130.73 (CH), 130.34 (CH), 129.52 (C), 129.31 (CH), 129.24 (C, q, *J* = 31.0 Hz), 128.94 (C), 128.77 (CH), 128.16 (CH), 127.83 (CH), 126.84 (CH), 125.03 (C), 124.55 (CH), 124.25 (C, q, *J* = 271.3 Hz), 124.15 (CH), 123.67 (C), 120.59 (C), 117.58 (CH), 114.75 (C), 114.69 (C), 114.58 (CH), 114.13 (CH, q, *J* = 3.6 Hz), 112.61 (CH), 110.03 (CH, q, *J* = 4.0 Hz).

HPLC-MS (B): t_R = 4.98; *m/z* = 636.0 [M + H]$^+$.

HRMS: *m/z* calcd for C$_{32}$H$_{21}$BrClF$_3$N$_3$O [M + H]$^+$: 634.0497; found: 634.0509.

(4-Bromophenyl){1-(4-methoxyphenylamino)-2-[3-(trifluoromethyl)phenylamino]pyrrolo[2,1-*a*]isoquinolin-3-yl}methanone (10cb)

Prepared according to the general procedure B using 4-methoxyphenyl isocyanide (25 mg, 0.189 mmol), **4c** (100 mg, 0.189 mmol),

heated (6 h, 80 °C), and eluted with CH_2Cl_2; yield: 29 mg (23%); yellow solid.

IR: 3313.8 (w), 1584.2 (w), 1559.0 (w), 1531.8 (w), 1506.6 (s), 1473.4 (w), 1441.6 (w), 1395.7 (s), 1373.2 (s), 1356.5 (m), 1331.5 (s), 1231.3 (s), 1162.2 (s), 1119.5 (s), 1066.3 (s), 1032.7 (m), 1010.0 (m), 942.7 (m), 884.5 (m), 821.2 (m), 786.7 (s), 745.1 (m), 711.0 (s), 697.2 (s), 663.3 (m) cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.98 (d, J = 7.6 Hz, 1 H, 2H-isoquin), 8.62 (d, J = 8.2 Hz, 1 H, 7H-isoquin), 7.66 (d, J = 7.8 Hz, 1 H, 4H-isoquin), 7.51–7.48 (m, 1 H, 5H-isoquin), 7.45–7.43 (m, 1 H, 6H-isoquin), 7.39 (d, J = 7.6 Hz, 1 H, 3H-isoquin), 7.38–7.36 (m, 4 H, PhBr), 7.10 [t, J = 7.9 Hz, 1 H, 5H-(CF$_3$)Ph], 7.01 [d, J = 7.9 Hz, 1 H, 4H-(CF$_3$)Ph], 6.99 [d, J = 7.9 Hz, 1 H, 6H-(CF$_3$)Ph], 6.68 [s, 1 H, 2H-(CF$_3$)Ph], 6.65 (d, J = 8.8 Hz, 2 H, *Ph*OMe), 6.39 (d, J = 8.8 Hz, 2 H, *Ph*OMe), 5.91 (s, 1 H, NH), 4.80 (s, 1 H, NH), 3.69 (s, 3 H, OCH$_3$).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 183.83 (C), 153.08 (C), 144.26 (C), 139.34 (C), 138.65 (C), 134.37 (C), 131.39 (CH), 131.27 (C, q, J = 30.9 Hz), 131.16 (C), 129.97 (CH), 129.45 (C), 129.37 (CH), 128.37 (CH), 128.26 (CH), 128.20 (CH), 127.84 (CH), 126.55 (CH), 126.08 (C), 125.02 (CH), 124.21 (C), 123.85 (C, q, J = 273.6 Hz), 117.09 (CH, q, J = 3.8 Hz), 114.85 (CH), 114.74 (CH), 114.69 (C), 114.30 (C), 112.99 (CH, q, J = 3.8 Hz), 112.74 (CH), 55.64 (CH$_3$).

HPLC-MS (B): t_R = 4.58; m/z = 630.0 [M + H]$^+$.

HRMS: m/z calcd for C$_{33}$H$_{24}$BrF$_3$N$_3$O$_2$ [M + H]$^+$: 630.1004; found: 630.1002.

(Z)-3-(4-Bromophenyl)-1-(4-cyanophenylamino)-2-(isoquinolinium-2-yl)-3-oxoprop-1-ene-1-thiolate (4d)

A suspension of compound **3** (4.00 g, 9.83 mmol), 4-cyanophenyl isothiocyanate (1.57 g, 9.83 mmol) and PS-NEt$_2$ (3.38 g, 10.81 mmol) in CH$_2$Cl$_2$ (50 mL) was stirred overnight at r.t. The mixture was filtered, the product washed from the polymer with CH$_2$Cl$_2$ (100 mL) and DMF (30 mL), and the solvent removed in vacuo. The resultant solid was washed with PE (20 mL), a minimal volume of CH$_2$Cl$_2$, and the product dried in vacuo to yield the title compound as a bright yellow powder; yield: 4.28 g (89%).

IR: 3079.0 (w), 3027.2 (w), 2955.8 (w), 2881.7 (w), 2845.2 (w), 2223.2 (w), 1670.3 (w), 1634.2 (w), 1583.1 (m), 1564.5 (w), 1537.4 (m), 1507.8 (s), 1490.2 (m), 1416.8 (m), 1394.4 (s), 1370.0 (s), 1305.4 (m), 1271.4 (s), 1203.7 (m), 1181.4 (m), 1167.8 (s), 1155.9 (m), 1118.3 (m), 1083.0 (w), 1058.3 (m), 1008.9 (m), 968.2 (w), 949.5 (w), 934.5 (w), 890.4 (w), 874.2 (m), 840.9 (s), 820.4 (m), 783.4 (s), 766.7 (m), 754.5 (m), 745.2 (m), 732.9 (m), 709.2 (m), 692.5 (m), 672.4 (s) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 14.92 (s, 1 H, NH), 10.10 (s, 1 H, 8H-isoquin), 8.57 (d, J = 6.8 Hz, 1 H, 2H-isoquin), 8.32 (d, J = 8.3 Hz, 1 H, 7H-isoquin), 8.28 (d, J = 6.9 Hz, 1 H, 3H-isoquin), 8.20 (d, J = 7.8 Hz, 1 H, 4H-isoquin), 8.18–8.14 (m, 1 H, 5H-isoquin), 8.15 (d, J = 8.8 Hz, 2 H, 3H-PhCN), 7.96–7.92 (m, 1 H, 6H-isoquin), 7.76 (d, J = 8.8 Hz, 2 H, 2H-PhCN), 7.28 (d, J = 8.6 Hz, 2 H, 2H-PhBr), 7.17 (d, J = 8.6 Hz, 2 H, 3H-PhBr).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 184.50 (C), 177.22 (C), 156.26 (CH), 145.20 (C), 141.25 (CH), 139.86 (C), 137.19 (CH), 136.80 (C), 132.85 (CH), 130.92 (CH), 130.76 (CH), 130.39 (CH), 128.42 (CH), 127.11 (CH), 126.91 (C), 125.28 (C), 124.23 (CH), 121.97 (CH), 121.84 (C), 119.19 (C), 105.19 (C).

HPLC-MS (A): t_R = 4.65; m/z = 486.5 [M + H]$^+$.

HRMS: m/z calcd for C$_{25}$H$_{17}$BrN$_3$OS [M + H]$^+$: 486.0276; found: 486.0283.

Table 6 Biotage Continuous Solvent Gradient

Column volume	% EtOAc–PE
0	6
1	6
16	40
19	100
21	100
23	6

Purification of Products by Flash Column Chromatography Using a Biotage SP4 Purification System;[36] General Procedure C

The sample was dissolved in a minimum amount of CH$_2$Cl$_2$, then loaded onto a Biotage 25+^{TM} samplet and dried in vacuo at r.t. A 48 mL Biotage FLASH 25+^{TM} M silica cartridge was primed with 60 mL of a 6% EtOAc–PE solution at a flow rate of 25 mL/min, then the samplet was loaded onto the top of the column. A solvent gradient was run according to Table 6 with a flow rate of 20 mL/min, with the initial 2 column volumes directed to waste, then the remaining eluent collected in 24 mL fractions.

4-[4-(4-Bromobenzoyl)-1-(4-chlorophenylimino)-1,11b-dihydro-[1,4]thiazino[3,4-*a*]isoquinolin-3-ylamino]benzonitrile (6d)

A suspension of compound **3** (100 mg, 0.246 mmol), 4-cyanophenyl isothiocyanate (40 mg, 0.250 mmol) and PS-NEt$_2$ (86 mg, 0.270 mmol) in CH$_2$Cl$_2$ (4.5 mL) was stirred overnight at r.t. 4-Chlorophenyl isocyanide (52 mg, 0.378 mmol) was added and the mixture was heated (microwave irradiation, 90 °C, 6 h). The mixture was filtered, washed with CH$_2$Cl$_2$ (20 mL), and the solvent removed in vacuo. The residue was purified using the Biotage SP4 general procedure C, and the product recrystallised by dissolving the sample in a minimum amount of CH$_2$Cl$_2$ and allowing *n*-hexane to diffuse into the solution; yield: 50 mg (32%); red crystals; mp 174–176 °C.

IR: 3315.2 (w), 2916.9 (w), 2217.5 (w), 1651.7 (m), 1617.8 (w), 1578.2 (m), 1546.4 (m), 1508.1 (m), 1483.2 (s), 1457.9 (m), 1413.6 (m), 1393.9 (m), 1372.5 (s), 1326.2 (m), 1294.3 (m), 1267.2 (m), 1244.1 (s), 1212.2 (s), 1173.6 (s), 1124.1 (m), 1112.7 (m), 1091.7 (m), 1069.8 (m), 1050.3 (m), 1035.9 (m), 1024.1 (m), 1008.9 (s), 962.2 (m), 941.0 (m), 896.1 (w), 880.8 (w), 867.1 (m), 844.8 (s), 832.1 (s), 779.9 (m), 768.4 (s), 758.2 (s), 729.7 (s), 713.3 (s), 702.5 (m), 680.9 (s), 657.9 (s) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.84 (s, 1 H, NH), 7.64 (d, J = 8.6 Hz, 2 H, 2H-PhBr), 7.59 (d, J = 8.8 Hz, 2 H, 3H-PhCN), 7.50 (d, J = 8.6 Hz, 2 H, 3H-PhBr), 7.34 (d, J = 8.7 Hz, 2 H, 3H-PhCl), 7.31 (d, J = 7.6 Hz, 1 H, 7H-isoquin), 7.24–7.20 (m, 1 H, 5H-isoquin), 7.18–7.14 (m, 1 H, 6H-isoquin), 7.06 (d, J = 8.8 Hz, 2 H, 2H-PhCN), 7.02 (d, J = 7.5 Hz, 1 H, 4H-isoquin), 6.71 (d, J = 8.7 Hz, 2 H, 2H-PhCl), 6.23 (d, J = 7.4 Hz, 1 H, 2H-isoquin), 5.80 (s, 1 H, CH), 5.50 (d, J = 7.5 Hz, 1 H, 3H-isoquin).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 188.00 (C), 160.95 (C), 147.40 (C), 146.04 (C), 137.07 (C), 136.94 (C), 133.41 (CH), 131.75 (CH), 131.27 (CH), 131.24 (C), 130.61 (CH), 129.50 (CH), 129.30 (CH), 129.10 (C), 128.57 (C), 128.42 (CH), 126.14 (C), 125.58 (C), 125.39 (CH), 123.91 (CH), 120.92 (CH), 119.35 (C), 118.31 (CH), 102.98 (C), 101.91 (CH), 61.85 (CH).

HPLC-MS (A): t_R = 5.62, m/z = 625.8 [M + H]$^+$.

HRMS: m/z calcd for C$_{32}$H$_{19}$BrClN$_4$OS [M – H]$^-$: 621.0157; found: 621.0140.

X-ray Data[38]

Formula: $C_{32}H_{20}BrClN_4OS·CH_2Cl_2$; Unit cell parameters: $a = 6.3155(1)$, $b = 13.5360(3)$, $c = 17.2911(4)$, $a = 92.617(1)$, $b = 92.544(1)$, $g = 92.462(1)$, space group $P\overline{1}$.

One-Pot Preparation for Indolizines; General Procedure D

A suspension of compound **3** (100 mg, 0.246 mmol), an isothiocyanate, and PS-NEt$_2$ (86 mg, 0.270 mmol) in CH$_2$Cl$_2$ (4.5 mL) was stirred at r.t. overnight. An isocyanide (1 equiv) was added and the mixture heated (microwave irradiation, 90 °C, 6 h). TFA (37 μL, 0.5 mmol) was added and the mixture again heated (microwave irradiation, 90 °C, 10 min). PS-CO$_3$ (239 mg, 0.626 mmol) was added, and after stirring (15 min), the mixture was filtered, washed with CH$_2$Cl$_2$ (20 mL) and the solvent removed in vacuo. The residue was purified by chromatography using a Biotage SP4 following general procedure C.

4-[3-(4-Bromobenzoyl)-1-(4-chlorophenylamino)pyrrolo[2,1-*a*]isoquinolin-2-ylamino]benzonitrile (10da)

Method 1: Prepared according to the general procedure D using 4-cyanophenyl isothiocyanate (40 mg, 0.250 mmol) and 4-chlorophenyl isocyanide (52 mg, 0.378 mmol). The product was recrystallised by dissolving the sample in a minimum amount of CH$_2$Cl$_2$ and allowing *n*-hexane to diffuse into the solution.

Method 2: The reaction was repeated using identical conditions to Method 1, except TFA (3.7 μL, 0.050 mmol) followed by heating (90 °C, 45 min) and PS-CO$_3$ (48 mg, 0.126 mmol).

Method 3: The reaction was repeated using identical conditions to Method 2, except heating was performed in both cases by immersing the sealed microwave tube into a pre-heated oil bath at 90 °C. After 6 h, the tube was removed and cooled under running cold H$_2$O; yield: Method 1, 70 mg (47%); Method 2, 67 mg (45%); Method 3, 67 mg (45%); yellow solid; mp 134–136 °C.

IR: 3331.4 (w), 3224.1 (w), 3157.2 (w), 3049.9 (w), 2927.2 (w), 2854.1 (w), 2204.8 (m), 1733.0 (w), 1681.3 (w), 1599.2 (m), 1575.5 (s), 1554.1 (m), 1522.4 (s), 1489.4 (s), 1433.4 (m), 1404.7 (s), 1391.6 (s), 1372.8 (s), 1355.7 (s), 1320.3 (s), 1263.6 (s), 1213.3 (s), 1168.4 (s), 1144.7 (s), 1104.3 (m), 1091.4 (s), 1065.5 (s), 1033.3 (m), 1007.8 (s), 960.6 (m), 939.4 (s), 890.0 (m), 869.8 (m), 853.9 (m), 835.6 (s), 818.0 (s), 796.9 (s), 776.2 (s), 758.4 (s), 743.0 (s), 734.6 (s), 697.7 (s), 685.1 (s), 673.4 (m), 654.9 (s) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.18 (d, $J = 7.6$ Hz, 1 H, 2H-isoquin), 8.43 (d, $J = 7.8$ Hz, 1 H, 7H-isoquin), 8.07 (s, 1 H, NH), 7.82 (d, $J = 7.9$ Hz, 1 H, 4H-isoquin), 7.54 (s, 1 H, NH), 7.57–7.53 (m, 1 H, 5H-isoquin), 7.51–7.47 (m, 1 H, 6H-isoquin), 7.39 (d, $J = 8.7$ Hz, 2 H, 2H-PhBr), 7.34 (d, $J = 8.7$ Hz, 2 H, 3H-PhBr), 7.28 (d, $J = 7.6$ Hz, 1 H, 3H-isoquin), 7.23 (d, $J = 8.9$ Hz, 2 H, 3H-PhCN), 6.99 (d, $J = 8.9$ Hz, 2 H, 3H-PhCl), 6.48 (d, $J = 8.9$ Hz, 2 H, 2H-PhCl), 6.40 (d, $J = 8.9$ Hz, 2 H, 2H-PhCN).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 183.91 (C), 149.84 (C), 145.79 (C), 138.29 (C), 132.80 (CH), 132.20 (C), 130.94 (CH), 130.41 (CH), 129.45 (C), 128.85 (C), 128.75 (CH), 128.26 (CH), 127.94 (CH), 126.91 (CH), 125.11 (C), 124.54 (CH), 124.09 (CH), 123.76 (C), 120.56 (C), 120.29 (C), 115.76 (C), 115.54 (C), 114.54 (CH), 113.87 (CH), 113.01 (CH), 98.19 (C).

HPLC-MS (A): $t_R = 5.42$; $m/z = 593.8$ [M + H]$^+$.

HRMS: m/z calcd for $C_{32}H_{19}BrClN_4O$ [M – H]$^-$: 589.0436; found: 589.0463.

X-ray Data[39]

Formula: $C_{32}H_{20}BrClN_4O·0.5(C_6H_{14})$; Unit cell parameters: $a = 24.3218(3)$, $b = 14.9314(2)$, $c = 7.88920(10)$, $a = 90.00$, $b = 90.00$, $g = 90.00$, space group $Pca2(1)$.

4-[3-(4-Bromobenzoyl)-1-(4-methoxyphenylamino)pyrrolo[2,1-*a*]isoquinolin-2-ylamino]benzonitrile (10db)

Prepared according to the general procedure D using 4-cyanophenyl isothiocyanate (40 mg, 0.250 mmol) and 4-methoxyphenyl isocyanide (50 mg, 0.375 mmol); yield: 56 mg (38%); yellow solid; mp 129–132 °C.

IR: 3319.0 (w), 3059.2 (w), 2831.8 (w), 2215.3 (w), 1728.1 (w), 1602.2 (m), 1584.3 (m), 1559.0 (w), 1505.9 (s), 1479.9 (m), 1435.5 (m), 1396.6 (s), 1372.3 (s), 1357.0 (s), 1319.8 (m), 1286.4 (m), 1231.6 (s), 1170.1 (s), 1127.0 (m), 1108.3 (m), 1067.2 (m), 1034.2 (m), 1009.5 (m), 937.0 (s), 891.9 (w), 857.9 (m), 821.1 (s), 794.5 (s), 766.3 (m), 744.5 (m), 713.4 (m), 691.1 (m), 679.1 (m) cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.19 (d, $J = 7.6$ Hz, 1 H, 2H-isoquin), 8.45 (d, $J = 8.2$ Hz, 1 H, 7H-isoquin), 8.07 (s, 1 H, NH), 7.80 (d, $J = 7.8$ Hz, 1 H, 4H-isoquin), 7.54–7.52 (m, 1 H, 5H-isoquin), 7.46–7.44 (m, 1 H, 6H-isoquin), 7.37 (d, $J = 8.6$ Hz, 2 H, 2H-PhBr), 7.33 (d, $J = 8.6$ Hz, 2 H, 3H-PhBr), 7.27 (d, $J = 7.6$ Hz, 1 H, 3H-isoquin), 7.21 (d, $J = 8.8$ Hz, 2 H, 3H-PhCN), 7.00 (s, 1 H, NH), 6.60 (d, $J = 9.0$ Hz, 2 H, 3H-*Ph*OMe), 6.43 (d, $J = 9.0$ Hz, 2 H, 2H-*Ph*OMe), 6.38 (d, $J = 8.8$ Hz, 2 H, 2H-PhCN), 3.56 (s, 3 H, OCH$_3$).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 184.19 (C), 152.12 (C), 150.42 (C), 140.85 (C), 138.68 (C), 133.13 (CH), 132.37 (C), 131.24 (CH), 130.72 (CH), 129.84 (C), 129.15 (C), 128.42 (CH), 128.15 (CH), 127.07 (CH), 125.36 (C), 124.89 (CH), 124.81 (CH), 124.28 (C), 120.62 (C), 117.63 (C), 115.95 (C), 115.00 (CH), 114.55 (CH), 114.13 (CH), 113.28 (CH), 98.47 (C), 55.62 (CH$_3$).

HPLC-MS (A): $t_R = 5.25$; $m/z = 589.8$ [M + H]$^+$.

HRMS: m/z calcd for $C_{33}H_{22}BrN_4O_2$ [M – H]$^-$: 585.0926; found: 585.0944.

{2-[3,5-Bis(trifluoromethyl)phenylamino]-1-(4-chlorophenylamino)pyrrolo[2,1-*a*]isoquinolin-3-yl}(4-bromophenyl)methanone (10ea)

Prepared according to the general procedure D using 3,5-bis(trifluoromethyl)phenyl isothiocyanate (46 μL, 0.251 mmol) and 4-chlorophenyl isocyanide (52 mg, 0.378 mmol); yield: 87 mg (48%); yellow solid; mp 103–106 °C.

IR: 3318.6 (w), 3133.2 (w), 3060.9 (w), 2968.6 (w), 2928.2 (w), 1723.0 (w), 1620.0 (w), 1585.7 (m), 1560.0 (w), 1527.5 (w), 1490.8 (m), 1471.0 (m), 1446.4 (m), 1422.0 (w), 1373.4 (s), 1357.0 (s), 1327.0 (w), 1274.0 (s), 1215.0 (w), 1168.4 (s), 1124.8 (s), 1093.8 (m), 1067.9 (m), 1045.8 (m), 1010.5 (m), 958.4 (m), 936.0 (m), 886.6 (m), 870.3 (m), 847.5 (m), 835.7 (m), 818.8 (m), 795.1 (m), 743.6 (m), 720.0 (m), 700.7 (m), 681.8 (m) cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.19 (d, $J = 7.5$ Hz, 1 H, 2H-isoquin), 8.38 (d, $J = 8.4$ Hz, 1 H, 7H-isoquin), 8.15 (s, 1 H, NH), 7.84 (d, $J = 7.8$ Hz, 1 H, 4H-isoquin), 7.73 (s, 1 H, NH), 7.57–7.55 (m, 1 H, 5H-isoquin), 7.50–7.48 (m, 1 H, 6H-isoquin), 7.32–7.31 (m, 4 H, PhBr), 7.30 (d, $J = 7.5$ Hz, 1 H, 3H-isoquin), 7.03 [s, 1 H, 4H-bis(CF$_3$)Ph], 7.02 (d, $J = 8.4$ Hz, 2 H, 3H-PhCl), 6.79 [s, 2 H, 2H-bis(CF$_3$)Ph], 6.56 (d, $J = 8.4$ Hz, 2 H, 2H-PhCl).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 183.81 (C), 147.94 (C), 145.79 (C), 138.21 (C), 132.22 (C), 130.55 (CH), 130.43 (C, q, $J = 32.3$ Hz), 130.38 (CH), 129.57 (C), 128.91 (C), 128.80 (C), 128.26 (CH), 127.93 (CH), 126.87 (CH), 125.16 (C), 124.65 (C), 124.20 (CH), 123.70 (CH), 123.38 (C, q, $J = 272.8$ Hz), 120.79 (C), 115.41 (C), 115.00 (C), 114.66 (CH), 113.41 (CH, q, $J = 3.4$ Hz), 113.10 (CH), 109.70 (CH, sept, $J = 3.8$ Hz).

HPLC-MS (A): $t_R = 5.86$; $m/z = 704.7$ [M + H]$^+$.

HRMS: m/z calcd for $C_{33}H_{18}BrClF_6N_3O$ [M – H]$^-$: 700.0226; found: 700.0228.

{2-[3,5-Bis(trifluoromethyl)phenylamino]-1-(4-methoxyphenylamino)pyrrolo[2,1-*a*]isoquinolin-3-yl}(4-bromophenyl)methanone (10eb)

Prepared according to the general procedure D using 3,5-bis(trifluoromethyl)phenyl isothiocyanate (46 μL, 0.251 mmol), 4-methoxyphenyl isocyanide (50 mg, 0.375 mmol), except heated (7 h) after the addition of isocyanide; yield: 69 mg (40%); yellow solid; mp 94–96 °C.

IR: 3313.3 (w), 3067.2 (w), 2930.8 (w), 2836.7 (w), 1585.4 (m), 1560.0 (w), 1526.9 (w), 1507.8 (s), 1470.5 (m), 1445.0 (m), 1421.9 (m), 1373.1 (s), 1356.7 (s), 1327.2 (w), 1274.3 (s), 1234.6 (m), 1168.5 (s), 1124.5 (s), 1108.1 (s), 1067.8 (m), 1035.0 (m), 1010.8 (m), 958.4 (m), 935.4 (m), 886.6 (m), 869.7 (m), 847.0 (m), 821.8 (m), 794.6 (m), 744.4 (m), 720.4 (m), 700.8 (m), 681.7 (s), 654.3 (m) cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.21 (d, J = 7.5 Hz, 1 H, 2H-isoquin), 8.43 (d, J = 8.2 Hz, 1 H, 7H-isoquin), 8.13 (s, 1 H, NH), 7.82 (d, J = 7.6 Hz, 1 H, 4H-isoquin), 7.55–7.53 (m, 1 H, 5H-isoquin), 7.47–7.45 (m, 1 H, 6H-isoquin), 7.31–7.29 (m, 4 H, PhBr), 7.28 (d, J = 7.5 Hz, 1 H, 3H-isoquin), 7.18 (s, 1 H, NH), 7.02 [s, 1 H, 4H-bis(CF$_3$)Ph], 6.76 [s, 2 H, 2H-bis(CF$_3$)Ph], 6.63 (d, J = 9.0 Hz, 2 H, 3H-*Ph*OMe), 6.49 (d, J = 9.0 Hz, 2 H, 2H-*Ph*OMe), 3.57 (s, 3 H, OCH$_3$).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 183.72 (C), 151.84 (C), 148.12 (C), 140.49 (C), 138.24 (C), 132.01 (C), 130.52 (CH), 130.38 (C, q, J = 34.7 Hz), 130.34 (CH), 129.59 (C), 128.85 (C), 128.12 (CH), 127.82 (CH), 126.72 (CH), 125.08 (C), 124.68 (CH), 124.55 (CH), 123.86 (C), 123.39 (C, q, J = 272.8 Hz), 117.14 (C), 114.84 (C), 114.68 (CH), 114.24 (CH), 113.27 (CH, q, J = 3.3 Hz), 113.05 (CH), 109.55 (CH, septet, J = 3.8 Hz), 55.25 (CH$_3$).

HPLC-MS (A): t_R = 5.67; m/z = 698.7 [M + H]$^+$.

HRMS: m/z calcd for C$_{34}$H$_{21}$BrF$_6$N$_3$O$_2$ [M – H]$^-$: 696.0721; found: 696.0748.

[2-(Benzylamino)-1-(4-methoxyphenylamino)pyrrolo[2,1-*a*]isoquinolin-3-yl](4-bromophenyl)methanone (10fb)

A suspension of **3** (100 mg, 0.246 mmol), benzyl isothiocyanate (33 μL, 0.248 mmol) and PS-NEt$_2$ (86 mg, 0.270 mmol) in CH$_2$Cl$_2$ (4.5 mL) was stirred overnight at r.t., and then heated (microwave irradiation, 90 °C, 30 min). 4-Methoxyphenyl isocyanide (50 mg, 0.375 mmol) was added and the mixture heated (microwave irradiation, 90 °C, 8 h). TFA (3.7 μL, 0.050 mmol) was then added and the mixture heated (microwave irradiation, 90 °C, 40 min). PS-CO$_3$ (48 mg, 0.126 mmol) was added, and after stirring (15 min), the mixture was filtered, washed with CH$_2$Cl$_2$ (20 mL) and the solvent removed in vacuo. The residue was purified by chromatography using a Biotage SP4 following general procedure C; yield: 45 mg (31%); yellow solid; mp 82–84 °C.

IR: 3291.7 (w), 3028.9 (w), 2928.8 (w), 2831.0 (w), 1731.5 (w), 1691.3 (w), 1575.8 (m), 1558.1 (m), 1506.1 (s), 1483.1 (m), 1463.7 (m), 1449.2 (m), 1409.0 (s), 1376.4 (m), 1352.1 (s), 1288.6 (m), 1232.0 (s), 1173.0 (m), 1106.1 (m), 1067.3 (m), 1033.2 (m), 1005.4 (m), 919.5 (m), 820.1 (s), 786.1 (s), 735.1 (s), 697.0 (s), 664.6 (s) cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.54 (d, J = 8.1 Hz, 1 H, 7H-isoquin), 8.10 (d, J = 7.4 Hz, 1 H, 2H-isoquin), 7.69 (d, J = 8.4 Hz, 2 H, 2H-PhBr), 7.65 (d, J = 7.7 Hz, 1 H, 4H-isoquin), 7.53 (d, J = 8.4 Hz, 2 H, 3H-PhBr), 7.48–7.45 (m, 1 H, 5H-isoquin), 7.39–7.37 (m, 1 H, 6H-isoquin), 7.21–7.17 (m, 4 H, 3H-Ph, 4H-Ph and NH), 6.98 (d, J = 6.6 Hz, 2 H, 2H-Ph), 6.86 (d, J = 7.4 Hz, 1 H, 3H-isoquin), 6.72 (d, J = 8.9 Hz, 2 H, 3H-*Ph*OMe), 6.55 (d, J = 8.9 Hz, 2 H, 2H-*Ph*OMe), 6.12 (br s, 1 H, NH), 4.27 (br s, 2 H, CH$_2$), 3.62 (s, 3 H, OCH$_3$).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 181.42 (C), 151.55 (C), 145.14 (C), 141.59 (C), 139.74 (C), 139.44 (C), 132.05 (CH), 132.03 (C), 130.21 (CH), 129.54 (C), 128.42 (CH), 128.28 (CH), 127.34 (CH), 127.30 (CH), 127.10 (CH), 126.57 (CH), 125.11 (CH), 124.77 (C), 124.62 (CH), 123.36 (C), 115.00 (CH), 113.63 (CH), 112.15 (C), 109.79 (CH), 108.84 (C), 55.29 (CH$_3$), 48.52 (CH$_2$).

HPLC-MS (A): t_R = 5.54; m/z = 576.3 [M + H]$^+$.

HRMS: m/z calcd for C$_{33}$H$_{27}$BrN$_3$O$_2$ [M + H]$^+$: 576.1281; found: 576.1275.

2-(4-Nitrobenzyl)isoquinolinium Bromide

4-Nitrobenzyl bromide (10.00 g, 46.29 mmol) was dissolved in CH$_2$Cl$_2$ (80 mL). Isoquinoline (5.46 mL, 46.45 mmol) was added dropwise to the mixture followed by stirring overnight at r.t. The mixture was filtered under suction and the product washed with ice-cold CH$_2$Cl$_2$ (20 mL). The solid was dried in vacuo; yield: 14.1 g (88%); pale yellow solid.

IR: 3442.4 (w), 3395.4 (w), 3052.2 (w), 3015.3 (w), 2968.6 (w), 2934.6 (m), 1641.7 (m), 1608.5 (m), 1532.6 (m), 1515.7 (m), 1493.8 (w), 1471.8 (w), 1393.6 (m), 1370.7 (m), 1345.0 (s), 1323.2 (m), 1284.9 (m), 1247.7 (w), 1212.4 (w), 1172.9 (w), 1150.8 (m), 1119.4 (m), 1108.5 (m), 1017.6 (w), 975.4 (w), 921.9 (w), 869.1 (w), 854.0 (m), 838.7 (m), 810.6 (m), 783.7 (w), 770.6 (w), 758.2 (m), 717.9 (s), 692.8 (m), 655.8 (w) cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.30 (s, 1 H, 8H-isoquin), 8.83 (d, J = 6.9 Hz, 1 H, 2H-isoquin), 8.63 (d, J = 6.9 Hz, 1 H, 3H-isoquin), 8.53 (d, J = 8.3 Hz, 1 H, 7H-isoquin), 8.36 (d, J = 8.3 Hz, 1 H, 4H-isoquin), 8.30–8.27 (m, 1 H, 5H-isoquin), 8.27 (d, J = 8.7 Hz, 2 H, 3H-PhNO$_2$), 8.11–8.08 (m, 1 H, 6H-isoquin), 7.81 (d, J = 8.7 Hz, 2 H, 2H-PhNO$_2$), 6.15 (s, 2 H, CH$_2$).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 151.33 (CH), 148.35 (C), 141.70 (C), 137.82 (CH), 137.64 (C), 135.41 (CH), 131.87 (CH), 131.19 (CH), 130.60 (CH), 127.83 (CH, C), 126.88 (CH), 124.55 (CH), 62.64 (CH$_2$).

HPLC-MS (A): t_R = 3.16; m/z = 265.3 [M – Br]$^+$.

HRMS: m/z calcd for C$_{16}$H$_{13}$N$_2$O$_2$ [M – Br]$^+$: 265.0977; found: 265.0974.

This compound was not used in the procedures due to the insolubility of the compound in CH$_2$Cl$_2$.

2-(Cyanomethyl)isoquinolinium Bromide (12)

Bromoacetonitrile (7.50 mL, 107.54 mmol) was dissolved in CH$_2$Cl$_2$ (80 mL). Isoquinoline (12.64 mL, 108.62 mmol) was added dropwise to the mixture followed by stirring overnight at r.t. The solvent was removed in vacuo, the residue was washed with PE (20 mL) and Et$_2$O (10 mL), and dried in vacuo; yield: 17.3 g (65%); pale yellow solid.

IR: 3028.6 (w), 2999.2 (w), 2916.6 (w), 2885.4 (w), 2252.7 (w), 1637.6 (m), 1605.2 (w), 1505.4 (w), 1465.8 (w), 1395.8 (m), 1377.8 (m), 1332.8 (w), 1287.7 (w), 1222.7 (w), 1189.3 (m), 1158.8 (m), 1126.0 (m), 1015.4 (w), 989.6 (m), 972.0 (w), 948.5 (w), 897.7 (m), 880.8 (s), 846.3 (s), 771.6 (s), 761.2 (s), 741.1 (m) cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.26 (s, 1 H, 8H-isoquin), 8.88 (d, J = 6.8 Hz, 1 H, 2H-isoquin), 8.69 (d, J = 6.8 Hz, 1 H, 3H-isoquin), 8.59 (d, J = 8.3 Hz, 1 H, 7H-isoquin), 8.40 (d, J = 8.3 Hz, 1 H, 4H-isoquin), 8.34–8.31 (m, 1 H, 5H-isoquin), 8.13–8.10 (m, 1 H, 6H-isoquin), 6.17 (s, 2 H, CH$_2$).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 151.67 (CH), 138.11 (CH), 137.57 (C), 134.70 (CH), 131.75 (CH), 131.09 (CH), 127.54 (CH), 127.09 (C), 126.38 (CH), 114.42 (C), 47.60 (CH$_2$).

HPLC-MS (A): t_R = 3.67; m/z = 169.8 [M – Br]$^+$.

One-Pot Preparation of Nitrile-Substituted Indolizines; General Procedure E

A mixture of compound **12** (63 mg, 0.253 mmol), an isothiocyanate (1 equiv), and PS-NEt$_2$ (86 mg, 0.270 mmol) in CH$_2$Cl$_2$ (4.5 mL) was stirred at r.t. overnight. An isocyanide was then added and the mixture heated (microwave irradiation, 90 °C, 6 h). TFA (3.7 μL, 0.050 mmol) was added and the mixture again heated (microwave irradiation, 90 °C, 1 h). PS-CO$_3$ (48 mg, 0.126 mmol) was added, and after stirring (15 min), the mixture was filtered, washed with CH$_2$Cl$_2$ (20 mL), and the solvent removed in vacuo. The residue was purified by chromatography using a Biotage SP4 following general procedure C.

1-(4-Chlorophenylamino)-2-(4-cyanophenylamino)pyrrolo[2,1-*a*]isoquinoline-3-carbonitrile (13da)

Prepared according to the general procedure E using 4-cyanophenyl isothiocyanate (40 mg, 0.250 mmol) and 4-chlorophenyl isocyanide (52 mg, 0.378 mmol); yield: 15 mg (14%); pale red solid; mp 206 °C (dec.).

IR: 3362.9 (w), 3275.0 (w), 3051.3 (w), 2924.0 (w), 2853.0 (w), 2222.7 (m), 2194.7 (m), 1602.7 (m), 1578.0 (m), 1543.0 (m), 1509.3 (m), 1491.7 (s), 1455.7 (m), 1430.2 (m), 1418.9 (m), 1381.4 (m), 1357.4 (m), 1304.3 (m), 1287.3 (m), 1258.5 (m), 1240.9 (m), 1213.0 (w), 1173.4 (m), 1153.3 (m), 1114.3 (w), 1087.7 (m), 1064.4 (w), 1007.0 (w), 966.9 (w), 949.6 (w), 923.0 (w), 900.8 (w), 884.1 (w), 861.3 (w), 828.8 (m), 814.7 (s), 786.9 (s), 770.7 (m), 739.8 (m), 687.3 (w), 670.6 (m) cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.82 (s, 1 H, NH), 8.29 (d, J = 8.0 Hz, 1 H, 7H-isoquin), 8.17 (d, J = 7.3 Hz, 1 H, 2H-isoquin), 7.83 (d, J = 7.8 Hz, 1 H, 4H-isoquin), 7.72 (s, 1 H, NH), 7.54–7.52 (m, 1 H, 5H-isoquin), 7.50 (d, J = 8.7 Hz, 2 H, 3H-PhCN), 7.50–7.47 (m, 1 H, 6H-isoquin), 7.27 (d, J = 7.3 Hz, 1 H, 3H-isoquin), 7.01 (d, J = 8.8 Hz, 2 H, 3H-PhCl), 6.94 (d, J = 8.7 Hz, 2 H, 2H-PhCN), 6.49 (d, J = 8.8 Hz, 2 H, 2H-PhCl).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 148.40 (C), 145.60 (C), 134.03 (C), 133.32 (CH), 128.77 (CH), 128.39 (C), 128.17 (CH), 128.13 (CH), 128.01 (C), 127.34 (CH), 123.84 (C), 123.48 (CH), 123.36 (CH), 120.73 (C), 120.01 (C), 114.91 (CH), 114.52 (CH), 113.17 (CH), 113.03 (C), 112.82 (C), 99.69 (C), 90.14 (C).

HPLC-MS (A): t_R = 5.03; m/z = 576.3 [M + H]$^+$.

HRMS: m/z calcd for C$_{26}$H$_{15}$ClN$_5$ [M − H]$^-$: 432.1016; found: 432.1036.

2-(4-Cyanophenylamino)-1-(4-methoxyphenylamino)pyrrolo[2,1-*a*]isoquinoline-3-carbonitrile (13db)

Prepared according to the general procedure E using 4-cyanophenyl isothiocyanate (40 mg, 0.250 mmol) and 4-methoxyphenyl isocyanide (50 mg, 0.375 mmol); yield: 23 mg (21%); pale yellow solid; mp 215 °C (dec.).

IR: 3369.9 (w), 3273.9 (w), 3051.1 (w), 2953.7 (w), 2833.3 (w), 2221.9 (m), 2189.2 (m), 1604.1 (m), 1578.3 (m), 1543.1 (m), 1506.7 (s), 1494.0 (s), 1456.0 (m), 1431.4 (m), 1419.8 (m), 1402.5 (s), 1378.6 (s), 1356.4 (m), 1314.9 (m), 1289.7 (m), 1257.0 (m), 1230.3 (s), 1173.6 (s), 1129.9 (m), 1107.2 (m), 1064.1 (w), 1034.8 (m), 968.0 (w), 947.9 (w), 900.6 (w), 885.1 (w), 860.3 (w), 838.6 (m), 815.4 (s), 784.0 (s), 759.3 (m), 742.5 (m), 718.4 (m), 697.1 (m), 670.0 (m) cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.77 (s, 1 H, NH), 8.32 (d, J = 8.1 Hz, 1 H, 7H-isoquin), 8.15 (d, J = 7.3 Hz, 1 H, 2H-isoquin), 7.81 (d, J = 7.9 Hz, 1 H, 4H-isoquin), 7.52–7.50 (m, 1 H, 5H-isoquin), 7.49 (d, J = 8.8 Hz, 2 H, 3H-PhCN), 7.46–7.44 (m, 1 H, 6H-isoquin), 7.24 (d, J = 7.3 Hz, 1 H, 3H-isoquin), 7.17 (s, 1 H, NH), 6.95 (d, J = 8.8 Hz, 2 H, 2H-PhCN), 6.62 (d, J = 8.9 Hz, 2 H, 3H-*Ph*OMe), 6.44 (d, J = 8.9 Hz, 2 H, 2H-*Ph*OMe), 3.57 (s, 3 H, OCH$_3$).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 151.79 (C), 148.57 (C), 140.33 (C), 133.92 (C), 133.33 (CH), 128.30 (C), 128.04 (CH), 128.01 (C), 127.94 (CH), 127.18 (CH), 124.01 (C), 123.80 (CH), 123.35 (CH), 120.03 (C), 114.81 (CH), 114.68 (C), 114.66 (CH), 114.05 (CH), 113.04 (CH), 112.92 (C), 99.57 (C), 89.94 (C), 55.28 (CH$_3$).

HPLC-MS (A): t_R = 4.89; m/z = 430.3 [M + H]$^+$.

HRMS: m/z calcd for C$_{27}$H$_{18}$N$_5$O [M − H]$^-$: 428.1511; found: 428.1527.

2-[3,5-Bis(trifluoromethyl)phenylamino]-1-(4-chlorophenylamino)pyrrolo[2,1-*a*]isoquinoline-3-carbonitrile (13ea)

Prepared according to the general procedure E using 3,5-bis(trifluoromethyl)phenyl isothiocyanate (46 μL, 0.251 mmol) and 4-chlorophenyl isocyanide (52 mg, 0.378 mmol); yield: 31 mg (23%); pale red solid; mp 174–178 °C.

IR: 3313.0 (w), 3075.0 (w), 2934.1 (w), 2199.3 (w), 1621.2 (w), 1597.5 (w), 1549.9 (w), 1492.0 (m), 1473.3 (m), 1450.0 (m), 1429.4 (w), 1409.8 (w), 1374.6 (s), 1302.9 (w), 1274.3 (s), 1169.2 (s), 1124.1 (s), 1046.3 (m), 1001.1 (m), 950.8 (m), 871.6 (m), 843.6 (w), 819.1 (m), 787.1 (s), 772.9 (m), 748.9 (m), 724.9 (m), 701.0 (m), 682.1 (s) cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.88 (s, 1 H, NH), 8.27 (d, J = 7.7 Hz, 1 H, 7H-isoquin), 8.18 (d, J = 7.3 Hz, 1 H, 2H-isoquin), 7.83 (d, J = 7.7 Hz, 1 H, 4H-isoquin), 7.80 (s, 1 H, NH), 7.54–7.52 (m, 1 H, 5H-isoquin), 7.49–7.47 (m, 1 H, 6H-isoquin), 7.39 [s, 2 H, 2H-bis(CF$_3$)Ph], 7.27 [s, 1 H, 4H-bis(CF$_3$)Ph], 7.26 (d, J = 7.3 Hz, 1 H, 3H-isoquin), 7.01 (d, J = 8.8 Hz, 2 H, 3H-PhCl), 6.50 (d, J = 8.8 Hz, 2 H, 2H-PhCl).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 145.73 (C), 145.21 (C), 133.64 (C), 130.90 (C, q, J = 32.4 Hz), 128.76 (CH), 128.73 (CH), 128.43 (C), 128.10 (CH), 127.90 (C), 127.30 (CH), 123.83 (C), 123.61 (CH), 123.47 (CH), 123.45 (C, q, J = 272.9 Hz), 120.89 (C), 114.87 (CH, q, J = 3.2 Hz), 114.62 (CH), 113.07 (CH), 112.78 (C), 112.53 (C), 111.33 (CH, sept, J = 3.6 Hz), 89.38 (C).

HPLC-MS (A): t_R = 5.55; m/z = 545.3 [M + H]$^+$.

HRMS: m/z calcd for C$_{27}$H$_{14}$ClF$_6$N$_4$ [M − H]$^-$: 543.0811; found: 543.0837.

2-[3,5-Bis(trifluoromethyl)phenylamino]-1-(4-methoxyphenylamino)pyrrolo[2,1-*a*]isoquinoline-3-carbonitrile (13eb)

Prepared according to the general procedure E using 3,5-bis(trifluoromethyl)phenyl isothiocyanate (46 μL, 0.251 mmol), 4-methoxyphenyl isocyanide (50 mg, 0.375 mmol); yield: 39 mg (29%); pale yellow solid; mp 159–161 °C.

IR: 3326.3 (w), 3070.8 (w), 2936.7 (w), 2836.0 (w), 2197.9 (w), 1620.7 (w), 1557.5 (w), 1507.7 (s), 1471.6 (m), 1448.8 (w), 1429.0 (w), 1410.4 (w), 1368.1 (s), 1327.3 (w), 1274.4 (s), 1233.0 (m), 1168.8 (s), 1123.7 (s), 1067.1 (m), 1035.6 (m), 999.3 (m), 949.9 (m), 870.1 (m), 821.5 (m), 786.6 (m), 744.5 (m), 722.4 (m), 701.0 (m), 681.5 (m) cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.84 (s, 1 H, NH), 8.31 (d, J = 8.2 Hz, 1 H, 7H-isoquin), 8.16 (d, J = 7.3 Hz, 1 H, 2H-isoquin), 7.81 (d, J = 7.8 Hz, 1 H, 4H-isoquin), 7.52–7.50 (m, 1H, 5H-isoquin), 7.46–7.44 (m, 1 H, 6H-isoquin), 7.38 [s, 2 H, 2H-bis(CF$_3$)Ph], 7.25 [s, 2 H, NH and 4H-bis(CF$_3$)Ph], 7.24 (d, J = 7.3 Hz, 1 H, 3H-isoquin), 6.61 (d, J = 8.8 Hz, 2 H, 3H-*Ph*OMe), 6.44 (d, J = 8.8 Hz, 2 H, 2H-*Ph*OMe), 3.57 (s, 3 H, OCH$_3$).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 151.86 (C), 145.93 (C), 139.93 (C), 133.48 (C), 130.87 (C, q, J = 32.3 Hz), 128.34 (C), 127.98 (CH), 127.92 (CH), 127.86 (C), 127.15 (CH), 124.03 (C), 123.90 (CH), 123.61 (CH), 123.48 (C, q, J = 272.9 Hz), 123.45 (CH), 114.71 (CH, q, J = 3.6 Hz), 114.60 (CH), 114.24 (C), 114.13

(CH), 112.96 (CH), 112.87 (C), 111.12 (CH, sept, $J = 3.6$ Hz), 89.22 (C), 55.25 (CH$_3$).

HPLC-MS (A): $t_R = 5.38$; $m/z = 541.3$ [M + H]$^+$.

HRMS: m/z calcd for C$_{28}$H$_{17}$F$_6$N$_4$O [M – H]$^-$: 539.1307; found: 539.1318.

1-[2-(4-Bromophenyl)-2-oxoethyl]quinolinium Bromide (14)
To a solution of 2,4′-dibromoacetophenone (5.56 g, 20 mmol) in CH$_2$Cl$_2$ (60 mL) was added quinoline (1.90 mL, 20 mmol) drop-wise. The mixture was stirred (r.t., 48 h), concentrated in vacuo and filtered. The residual solid was washed with ice-cold CH$_2$Cl$_2$ (20 mL) and dried in vacuo; yield: 6.36 g (83%); cream solid.

IR: 3022.7 (w), 2957.2 (w), 1682.5 (s), 1625.5 (w), 1600.4 (w), 1585.8 (m), 1567.0 (m), 1529.5 (m), 1481.0 (w), 1458.8 (w), 1402.0 (m), 1375.2 (m), 1366.9 (m), 1347.3 (w), 1286.2 (w), 1236.7 (m), 1206.6 (w), 1187.2 (w), 1171.9 (w), 1149.0 (w), 1102.3 (w), 1075.3 (m), 1056.1 (w), 1011.3 (w), 992.8 (m), 966.4 (m), 952.6 (w), 878.2 (w), 869.5 (m), 838.8 (m), 825.9 (m), 811.0 (m), 800.5 (s), 772.8 (s), 748.9 (m), 734.0 (m), 695.7 (w) cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.48 (d, $J = 5.9$ Hz, 1 H, 2H-quin), 9.43 (d, $J = 8.4$ Hz, 1 H, 4H-quin), 8.53 (dd, $J = 8.2$, 1.3 Hz, 1 H, 5H-quin), 8.46 (d, $J = 9.0$ Hz, 1 H, 8H-quin), 8.31 (dd, $J = 8.4$, 5.9 Hz, 1 H, 3H-quin), 8.21 (m, 1 H, 7H-quin), 8.06 (d, $J = 8.6$ Hz, 2 H, 2H-PhBr), 8.05 (m, 1 H, 6H-quin), 7.92 (d, $J = 8.6$ Hz, 2 H, 3H-PhBr), 6.98 (s, 2 H, CH$_2$).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 190.61 (C), 151.45 (CH), 149.13 (CH), 139.13 (C), 136.40 (CH), 133.16 (C), 132.61 (CH), 131.08 (CH), 131.03 (CH), 130.46 (CH), 129.85 (C), 129.42 (C), 122.64 (CH), 119.65 (CH), 65.36 (CH$_2$).

HPLC-MS (B): $t_R = 2.66$; $m/z = 328.0$ [M – Br]$^+$.

HRMS: m/z calcd for C$_{17}$H$_{13}$BrNO [M – Br]$^+$: 328.0160; found 328.0163.

Quinoline Based Indolizines; General Procedure F
A suspension of compound **14** (100 mg, 0.246 mmol), an isothiocyanate (1 equiv) and PS-NEt$_2$ (86 mg, 0.270 mmol) in CH$_2$Cl$_2$ (4.5 mL) was stirred at r.t. (2 d). 4-Chlorophenyl isocyanide (52 mg, 0.378 mmol) was added and the mixture heated (microwave irradi-ation, 90 °C, 6 h). TFA (3.7 µL, 0.050 mmol) was added and the mixture again heated (microwave irradiation, 90 °C). PS-CO$_3$ (48 mg, 0.126 mmol) was added, and after stirring (15 min), the mixture was filtered, washed with CH$_2$Cl$_2$ (20 mL), and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica gel 60 (0.040–0.063 mm) purchased from Breckland Sci-entific Supplies.

4-[1-(4-Bromobenzoyl)-3-(4-chlorophenylamino)pyrrolo[1,2-a]quinolin-2-ylamino]benzonitrile (15da)
Prepared according to the general procedure F using 4-cyanophenyl isothiocyanate (40 mg, 0.250 mmol), heating with TFA (50 min), and eluted with 20% EtOAc in PE, then 10% PE in CH$_2$Cl$_2$; yield: 52 mg (35%); yellow solid; mp 114–118 °C.

IR: 3325.0 (w), 3063.1 (w), 2970.0 (w), 2217.2 (m), 1602.3 (s), 1582.7 (s), 1509.0 (s), 1489.7 (s), 1445.1 (m), 1398.7 (m), 1371.1 (s), 1345.0 (m), 1319.8 (m), 1302.8 (m), 1285.3 (m), 1250.4 (m), 1204.2 (m), 1171.2 (s), 1092.4 (m), 1068.3 (m), 1038.3 (w), 1003.7 (m), 954.8 (w), 917.8 (w), 884.8 (w), 818.5 (s), 800.1 (s), 776.2 (m), 746.6 (s), 691.1 (m), 680.5 (m) cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.24 (s, 1 H, NH), 7.85 (d, $J = 7.4$ Hz, 1 H, 5H-quin), 7.58 (d, $J = 8.4$ Hz, 2 H, 2H-BrPh), 7.55 (s, 1 H, NH), 7.50 (d, $J = 8.8$ Hz, 1 H, 4H-quin), 7.48 (d, $J = 8.4$ Hz, 2 H, 3H-PhBr), 7.45 (d, $J = 8.2$ Hz, 1 H, 8H-quin), 7.42-7.39 (m, 1 H, 7H-quin), 7.39-7.36 (m, 1 H, 6H-quin), 7.29 (d, $J = 8.8$ Hz, 1 H, 3H-quin), 7.27 (d, $J = 8.7$ Hz, 2 H, 3H-PhCN), 7.00 (d, $J = 8.8$

2 H, 3H-PhCl), 6.52 (d, $J = 8.8$ Hz, 2 H, 2H-PhCl), 6.48 (d, $J = 8.7$ Hz, 2 H, 2H-PhCN).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 184.39 (C), 149.53 (C), 145.78 (C), 137.57 (C), 132.81 (CH), 132.42 (C), 131.36 (CH), 131.21 (CH), 130.99 (C), 130.84 (C), 129.28 (CH), 128.51 (2 CH), 126.65 (C), 124.76 (C), 124.56 (CH), 123.91 (CH), 120.36 (C), 120.24 (C), 119.65 (C), 118.83 (CH), 115.69 (CH), 114.74 (C), 114.61 (CH), 114.14 (CH), 98.17 (C).

HPLC-MS (A): $t_R = 5.45$; $m/z = 593.2$ [M + H]$^+$.

HRMS: m/z calcd for C$_{32}$H$_{21}$BrClN$_4$O [M + H]$^+$: 591.0582; found 591.0557.

[2-(3,5-Bis(trifluoromethyl)phenylamino)-3-(4-chlorophenyl-amino)pyrrolo[1,2-a]quinolin-1-yl](4-bromophenyl)metha-none (15ea)
Prepared according to the general procedure F using 3,5-bis(tri-fluoromethyl)phenyl isothiocyanate (46 µL, 68 mg, 0.251 mmol), heating with TFA (30 min), and eluted with 40% PE in CH$_2$Cl$_2$; yield: 80 mg (46%); yellow solid; mp 92–95 °C.

IR: 3315.4 (w), 3066.8 (w), 1583.5 (m), 1533.9 (m), 1505.8 (m), 1491.2 (m), 1471.1 (m), 1456.2 (m), 1404.3 (m), 1372.0 (s), 1325.4 (w), 1302.2 (w), 1275.0 (s), 1206.4 (w), 1169.8 (s), 1126.7 (s), 1107.7 (s), 1068.8 (m), 1006.2 (m), 956.1 (m), 912.5 (w), 873.9 (m), 841.9 (m), 818.6 (m), 800.0 (m), 776.3 (w), 746.4 (m), 724.5 (w), 700.9 (m), 681.8 (m) cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.30 (s, 1 H, NH), 7.86 (d, $J = 7.5$ Hz, 1 H, 5H-quin), 7.71 (s, 1 H, NH), 7.57 (d, $J = 8.5$ Hz, 2 H, 2H-PhBr), 7.51 (d, $J = 9.2$ Hz, 1 H, 4H-quin), 7.47 (d, $J = 8.7$ Hz, 1 H, 8H-quin), 7.45 (d, $J = 8.5$ Hz, 2 H, 3H-PhBr), 7.42–7.40 (m, 1 H, 7H-quin), 7.39–7.37 (m, 1 H, 6H-quin), 7.31 (d, $J = 9.2$ Hz, 1 H, 3H-quin), 7.06 [s, 1 H, 4H-bis(CF$_3$)Ph], 7.00 (d, $J = 8.8$ Hz, 2 H, 3H-PhCl), 6.88 [s, 2 H, 2H-bis(CF$_3$)Ph], 6.53 (d, $J = 8.8$ Hz, 2 H, 2H-PhCl).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 184.33 (C), 146.94 (C), 145.25 (C), 137.60 (C), 132.48 (C), 131.26 (CH), 131.11 (CH), 130.63 (C), 130.51 (C), 130.35 (C, q, $J = 32.8$ Hz), 129.25 (CH), 128.46 (2 CH), 126.60 (C), 124.79 (C), 124.56 (CH), 123.92 (CH), 123.43 (C, q, $J = 272.8$ Hz), 120.65 (C), 119.22 (C), 118.97 (CH), 115.80 (CH), 114.70 (CH), 114.41 (C), 113.99 (CH, q, $J = 3.4$ Hz), 109.76 (CH, sept, $J = 4.0$ Hz).

HPLC-MS (A): $t_R = 5.87$; $m/z = 704.3$ [M + H]$^+$.

HRMS: m/z calcd for C$_{33}$H$_{18}$BrClF$_6$N$_3$O [M – H]$^-$: 700.0226; found: 700.0253.

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(39) Crystallographic data for **10da** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 678908 (Authors: J. E. Davies, M. D. Hopkin, S. V. Ley). Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 33603 or e-mail: deposit@ccdc.cam.ac.uk).