Automated Multistep Continuous Flow Synthesis of 2-(1*H*-Indol-3-yl)thiazole Derivatives

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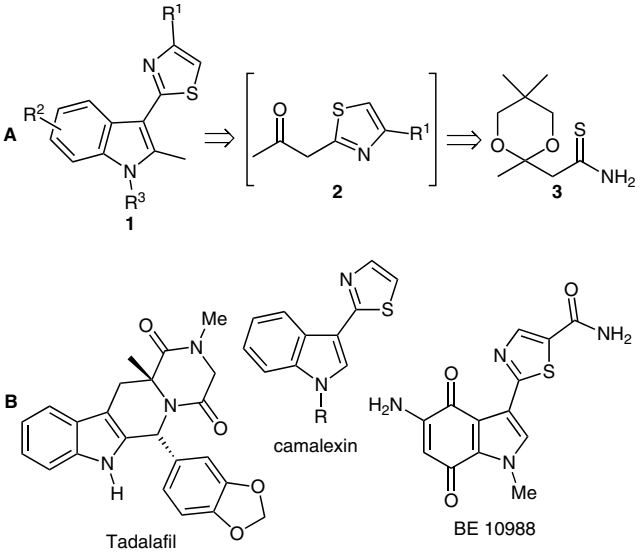
Abstract: The multistep continuous flow assembly of 2-(1*H*-indol-3-yl)thiazoles using a Syrris AFRICA® synthesis station is reported. Sequential Hantzsch thiazole synthesis, deketalization, and Fischer indole synthesis provides rapid and efficient access to highly functionalized, pharmacologically significant 2-(1*H*-indol-3-yl)thiazoles. These complex drug-like small molecules are generated in reaction times of less than 15 minutes and in high yields (38–82% over three chemical steps without isolation of intermediates).

Key words: heterocycles, indoles, condensation, tandem reactions, microreactor, microfluidic synthesis

The interaction of small molecule compounds with specific human proteins, such as enzymes, receptors, or ion channels, is one of the fundamental principles upon which the discovery of new medicines is based. Advantages of low molecular weight drugs include the potential for oral bioavailability, efficient tissue (e.g., brain) penetration and low cost of manufacture, among others. The vast majority of low molecular weight drugs are heterocyclic compounds, often comprising several connected heterocyclic rings. This is not surprising considering the propensity of heteroatoms within drug scaffolds to form reversible interactions (electrostatic, H-bonds etc.) within the active sites of proteins, thereby exerting a modulatory effect. High-throughput screening is one of the most common and effective methods to identify small molecule compounds with activity against the target protein of interest. Invariably, however, the initial hit structure identified in a screening campaign exhibits relatively low potency and selectivity for the target protein, in addition to sub-optimal physicochemical (drug-like) properties. Therefore, the development of new synthetic chemistry methods for the rapid and efficient generation of analogues for in vitro testing is critical for the hit-to-lead optimization of screening hits.[1–8] Accordingly, we have established a research program focused on developing automated flow chemistry methods to rapidly access complex, drug-like compounds from readily available precursors. More specifically, we are developing highly efficient flow chemistry methods that combine multiple chemical transformations into single, continuous processes.



Scheme 1 (a) Indolylthiazoles **1** from intermediate β-ketothiazoles **2** and prepared thioamide **3**. (b) Marketed indole Tadalafil and biologically active natural products camalexin and BE 10988.

Advantages of this technology include optimal heat transfer, enhanced reagent mixing, precise reaction times, small reaction volumes, and the ability to conduct multistep reactions in a single, unbroken microreactor sequence.[9] Thus, flow processes are safe, environmentally friendly, and cost effective on a manufacturing scale. To demonstrate the utility of flow synthesis, we have previously reported the continuous flow preparation of bis-substituted 1,2,4-oxadiazoles,[5] functionalized imidazo[1,2-*a*] heterocycles,[6] pyrrole-3-carboxylic acid derivatives,[7] and 5-(thiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-ones.[8] We now report a methodology for consecutive heterocycle formation reactions to access 2-(1*H*-indol-3-yl)thiazoles (indolylthiazoles, **1**), which are privileged scaffolds with demonstrated biological activity, using an uninterrupted continuous flow microreactor sequence. In this unique continuous process, sequential thiazole formation, deketalization, and Fischer indole synthesis provides rapid and efficient access to novel indolylthiazole derivatives **1**. These structures, which are generated from β-ketothiazoles **2** and prepared thioamide **3** (Scheme 1), are formed cleanly and without isolation of intermediates.

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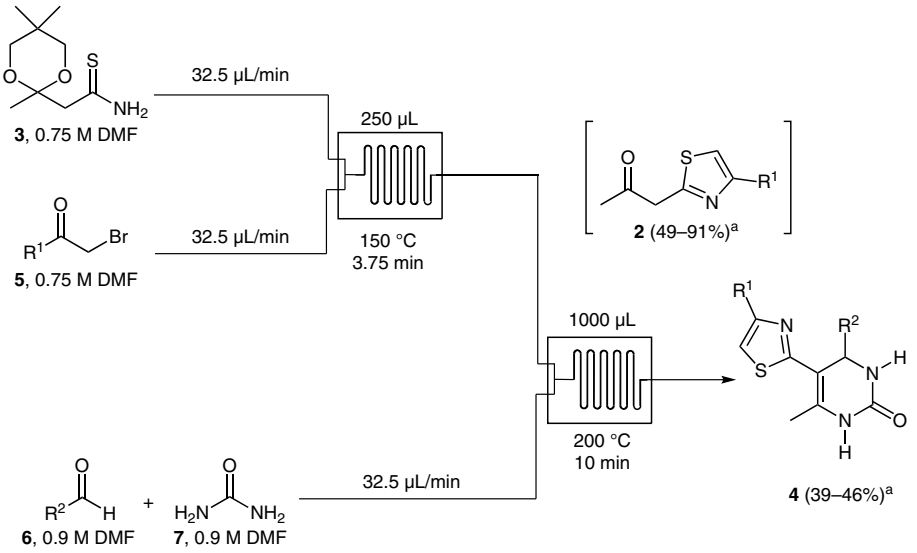
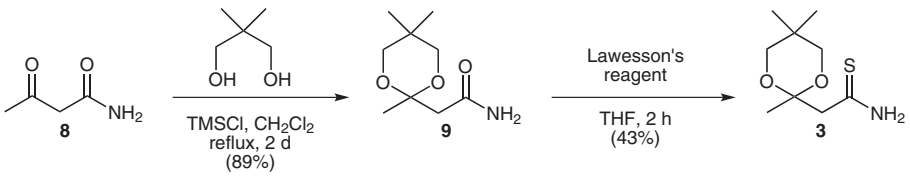


Scheme 2 Microfluidic synthesis of 5-(thiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-ones **4**. Yields for one-chip reactions determined using 5 min retention times and 1 equiv of water. [a] Refer to ref.[8] for complete details of this study.

Indoles constitute a ubiquitous structural motif present in a broad range of biologically active small molecules and natural products. These heterocycles are present in investigational and approved drugs such as Tadalafil, an inhibitor of phosphodiesterase 5 (PDE5) (Scheme 1).[10] Tadalafil is currently indicated for the treatment of both erectile dysfunction (Cialis®) and pulmonary arterial hypertension (Adcirca®). Indolylthiazole derivatives also constitute a large family of medicinally significant compounds displaying a wide range of pharmacological properties. For example, the camalexin class of natural products has received much attention in recent years because of its antifungal and antiviral activity (Scheme 1).[11] In addition, closely related thiazolyl indolequinones, such as the natural product BE 10988, have been identified as potent topoisomerase II inhibitors and have been shown to possess promising anticancer activity (Scheme 1).[12] Due to this broad spectrum of therapeutic areas, methods for the high-throughput synthesis of connected heterocyclic derivatives, such as the indolylthiazoles, are of significant interest.

Although continuous flow methods for the synthesis of simple indoles have been reported separately by Watts[13] and Seeberger,[14] the inspiration for our multistep flow assembly of indolylthiazoles **1** stems from our recently reported synthesis of 5-(thiazol-2-yl)-3,4-dihydropyrimidin-2(1*H*)-ones **4** (Scheme 2).[8] In this method, intermediate β-ketothiazoles **2** from ketal-protected thioamide **3** provided access to a novel class of connected heterocycles in high yield (39–46%) over three chemical steps. This automated process comprised Hantzsch thiazole synthesis of thioamide **3** with α-bromoketones **5** liberating molar equivalents of HBr and water, triggering removal of the 1,3-dioxane protecting group to generate intermediate β-ketothiazoles **2**. The released acid was then further utilized to catalyze the subsequent Biginelli multicomponent reaction with aldehydes **6** and urea **7**. Knowing that the Fischer indole synthesis is also promoted by acid, we hypothesized that replacement of the aldehyde and urea components with hydrazines would provide a viable route to the 2-(1*H*-indol-3-yl)thiazole core (**1**).

At the outset of our experiments, we prepared the ketal-protected thioamide **3** (Scheme 3) from commercially available acetoacetamide **8** in two steps. First, ketone **8** was heated at reflux in the presence of neopentyl glycol and chlorotrimethylsilane in anhydrous dichloromethane to furnish known ketal-protected amide **9** in excellent yield (89%).[15] Compound **9** was then carefully treated with just over one-half equivalent of Lawesson's reagent at 0 °C in anhydrous tetrahydrofuran (THF) to generate protected thioamide **3** in 43% yield. In our hands, the necessary ketone required a protecting group for acceptable thioamide production. This reaction process is amenable to scale-up procedures, with crystalline **3** easily isolated by precipitation from toluene. Furthermore, this key building block can be stored at room temperature without significant decomposition and is stable in the *N*,*N*-dimeth-



Scheme 3 Synthesis of thioamide **3**

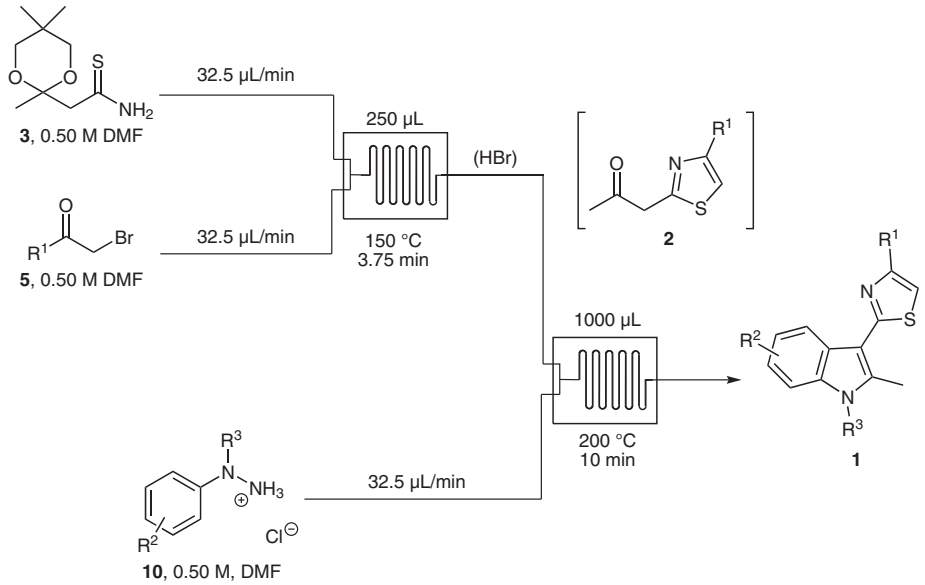
ylformamide (DMF) solutions used for all the microfluidic experiments described herein.

With freshly prepared thioamide **3** in hand, we next focused our efforts on using this building block for the microfluidic synthesis of indolylthiazoles **1** (Scheme 4). For this continuous multistep process, the setup was identical to that shown in Scheme 2 except that aldehydes **6** and urea **7** were exchanged for hydrazines **10**. As with the Biginelli process, we envisioned that the liberated HBr utilized to unmask the ketone intermediates could be harnessed to catalyze the subsequent Fischer indole synthesis. Gratifyingly, we found that the two-chip flow synthesis of indolylthiazoles **1** proceeded efficiently under the conditions shown in Scheme 4. Initially, 0.50 M solutions of thioamide **3** and α-bromoketones **5** in DMF were pumped (32.5 μL/min) into a 250 μL reactor heated to 150 °C for 3.75 minutes.

This reaction concentration was chosen as a compromise between general solubility and optimal yield for the sequence. The generated ketothiazole intermediate **2** was then introduced to a separate stream (32.5 μL/min) of hydrazine hydrochlorides **10** (0.50 M, DMF). The combined flow (97.5 μL/min) was pumped into a 1000 μL reactor heated to 200 °C. Overall, each continuous two-chip microfluidic sequence required less than one hour for completion from start to finish (injection, reaction, and 1000 μL collection).

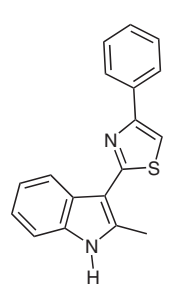
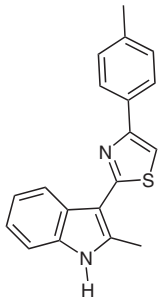
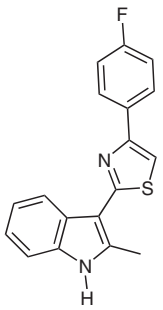
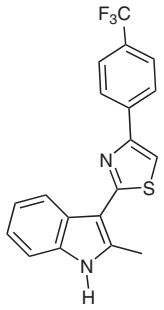
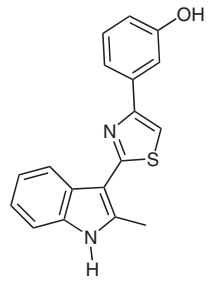
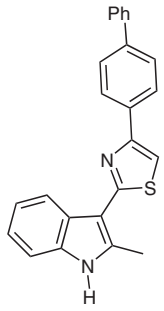
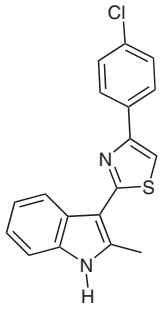
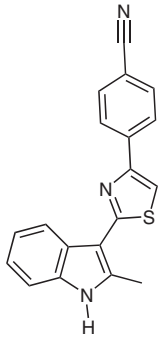
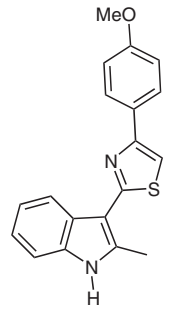
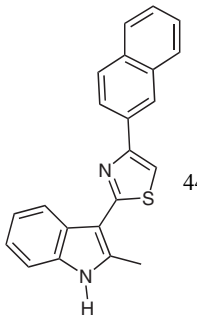
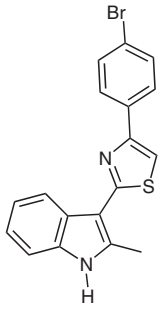
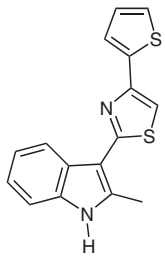
The multistep continuous flow synthesis of indolylthiazoles **1a**–**l** is presented in Table 1. For all entries, a DMF solution of phenylhydrazine hydrochloride (**10a**) was pumped into the second chip in order to study the reaction scope with respect to α-bromoketones **5**. The overall yields for the three-step, two-chip sequence were high (43–65%) when using aromatic α-bromoketones **5**, averaging at least 70% yield for each chemical transformation. Acetophenone substrates bearing either electron-donating (entries 2, 3 and 4), electron-withdrawing (entries 10 and 11), or halogen substitution (entries 7, 8 and 9) as well as 2-naphthyl (entry 6) and heteroaromatic (entry 12) were found to be suitable for this process. Importantly, these data largely represent the current supply of commercially available α-bromoketones yielding complex drug-like compounds for extensive biological evaluation and/or continued chemistry.

We next investigated the reaction scope with respect to hydrazines **10**; the multistep continuous flow synthesis of indolylthiazoles **1m**–**v** is presented in Table 2. For all entries, a DMF solution of 2-bromoacetophenone (**5a**) was pumped into the first microreactor chip. The overall yields for the three-step, two-chip sequence were also high (38–82%) when using free-base hydrazines or arylhydrazine hydrochlorides, again averaging at least 70% yield for each chemical transformation. Hydrazine substrates bearing either electron-donating (entries 1 and 6), alkyl (entries 7 and 8), or halogen substituents (entries 2, 3 and 4) were found to be suitable for this process. Whereas extended aromatic systems such as 1-naphthyl (entry 9) proceeded in excellent yield, hydrazine substrates bearing electron-withdrawing groups such as 4-cyano or 4-trifluoromethyl (not shown) failed to furnish sufficient quantities of the desired indolylthiazole product for isolation. Not surprisingly, this reaction sequence also proved futile with batch-mode standard heating using an oil bath and longer reaction times. Importantly, nitrogen-substituted hydrazines such as methyl and benzyl (entries 5 and 10) are also viable using this process. Since free-base hydrazines are known to be unstable, freshly opened bottles were used for these experiments. It should also be noted that hydrazines **10b** and **10c**, which were used to generate **1m** and **1n**, respectively, were not soluble in neat DMF and, therefore, stock solutions were prepared in 1:1 mixtures of DMF and ethylene glycol.



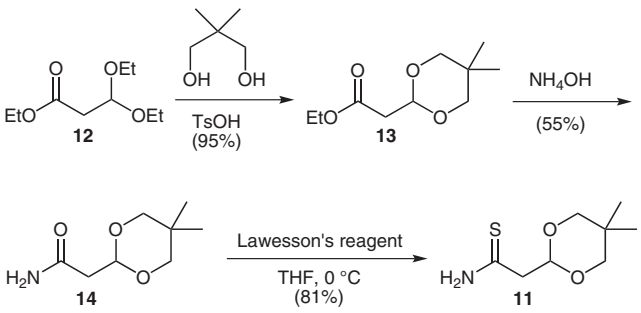
Scheme 4 Final microfluidic setup for the synthesis of indolylthiazoles **1**

Table 1 Synthesis of Indolylthiazoles **1a–l**; Scope of α-Bromoketones

Entry[a]	Product	Yield (%)	Entry[a]	Product	Yield (%)	Entry[a]	Product	Yield (%)	Entry[a]	Product	Yield (%)
1	 **1a**	50[b]	4	 **1d**	49	7	 **1g**	49	10	 **1j**	43
2	 **1b**	65	5	 **1e**	44	8	 **1h**	46	11	 **1k**	48
3	 **1c**	49	6	 **1f**	44	9	 **1i**	46	12	 **1l**	41

[a] Refer to Supporting Information for structures of α-bromoketones **5a–l**.
[b] Isolated yields based on 1000 μL collection volumes and following silica gel chromatography.

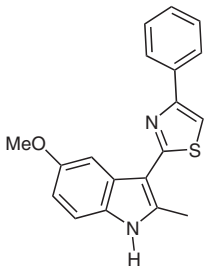
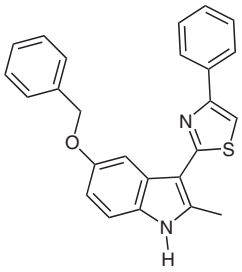
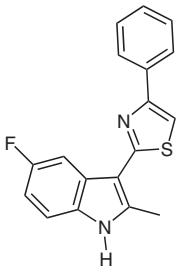
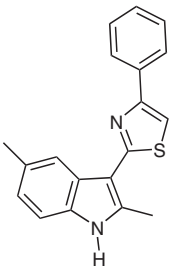
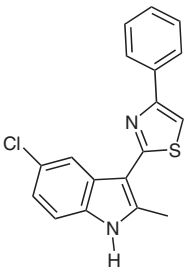
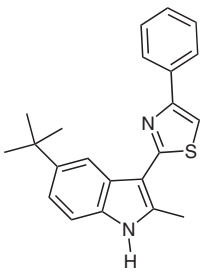
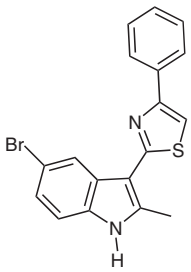
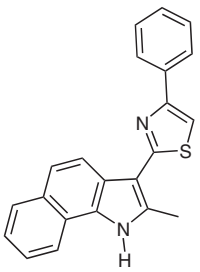
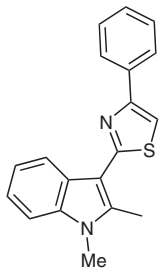
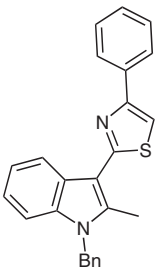
Each of the indolylthiazoles (**1a–v**) thus far described was a derivative of 2-methylindole as a direct result of using thioamide **3** in the experiments. To broaden the scope of the methodology and increase the structural diversity of the scaffold, we became interested in methods that could be used to rapidly prepare 2-(1*H*-indol-3-yl)thiazoles lacking a 2-methyl group. In addition to enhancing the utility of our methodology, functionalization of the 2-position of an indole heterocycle is well-established[16] and would provide access to highly complex and valuable intermediates for continued chemistry. Thus, we envisioned that a dioxane-protected thioamide precursor such as **11** might accomplish this goal (Scheme 5).



Scheme 5 Batch synthesis of acetyl-protected thioamide **11**

Beginning from commercially available ethyl ester **12**, reaction with neopentyl glycol in the presence of a catalytic amount of acid (TsOH) provided acetal **13** in near quantitative yield (95%).[17] Treatment with aqueous ammonium hydroxide (28–30% ammonia) under ambient conditions then afforded amide **14** in 55% yield. Lastly, reaction with

Table 2 Synthesis of Indolylthiazoles **1m–v**; Scope of Hydrazines

Entry[a]	Product	Yield (%)	Entry[a]	Product	Yield (%)
1	 **1m**	51[b]	6	 **1r**	38
2	 **1n**	47	7	 **1s**	57
3	 **1o**	54	8	 **1t**	53
4	 **1p**	44	9	 **1u**	82
5	 **1q**	63[c]	10	 **1v**	44[c]

[a] Refer to Supporting Information for structures of hydrazines **10a–k**.
[b] Isolated yields based on 1000 μL collection volumes and following silica gel chromatography.
[c] Freshly opened free-base hydrazines were used.

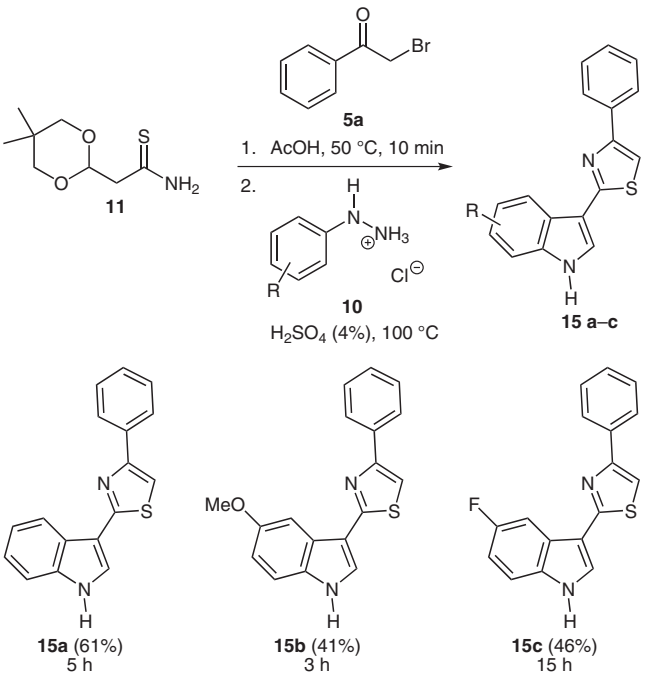
Lawesson's reagent furnished the target dioxane-protected thioamide **11** in high yield (81%) following column chromatography. Taken together, thioamide **11** was accessed in three steps in an overall yield of 42% with only one purification step necessary. Similar to thioamide **3**, **11** can be stored at room temperature without significant decomposition and is stable in both organic and aqueous solutions used for all the experiments described herein.

With building block **11** in hand, we turned our attention to the flow synthesis of 2-*H*-indolylthiazoles. To start, we simply exchanged thioamide **3** with **11** and used the same setup and reaction conditions shown in Scheme 4. Unfortunately, the liberated equivalents of HBr and water following thiazole formation proved insufficient to release the masked aldehyde necessary for the Fischer indole synthesis.

Higher microreactor temperatures, longer reaction times, acid additives, and increased water equivalents all failed to remove the 1,3-dioxane protection group. Thus, it became clear to us that a completely aqueous reaction environment would be necessary for deprotection. While this would likely preclude development of a continuous flow method using the AFRICA synthesis station due to decreased solubility, a one-pot procedure in batch mode remained an attractive option. In 1989, Speckamp and coworkers developed a one-pot deacetalation/Fischer indole reaction in their total synthesis of the *Aristotelia* alkaloid peduncularine.[18] For this, they heated 4% aqueous sulfuric acid at reflux for 16 hours in the presence of phenylhydrazine hydrochloride.

The one-pot batch synthesis of 2-*H*-indolylthiazoles **15** from acetyl-protected thioamide **11** is outlined in Scheme 6. For all experiments, 2-bromoacetophenone (**5a**) was first heated together with thioamide **11** for 10 minutes in water-soluble acetic acid. A solution of hydrazine **10** in sulfuric acid (4% aq) was then added and the progress of the reaction at reflux was monitored. Gratifyingly, hydrazines **10** bearing electron-donating, unsubstituted, or electron-withdrawing halogen substitution were all found to be suitable for this process (requiring 5, 3, and 15 h for completion, respectively). As expected, precipitates readily formed in the AFRICA chip during the course of all reactions, making such transformations impractical within our microfluidic chips.

In conclusion, we have engineered consecutive heterocycle formation reactions using an automated continuous flow process that allows efficient access to a novel class of indolylthiazoles **1**. These complex heterocyclic scaffolds are constructed rapidly and in high yield, allowing the facile synthesis of libraries of biologically active analogues. We have also developed an efficient one-pot (batch) procedure for the synthesis of related 2-*H*-indolylthiazoles. Further applications of both the continuous flow and batch methods to the generation of analogues with optimal biological activity are in progress.



Scheme 6 One-pot batch synthesis of 2-*H*-indolylthiazoles **15**

All reactions were carried out using oven-dried glassware and conducted under a positive pressure of nitrogen unless otherwise specified. NMR spectra were recorded with a 400 MHz spectrometer. All NMR samples were prepared using DMSO-d_6. High-resolution mass spectrometry data were obtained with a time of flight mass spectrometer (MS-TOF) using electrospray ionization at the Sanford-Burnham Medical Research Institute (SBMRI). LC/MS analyses were carried out using a 5 micron C18 column (50 × 2.1 mmID). Silica gel purifications were accomplished using prepacked columns. All reagents and solvents were used as received from standard suppliers. Microfluidic experiments were conducted using a Syrris AFRICA® synthesis station.

Synthesis of Indolylthiazoles (1a–l); General Procedure

All reactions were conducted in DMF under a positive pressure of nitrogen. Streams of the thioamide **3** (32.5 μL/min, 0.50 M in DMF, 1 equiv) and a solution of α-bromoketone **5** (32.5 μL/min, 0.50 M in DMF, 1 equiv) were mixed in a 250 μL glass reactor heated to 150 °C (3.75 min). After exiting the chip, the combined flow (65.0 μL/min) was introduced to a single stream (32.5 μL/min, 0.50 M in DMF, 1 equiv) of phenylhydrazine hydrochloride (**10a**) in a 1000 μL glass reactor heated to 200 °C (10 min). The reaction flow was then collected (1000 μL) after passing though a back-pressure regulator. These reactions were carried out with a back-pressure of 6.0 bar. The crude reaction mixtures were then adsorbed onto silica gel, loaded onto a pre-packed silica gel column (12 g), and purified by chromatography (hexanes–EtOAc; 30 mL/min, 100% hexanes for 2 min then ramped to 40% EtOAc in hexanes over 18 min).

2-(2-Methyl-1*H*-indol-3-yl)-4-phenylthiazole (1a)

Yield: 0.024 g (50%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.68 (s, 1 H), 8.24 (dd, *J* = 6.4, 1.8 Hz, 1 H), 8.08 (dd, *J* = 8.5, 1.1 Hz, 1 H), 7.98 (s, 1 H), 7.48 (m, 2 H), 7.41–7.33 (m, 2 H), 7.17 (m, 2 H), 2.78 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.6, 153.5, 137.6, 135.0, 134.5, 128.8, 127.9, 126.0, 125.8, 121.6, 120.5, 119.5, 111.2, 110.2, 107.0, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}N_2S$: 291.0950; found: 291.0965.

3-[2-(2-Methyl-1*H*-indol-3-yl)thiazol-4-yl]phenol (1b)
Yield: 0.033 g (65%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.67 (s, 1 H), 9.52 (s, 1 H), 8.24 (dd, *J* = 6.4, 2.8 Hz, 1 H), 7.89 (s, 1 H), 7.52 (m, 1 H), 7.48 (m, 1 H), 7.40 (m, 1 H), 7.25 (t, *J* = 7.8 Hz, 1 H), 7.17 (m, 2 H), 6.75 (ddd, *J* = 7.8, 2.3, 0.9 Hz, 1 H), 2.77 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.4, 157.7, 153.6, 137.5, 135.7, 135.0, 129.7, 125.8, 121.6, 120.5, 119.6, 116.8, 114.9, 113.0, 111.1, 110.1, 107.0, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}N_2OS$: 307.0900; found: 307.0931.

4-(4-Methoxyphenyl)-2-(2-methyl-1*H*-indol-3-yl)thiazole (1c)
Yield: 0.026 g (49%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.66 (s, 1 H), 8.23 (dd, *J* = 6.0, 2.3 Hz, 1 H), 8.00 (m, 2 H), 7.81 (s, 1 H), 7.40 (m, 1 H), 7.17 (m, 2 H), 7.04 (m, 2 H), 3.80 (s, 3 H), 2.78 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.4, 159.0, 153.4, 137.4, 135.0, 127.4, 125.8, 121.6, 120.5, 119.5, 114.1, 111.1, 108.2, 107.0, 55.1, 14.0, one hidden carbon.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2OS$: 321.1056; found: 321.1081.

2-(2-Methyl-1*H*-indol-3-yl)-4-(*p*-tolyl)thiazole (1d)
Yield: 0.025 g (49%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.67 (s, 1 H), 8.23 (dd, *J* = 6.4, 1.8 Hz, 1 H), 7.97 (m, 2 H), 7.92 (s, 1 H), 7.40 (m, 1 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 7.18 (m, 2 H), 2.78 (s, 3 H), 2.35 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.5, 153.6, 137.5, 137.1, 135.0, 131.8, 129.3, 126.0, 125.8, 121.6, 120.5, 119.5, 111.1, 109.3, 107.0, 20.9, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2S$: 305.1107; found: 305.1113.

4-[(1,1′-Biphenyl)-4-yl]-2-(2-methyl-1*H*-indol-3-yl)thiazole (1e)
Yield: 0.027 g (44%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.68 (s, 1 H), 8.24 (dd, *J* = 6.4, 1.8 Hz, 1 H), 8.15 (m, 2 H), 8.03 (s, 1 H), 7.77 (m, 2 H), 7.71 (m, 2 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.16 (m, 2 H), 7.39–7.33 (m, 2 H), 2.77 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.7, 153.1, 139.7, 139.4, 137.7, 135.0, 133.6, 129.0, 127.5, 127.0, 126.6, 126.6, 125.8, 121.7, 120.6, 119.5, 111.2, 110.4, 107.0, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{19}N_2S$: 367.1263; found: 367.1265.

2-(2-Methyl-1*H*-indol-3-yl)-4-(naphthalen-2-yl)thiazole (1f)
Yield: 0.025 g (44%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.71 (s, 1 H), 8.62 (s, 1 H), 8.29 (d, *J* = 7.3 Hz, 1 H), 8.22 (dd, *J* = 8.7, 1.8 Hz, 1 H), 8.14 (s, 1 H), 8.03–8.00 (m, 2 H), 7.93 (d, *J* = 7.3 Hz, 1 H), 7.53 (m, 2 H), 7.41 (d, *J* = 7.3, 1 H), 7.20 (m, 2 H), 2.82 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.8, 153.5, 137.7, 135.0, 133.2, 132.6, 132.0, 128.3, 128.2, 127.6, 126.4, 126.1, 125.8, 124.6, 124.4, 121.6, 120.6, 119.6, 111.2, 110.9, 107.0, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}N_2S$: 341.1107; found: 341.1103.

4-(4-Fluorophenyl)-2-(2-methyl-1*H*-indol-3-yl)thiazole (1g)
Yield: 0.025 g (49%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.70 (s, 1 H), 8.23 (dd, *J* = 6.0, 2.3 Hz, 1 H), 8.13 (m, 2 H), 7.98 (s, 1 H), 7.41 (m, 1 H), 7.32 (m, 2 H), 7.18 (m, 2 H), 2.78 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.8, 161.8 (d, $J_{C–F}$ = 245.4 Hz), 152.4, 137.7, 135.0, 131.1, 128.0 (d, $J_{C–F}$ = 8.6 Hz), 125.7, 121.6, 120.5, 119.5, 115.6 (d, $J_{C–F}$ = 21.1 Hz), 111.2, 110.0, 106.9, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}FN_2S$: 309.0856; found: 309.0866.

4-(4-Chlorophenyl)-2-(2-methyl-1*H*-indol-3-yl)thiazole (1h)
Yield: 0.025 g (46%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.70 (s, 1 H), 8.22 (dd, *J* = 6.0, 2.3 Hz, 1 H), 8.10 (m, 2 H), 8.06 (s, 1 H), 7.54 (m, 2 H), 7.40 (m, 1 H), 7.17 (m, 2 H), 2.77 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.9, 152.2, 137.8, 135.0, 133.3, 132.3, 128.8, 127.7, 125.7, 121.7, 120.6, 119.5, 111.2, 111.0, 106.8, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}ClN_2S$: 325.0561; found: 325.0568.

4-(4-Bromophenyl)-2-(2-methyl-1*H*-indol-3-yl)thiazole (1i)
Yield: 0.028 g (46%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.71 (s, 1 H), 8.23 (dd, *J* = 6.4, 2.8 Hz, 1 H), 8.07 (s, 1 H), 8.04 (m, 2 H), 7.68 (m, 2 H), 7.41 (m, 1 H), 7.18 (m, 2 H), 2.78 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.9, 152.3, 137.8, 135.0, 133.7, 131.7, 128.0, 125.7, 121.7, 120.9, 120.6, 119.5, 111.2, 111.0, 106.8, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}BrN_2S$: 371.0036; found: 371.0045.

2-(2-Methyl-1*H*-indol-3-yl)-4-[4-(trifluoromethyl)phenyl]thiazole (1j)
Yield: 0.026 g (43%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.73 (s, 1 H), 8.31–8.23 (m, 4 H), 7.85 (d, *J* = 8.2 Hz, 2 H), 7.41 (m, 1 H), 7.19 (m, 2 H), 2.79 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.2, 151.9, 138.2, 137.9, 135.0, 126.6, 125.8, 125.8, 125.7, 121.7, 120.6, 119.5, 112.9, 111.2, 106.8, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}F_3N_2S$: 359.0824; found: 359.0840.

4-[2-(2-Methyl-1*H*-indol-3-yl)thiazol-4-yl]benzonitrile (1k)
Yield: 0.025 g (48%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.74 (s, 1 H), 8.28–8.21 (m, 4 H), 7.94 (m, 2 H), 7.40 (m, 1 H), 7.18 (m, 1 H), 2.77 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.2, 151.7, 138.5, 138.1, 135.0, 132.9, 126.6, 125.7, 121.7, 120.7, 119.5, 113.7, 111.2, 110.0, 106.7, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}N_3S$: 316.0903; found: 316.0907.

2-(2-Methyl-1*H*-indol-3-yl)-4-(thiophen-2-yl)thiazole (1l)
Yield: 0.020 g (41%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.71 (s, 1 H), 8.22 (s, 1 H), 7.82 (s, 1 H), 7.63 (dd, *J* = 3.4, 1.1 Hz, 1 H), 7.53 (dd, *J* = 5.0, 0.9 Hz, 1 H), 7.40 (m, 1 H), 7.19–7.13 (m, 3 H), 2.75 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.7, 148.2, 138.6, 137.8, 135.0, 128.0, 125.7, 123.8, 121.7, 120.6, 119.5, 111.2, 108.4, 106.6, 13.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_2S_2$: 297.0515; found: 297.0516.

Synthesis of Indolylthiazoles 1m–v; General Procedure

All reactions were conducted in DMF under a positive pressure of nitrogen. Streams of thioamide **3** (32.5 μL/min, 0.50 M in DMF, 1 equiv) and a solution of 2-bromoacetophenone (**5a**; 32.5 μL/min, 0.50 M in DMF, 1 equiv) were mixed in a 250 μL glass reactor heated to 150 °C (3.75 min). After exiting the chip, the combined flow (65.0 μL/min) was introduced to a single stream (32.5 μL/min, 0.50 M in DMF, 1 equiv) of hydrazines (**10d**–**k**) in a 1000 μL glass reactor heated to 200 °C (10 min). Streams of hydrazines **10b** and **10c** (0.50 M) were prepared using 1:1 DMF/ethylene glycol. The reaction flow was then collected (1000 μL) after passing though a back-pressure regulator. These reactions were carried out with a back pressure of 6.0 bar. The crude reaction mixtures were then adsorbed onto silica gel, loaded onto a pre-packed silica gel column (12 g), and purified by chromatography (hexanes–EtOAc; 30 mL/min, 100% hexanes for 2 min then ramped to 40% EtOAc in hexanes over 18 min).

2-(5-Methoxy-2-methyl-1*H*-indol-3-yl)-4-phenylthiazole (1m)

Yield: 0.027 g (51%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.55 (s, 1 H), 8.08 (d, J = 7.8 Hz, 2 H), 7.96 (s, 1 H), 7.81 (d, J = 2.8 Hz, 1 H), 7.48 (t, J = 7.8 Hz, 2 H), 7.35 (m, 1 H), 7.30 (d, J = 8.7 Hz, 1 H), 6.82 (dd, J = 8.7, 2.3 Hz, 1 H), 3.84 (s, 3 H), 2.74 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.7, 154.5, 153.4, 138.0, 134.5, 129.9, 128.8, 127.8, 126.4, 126.0, 111.8, 110.8, 109.9, 107.0, 102.3, 55.2, 14.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{17}N_2OS$: 321.1056; found: 321.1060.

2-(5-Fluoro-2-methyl-1*H*-indol-3-yl)-4-phenylthiazole (1n)

Yield: 0.024 g (47%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.81 (s, 1 H), 8.07 (m, 2 H), 8.00 (s, 1 H), 7.99 (dd, J = 10.0, 2.8 Hz, 1 H), 7.49 (m, 2 H), 7.40 (dd, J = 8.7, 4.6 Hz, 1 H), 7.36 (m, 1 H), 7.02 (m, 1 H), 2.75 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.2, 157.9 (d, $J_{C–F}$ = 232.9 Hz), 153.5, 139.5, 134.4, 131.6, 128.8, 127.9, 126.2 (d, $J_{C–F}$ = 10.5 Hz), 126.0, 112.2 (d, $J_{C–F}$ = 9.6 Hz), 110.4, 109.5 (d, $J_{C–F}$ = 25.9 Hz), 107.4, 104.7 (d, $J_{C–F}$ = 24.9 Hz), 14.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{14}FN_2S$: 309.0856; found: 309.0863.

2-(5-Chloro-2-methyl-1*H*-indol-3-yl)-4-phenylthiazole (1o)

Yield: 0.029 g (54%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.90 (s, 1 H), 8.27 (d, J = 1.8 Hz, 1 H), 8.06 (m, 2 H), 8.02 (s, 1 H), 7.49 (m, 2 H), 7.42 (d, J = 8.2 Hz, 1 H), 7.36 (m, 1 H), 7.18 (dd, J = 8.5, 2.1 Hz, 1 H), 2.76 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.0, 153.6, 139.3, 134.4, 133.5, 128.8, 128.0, 126.9, 126.0, 125.1, 121.6, 118.9, 112.7, 110.6, 106.9, 14.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{14}ClN_2S$: 325.0566; found: 325.0564.

2-(5-Bromo-2-methyl-1*H*-indol-3-yl)-4-phenylthiazole (1p)

Yield: 0.027 g (44%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.92 (s, 1 H), 8.42 (d, J = 1.1 Hz, 1 H), 8.06 (dd, J = 8.2, 1.4 Hz, 2 H), 8.03 (s, 1 H), 7.50 (t, J = 7.8 Hz, 2 H), 7.40–7.35 (m, 2 H), 7.30 (dd, J = 8.7, 1.8 Hz, 1 H), 2.76 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.0, 153.6, 139.1, 134.4, 133.7, 128.8, 128.0, 127.5, 126.0, 124.1, 121.9, 113.2, 113.1, 110.7, 106.7, 14.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{14}BrN_2S$: 371.0036; found: 371.0064.

2-(1,2-Dimethyl-1*H*-indol-3-yl)-4-phenylthiazole (1q)

Yield: 0.032 g (63%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.21 (m, 1 H), 8.07 (m, 2 H), 8.01 (s, 1 H), 7.55 (m, 1 H), 7.48 (m, 2 H), 7.35 (m, 1 H), 7.23 (m, 2 H), 3.78 (s, 3 H), 2.86 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.5, 153.5, 138.7, 136.4, 134.4, 128.8, 127.9, 126.0, 124.9, 121.7, 120.8, 119.2, 110.5, 110.0, 106.8, 29.7, 12.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{17}N_2S$: 305.1107; found: 305.1121.

2-[5-(Benzyloxy)-2-methyl-1*H*-indol-3-yl]-4-phenylthiazole (1r)

Yield: 0.024 g (38%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.23 (dd, J = 6.9, 1.4 Hz, 1 H), 8.05 (m, 2 H), 8.03 (s, 1 H), 7.52 (m, 1 H), 7.45 (m, 2 H), 7.34–7.18 (m, 6 H), 7.03 (m, 2 H), 5.55 (s, 2 H), 2.79 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.2, 153.6, 138.3, 137.5, 136.3, 134.4, 128.8, 128.8, 128.0, 127.3, 126.2, 126.1, 125.1, 122.1, 121.1, 119.5, 110.9, 110.4, 107.6, 39.9, 12.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{25}H_{21}N_2OS$: 397.1369; found: 397.1388.

2-(2,5-Dimethyl-1*H*-indol-3-yl)-4-phenylthiazole (1s)

Yield: 0.029 g (57%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.60 (s, 1 H), 8.11 (m, 2 H), 8.02 (s, 1 H), 8.00 (s, 1 H), 7.52 (m, 2 H), 7.39 (m, 1 H), 7.32 (d, J = 8.2 Hz, 1 H), 7.03 (dd, J = 8.5, 2.1 Hz, 1 H), 2.81 (s, 3 H), 2.49 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.8, 153.5, 137.7, 134.5, 133.3, 129.1, 128.8, 127.9, 126.0, 126.0, 123.0, 119.1, 110.9, 110.1, 106.5, 21.6, 14.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{17}N_2S$: 305.1107; found: 305.1121.

2-[5-(*tert*-Butyl)-2-methyl-1*H*-indol-3-yl]-4-phenylthiazole (1t)

Yield: 0.031 g (53%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.51 (s, 1 H), 8.30 (d, J = 1.4 Hz, 1 H), 8.06 (m, 2 H), 7.94 (s, 1 H), 7.44 (m, 2 H), 7.33 (m, 1 H), 7.29 (d, J = 8.7 Hz, 1 H), 7.28 (s, 1 H), 7.22 (dd, J = 8.7, 1.8 Hz, 1 H), 2.73 (s, 3 H), 1.36 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.7, 153.3, 142.8, 137.5, 134.6, 133.1, 128.8, 127.9, 126.0, 125.6, 119.7, 115.4, 110.6, 110.0, 107.1, 34.4, 31.8, 14.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{23}N_2S$: 347.1576; found: 347.1583.

2-(2-Methyl-1*H*-benzo[*g*]indol-3-yl)-4-phenylthiazole (1u)

Yield: 0.047 mg (82%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.40 (s, 1 H), 8.40 (d, J = 8.7 Hz, 1 H), 8.35 (d, J = 8.2 Hz, 1 H), 8.08 (d, J = 6.9 Hz, 1 H), 8.06 (m, 2 H), 8.01 (s, 1 H), 7.93 (d, J = 8.2 Hz, 1 H), 7.63 (d, J = 8.7 Hz, 1 H), 7.55 (t, J = 7.3 Hz, 1 H), 7.47 (t, J = 7.8 Hz, 2 H), 7.41 (t, J = 7.3 Hz, 1 H), 7.34 (t, J = 7.3 Hz, 1 H), 2.84 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.6, 153.7, 135.3, 134.5, 129.7, 129.4, 128.8, 128.4, 127.9, 126.1, 125.7, 123.9, 121.7, 121.3, 121.1, 120.6, 119.9, 110.7, 108.9, 14.0.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{17}N_2S$: 341.1107; found: 341.1109.

2-(1-Benzyl-2-methyl-1*H*-indol-3-yl)-4-phenylthiazole (1v)

Yield: 0.028 mg (44%); yellow-brown amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.26 (dd, J = 8.2, 1.4 Hz, 1 H), 8.07 (m, 2 H), 8.04 (s, 1 H), 7.55 (dd, J = 7.1, 1.1 Hz, 1 H), 7.47 (m, 2 H), 7.37–7.20 (m, 9 H), 7.05 (m, 2 H), 5.57 (s, 2 H), 2.82 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.3, 153.6, 138.3, 137.5, 136.2, 134.4, 128.8, 128.7, 127.9, 127.3, 126.2, 126.0, 125.1, 122.1, 121.1, 119.5, 110.8, 110.4, 107.6, 39.9, 12.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{21}N_2S$: 381.1420; found: 381.1439.

2-(5,5-Dimethyl-1,3-dioxan-2-yl)acetamide (14)
A solution of solution **13** (4.6 g, 22.8 mmol, 1 equiv) in aqueous ammonium hydroxide (28–30% ammonia, 50 mL) was sealed and stirred vigorously at r.t. overnight. The resulting pale-yellow reaction mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were then washed with brine (100 mL), dried using Na_2SO_4, and concentrated to dryness in vacuo to provide amide **14**.

Yield: 2.16 g (55%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.39 (s, 1 H), 6.08 (s, 1 H), 4.73 (t, *J* = 4.6 Hz, 1 H), 3.60 (d, *J* = 11.5 Hz, 2 H), 3.44 (d, *J* = 11.0 Hz, 2 H), 2.56 (d, *J* = 4.6 Hz, 2 H), 1.15 (s, 3 H), 0.70 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.4, 98.7, 41.8, 30.0, 22.9, 21.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{15}NNaO_3$: 196.0944; found: 196.0945.

2-(5,5-Dimethyl-1,3-dioxan-2-yl)ethanethioamide (11)
A solution of amide **14** (1.0 g, 5.78 mmol, 1 equiv) in anhydrous THF (30 mL) was prepared and cooled to 0 °C. Lawesson's reagent (1.3 g, 3.18 mmol, 0.55 equiv) was then added and the resulting yellow suspension was allowed to warm to r.t., stirring for a total of 2 h. The resulting light-yellow solution was concentrated in vacuo and re-dissolved in EtOAc (100 mL). The organic phase was washed with sat. aq $NaHCO_3$ (100 mL) followed by brine (100 mL), dried using Na_2SO_4, and concentrated to dryness in vacuo. The crude material was adsorbed onto silica gel, loaded onto a pre-packed silica gel column (80 g), and purified by chromatography (hexanes–EtOAc; 60 mL/min, 0% EtOAc to 30% EtOAc over 45 min). Following concentration of product eluents, **11** was isolated.

Yield: 0.88 g (81%); off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.96 (s, 1 H), 7.71 (s, 1 H), 4.75 (m, 1 H), 3.64 (d, *J* = 11.0 Hz, 2 H), 3.47 (d, *J* = 11.0 Hz, 2 H), 3.09 (m, 2 H), 1.18 (s, 3 H), 0.73 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 203.9, 99.4, 49.7, 29.9, 22.8, 21.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{16}NO_2S$: 190.0896; found: 190.0906.

Synthesis of Indolylthiazoles 15a–c; General Procedure
An aqueous solution of 4% sulfuric acid (2.5 mL) was heated to 50 °C following a thorough purge with nitrogen gas. Hydrazines **10** (0.294 mmol, 1.1 equiv) were then added to the reaction mixture and dissolved by heating for an additional 10 min. At the same time, a mixture of thioamide **11** (50 mg, 0.267 mmol, 1 equiv) and 2-bromoacetophenone (**5a**; 54 mg, 0.267 mmol, 1 equiv) in acetic acid (0.65 mL) was purged with nitrogen and then heated to 50 °C for 10 min. Lastly, the separate reaction mixtures were combined and monitored at reflux (105 °C). Each resulting suspension was extracted with EtOAc (2 × 50 mL), adsorbed onto silica gel, loaded onto a pre-packed silica gel column (12 g), and purified by chromatography (hexanes–EtOAc; 30 mL/min, 100% hexanes for 2 min then ramped to 40% EtOAc in hexanes over 18 min).

2-(1*H*-Indol-3-yl)-4-phenylthiazole (15a)
Yield: 0.045 g (61%); light yellow amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.76 (s, 1 H), 8.33 (m, 1 H), 8.14 (d, *J* = 2.8 Hz, 1 H), 8.08 (d, *J* = 7.3 Hz, 2 H), 7.91 (s, 1 H), 7.51–7.46 (m, 3 H), 7.35 (t, *J* = 7.3 Hz, 1 H), 7.23 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.9, 153.9, 136.6, 134.4, 128.8, 127.9, 126.7, 126.0, 124.3, 122.4, 120.8, 120.4, 112.2, 110.6, 110.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}N_2S$: 277.0794; found: 277.0791.

2-(5-Methoxy-1*H*-indol-3-yl)-4-phenylthiazole (15b)
Yield: 0.034 g (41%); light yellow amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.62 (s, 1 H), 8.07 (m, 3 H), 7.91 (s, 1 H), 7.84 (d, *J* = 2.8 Hz, 1 H), 7.48 (t, *J* = 7.3 Hz, 2 H), 7.40–7.33 (m, 2 H), 6.88 (dd, *J* = 8.7, 2.3 Hz, 1 H), 3.85 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.0, 154.6, 153.8, 134.4, 131.6, 128.8, 127.8, 127.1, 125.9, 124.9, 112.9, 112.2, 110.3, 110.2, 102.4, 55.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}N_2OS$: 307.0900; found: 307.0902.

2-(5-Fluoro-1*H*-indol-3-yl)-4-phenylthiazole (15c)
Yield: 0.036 g (46%); light yellow amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.87 (s, 1 H), 8.21 (d, *J* = 1.8 Hz, 1 H), 8.06 (m, 2 H), 8.03 (dd, *J* = 10.1, 2.8 Hz, 1 H), 7.92 (s, 1 H), 7.51–7.46 (m, 3 H), 7.35 (t, *J* = 7.3 Hz, 1 H), 7.09 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.6, 158.0 (d, $J_{C–F}$ = 232.9 Hz), 154.0, 134.3, 133.2, 128.8, 128.6, 127.9, 126.0, 124.6 (d, $J_{C–F}$ = 10.5 Hz), 113.4 (d, $J_{C–F}$ = 10.5 Hz), 110.7, 110.7 (d, $J_{C–F}$ = 26.8 Hz), 110.6, 105.2 (d, $J_{C–F}$ = 24.0 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{12}FN_2S$: 295.0700; found: 295.0696.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are NMR spectra for final compounds and the structures of α-bromoketones **5a–l** and hydrazines **10a–k**.

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