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ARTICLE

Continuous Flow Synthesis of the URAT1 Inhibitor Lesinurad

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Herein, the urate anion exchange transporter 1 (URAT1) inhibitor lesinurad is synthesized from commercially available building blocks by a five-step linear continuous flow sequence. Our previously developed continuous flow platform was successfully applied to generate the 3-thio-1,2,4-triazole key intermediate 2 in 88% yield, after 55 minutes of residence time. Condensation, cyclization and S-alkylation were telescoped in a single operation without conducting solvent exchanges and intermediate purifications. Next, 1,2,4-triazole bromination and ester hydrolysis were also performed in continuous flow regime to deliver lesinurad in 68% overall yield in a total residence time of 2 hours. Our approach enables the fast generation of lesinurad and can be directly applied to produce major quantities of this important API.

Introduction

Application of continuous flow chemistry[1] for the synthesis of compound libraries,[2–4] active pharmaceutical ingredients (APIs),[5–8] and natural products[9,10] has been strongly motivated by its key advantages relative to batch methodologies.[11–14] The use of small diameter tubes enables higher mass and heat transfer, and greater control of reaction selectivity. In addition, continuous flow processing allows simple scale-up of reactions, enhanced mixing, temperature and pressure control, decrease of waste generation, and integration of several reaction steps.[15–20] Regarding multistep approaches, a significant decrease of solvent-related waste production can be achieved when several steps are combined in one single process. Although solvents rarely enter into reaction chemistry,[21] they are commonly used during purification procedures, and to wash batch reactors, representing 80% of the total waste produced by the pharmaceutical industry, as reported by GlaxoSmithKline (GSK).[22,23] Indeed, the E-factor of the pharmaceutical industry is highly affected by solvent use, and typically, 25-100 kg of waste is generated for every kilogram of API synthesized.

While the majority of the reported continuous flow syntheses have focused on single-step reactions, several elegant examples have demonstrated multistep reaction sequences.[24–29] Recently, Russel and Jamison reported a seven-step telescoped sequence to synthesize the blockbuster antibacterial drug linezolid in only 23 minutes and 73% isolated yield.[28] This example beautifully illustrates how continuous flow technology can drastically increase synthesis efficiency by minimizing avoidable work-up procedures and waste generation. In 2010, the Ley group developed a flow synthesis for the tyrosine kinase inhibitor imatinib (Gleevec™, Novartis) featuring amidation, nucleophilic substitution and Buchwald-Hartwig coupling as key reaction steps.[29] A highlight of this approach was the application of scavenger columns for intermediate purification and use of in-line UV-monitoring to control different reagent streams. An alternative flow synthesis was recently published by Fu and Jamison, where imatinib is generated via sequential nitrile hydration, chemoselective amidation and C–N cross-coupling reactions.[30] This system does not require in-line purifications or packed-bed apparatuses to remove undesired reagents/byproducts, delivering the target compound in 48 minutes of residence time and 58% overall yield.

Our group is interested in the development of new methodologies that enable the rapid and efficient synthesis of important heterocycles, and generation of compound libraries for biological activity screening in drug discovery programs. We previously reported the application of a fully integrated continuous flow platform to rapidly deliver highly substituted 3-thio-1,2,4-triazoles in excellent yields and short residence times (**Scheme 1**).[31] The platform was developed based on the condensation of hydrazides and isothiocyanates to afford an in situ stream of a thiosemicarbazide, which is subsequently cyclized under basic conditions and alkylated with benzyl/alkyl halides to produce a library of 3-thio-1,2,4-triazoles.

Mercapto- and thio-substituted 1,2,4-triazole ring systems have been incorporated into a diversity of drug candidates, including the urate anion exchange transporter 1 (URAT1) inhibitor lesinurad 1 (Zurampic™, AstraZeneca). This API was approved in 2015 by the American Food and Drug Administration (FDA) for treating high blood uric acid levels associated with gout.[32] Gout is a crystal correlation arthropathy resulting from crystallization and deposition of monosodium urate, and it is related to the purine metabolic disorder and reduction of uric acid excretion.[33]

Several synthetic processes have been described to obtain lesinurad **1** in batch,[34–40] however there is still a need for new and improved processes characterized by easier purification of

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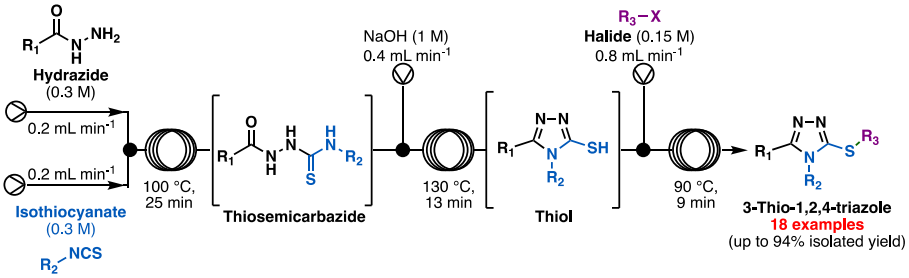


Scheme 1. Telescoped continuous flow synthesis of a library of 3-thio-1,2,4-triazoles.

intermediates, cost and time-effective syntheses, reduced handling of toxic and hazardous reagents, and higher overall yield. In 2017, Meng and co-workers published an interesting approach in four linear steps to afford lesinurad **1** in 48% overall yield in *ca.* 28 hours of total reaction time.[35]

Taking advantage of the benefits of continuous flow regime, we aimed to develop an alternative synthesis with increased efficiency, in order to produce lesinurad **1** by applying our existing integrated continuous flow platform. Our synthetic plan is outlined in **Scheme 2**.

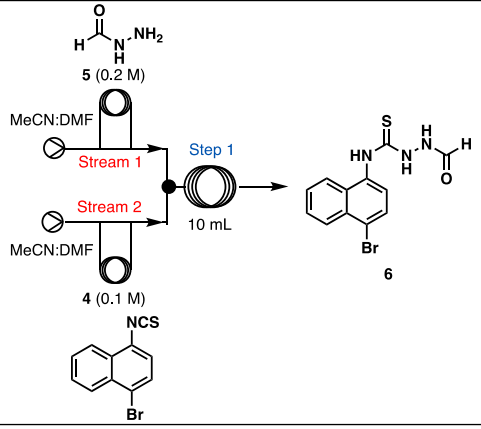
We envisioned that lesinurad **1** could be prepared from intermediate **2** after bromination and basic hydrolysis. Cyclopropyl insertion would be performed *via* a Suzuki cross-coupling to obtain compound **2**, and finally, 3-thio-1,2,4-triazole **3** could be synthesized by a condensation reaction between isothiocyanate **4** and formic hydrazide **5**, followed by cyclization and *S*-alkylation. Bearing this in mind, we report herein our efforts toward the development of a new continuous flow process to rapidly generate lesinurad **1** from readily available starting materials.

Results and Discussion

Initially, we briefly explored each step using batch conditions to investigate the generation of any precipitates, byproducts formation, reaction yield, and conversion of reagents (for more details, see the Supporting Information). Our best batch condition afforded lesinurad **1** after 41 hours in 13% overall yield.

Then, we began our investigation with the preparation of intermediate **3** through a three-step sequence under continuous flow conditions. The flow condensation between isothiocyanate **4** and formic hydrazide **5** was optimized as described in **Table 1**. Inspired by our previous work, we performed a condensation reaction between **4** and **5** under similar conditions. Thus, solutions of reactants **4** and **5** in acetonitrile (MeCN) and dimethylformamide (DMF) (8:2) were streamed through a 10 mL coil reactor at 100 °C with a residence time of 25 minutes (**Table 1**, entry 1). The reaction proceeded with complete conversion, and further optimization led to the discovery that lower temperature (70 °C) and shorter residence time (5 min) resulted in 97% yield for step 1, in view of the higher reactivity of formyl hydrazide **5** (Table 1, entry 6).

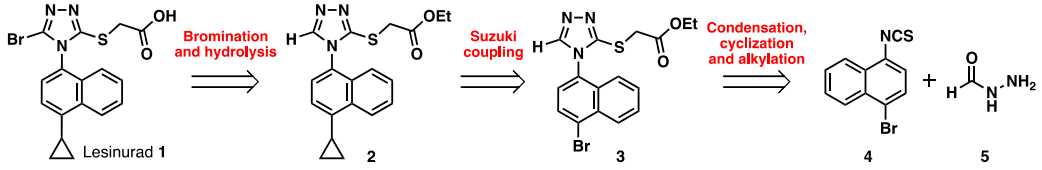
Table 1. Optimization of step 1 under continuous flow conditions.



Entry[a]	t_R (min)	Flow Rate of Streams 1/2 (mL min^{-1})	T (°C)	Equiv of 5	Yield (%)
1	25	0.2/0.2	100	2	96
2	10	0.5/0.5	100	2	97
3	10	0.5/0.5	50	2	93
4	10	0.5/0.5	rt.	2	74
5	5	1.0/1.0	50	2	81
6	**5**	**1.0/1.0**	**70**	**2**	**97**
7	5	1.0/1.0	70	1	92

[a]100 psi back-pressure regulator.

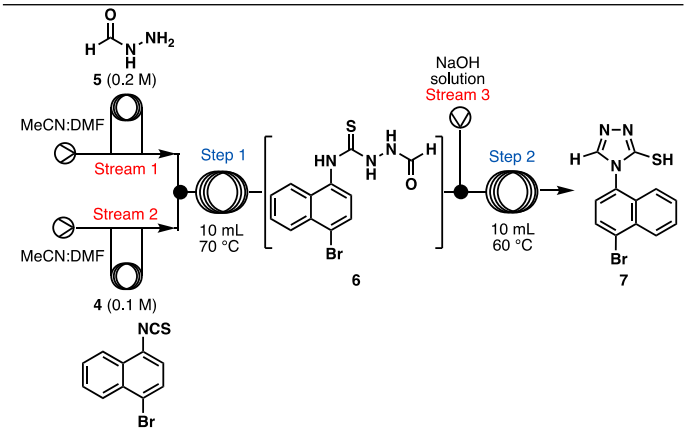
We next sought to telescope steps 1 and 2 in continuous flow regime, and it was achieved by connecting the output of reactor 1 with an aqueous solution of NaOH through a T-piece (**Table 2**).
It is important to mention that in our previous work, we had to operate at elevated reaction temperatures (100 °C and 130 °C, **Scheme 1**), and an excess of base was required to guarantee total conversion of the starting materials. Since isothiocyanate **4** and formic hydrazide **5** are highly reactive, we conducted the first and second steps at lower temperatures, and only 2 equivalents of NaOH



Scheme 2. Proposed synthetic route to lesinurad **1**.

were required to convert thiosemicarbazide **6** to thiol **7**. The use of a 1 M solution of NaOH (**Table 2**, entry 1) gave thiol **7** in lower yield when compared to entry 2, and TLC analysis revealed formation of byproducts. Small adjustments were required and the flow rate of streams 1 and 2 was reduced to 0.75 mL min^{-1} in order to achieve a 10 minutes residence time in reactor 2, and guarantee complete conversion of intermediate **6**, affording the cyclized product **7** in 94% yield.

Table 2. Optimization of step 2 under continuous flow conditions.

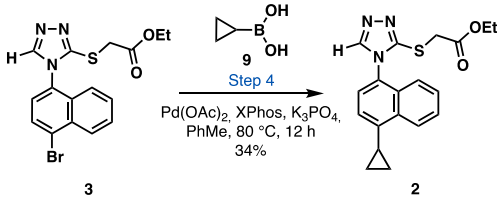


Entry[a]	t_R (min)	Flow Rate of Streams 1/2/3 (mL min^{-1})	Solution of NaOH (M)	Yield (%)
1[b,c]	7.5	1.0/1.0/2.0	1.0	77
2[b]	7.5	1.0/1.0/2.0	0.1	89
3	30	0.25/0.25/0.5	0.1	95
4	**10**	**0.75/0.75/1.5**	**0.1**	**94**

[a]100 psi back pressure regulator. [b]An excess of NaOH led to byproducts formation. [c]Incomplete conversion of intermediate **6**.

Next, we examined the telescoped alkylation of **7** with ethyl chloroacetate **8** to generate 3-thio-1,2,4-triazole **3** (**Table 3**). Following optimization of temperature and residence time, the best condition was obtained at 120 °C and in 20 minutes of residence time to afford 91% isolated yield of **3** in a telescoped three-step synthesis. We also performed a scale-up process using the parameters previously optimized, where the reactant solutions were directly pumped from the reservoir. Collection of the output stream over 3 hours gave a throughput of 0.86 g h^{-1}.

Next, the Suzuki coupling of bromide 3 with cyclopropylboronic acid 9 was evaluated in batch and furnished compound 2 in 34% yield (**Scheme 3**). Different catalysts, ligands and organoboron reagents were tested, however TLC analysis revealed incomplete conversion of 3 for all the conditions evaluated. We believe that the palladium catalyst was deactivated by the thioether group attached to the 1,2,4-triazole core, hampering the reaction to go to completion.



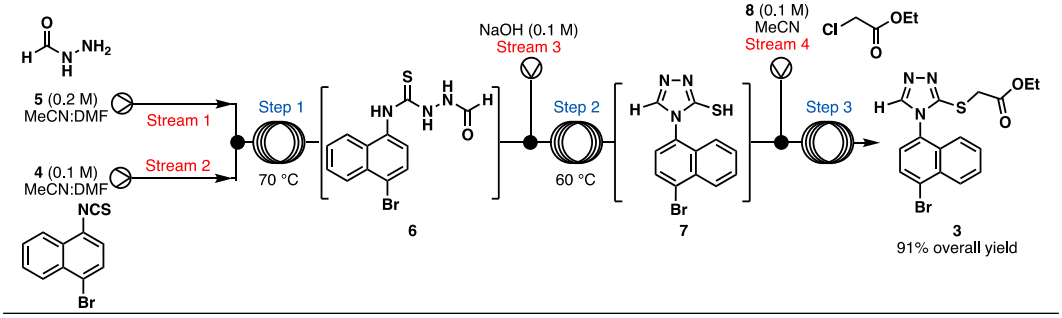
Scheme 3. Suzuki coupling to generate 3-thio-1,2,4-triazole **2**.

We continued our synthesis with the bromination of triazole **2** under continuous flow conditions (**Table 4**). Bromine (Br_2) is extensively used in bromination reactions; however, it is an extremely corrosive and toxic reagent in both liquid and vapour form.[41] Thus, we decided to use *N*-bromosuccinimide (NBS) as a safer alternative to Br_2, and the choice of solvent and temperature for this reaction proved to be crucial.

A solvent screen revealed that dichloromethane (DCM) afforded higher yields, compared to tetrahydrofuran (THF) and MeCN (26% and 30% yield, respectively) and the reaction temperature should not exceed 80 °C, thus avoiding formation of undesired byproducts. The flow synthesis of bromide **10** led to 81% isolated yield in a residence time of 60 minutes. Finally, hydrolysis of compound **10** and acidification were performed in batch affording lesinurad **1** in 95% yield.

In this first approach, we have developed an integrated batch and continuous flow synthesis of lesinurad **1**.

Table 3. Optimization of step 3 under continuous flow conditions.



Entry[a]	t_R (min)	Flow Rate of Streams 1/2/3/4 (mL min^{-1})	T for Reactor 3 (°C)	Yield (%)
1[b]	13	0.75/0.75/1.5/1.5	70	69
2[b]	13	0.75/0.75/1.5/1.5	100	80
3	20	0.5/0.5/1.0/1.0	100	85
4	**20**	**0.5/0.5/1.0/1.0**	**120**	**91**

[a]100 psi back-pressure regulator. [b]Incomplete conversion of intermediate **7**.

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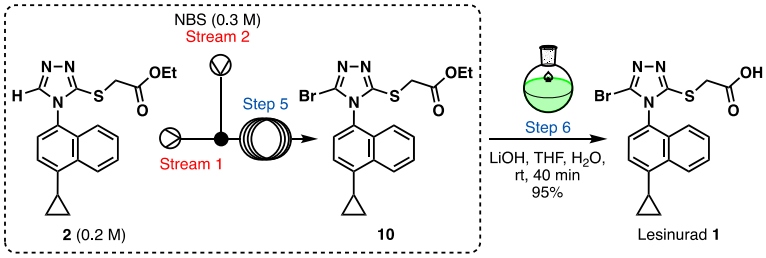
Table 4. Optimization of step 5 under continuous flow conditions and batch synthesis of lesinurad **1**.



Entry[a]	t_R (min)	Flow Rate of Streams 1 / 2 (mL min^{-1})	T (°C)	Solvent	Yield (%)
1	20	0.5/0.5	70	THF	26
2	20	0.5/0.5	70	MeCN	30
3	20	0.5/0.5	90	MeCN	40
4	40	0.25/0.25	90	MeCN	33
5	40	0.25/0.25	110	MeCN	35
6	20	0.5/0.5	90	DCM	48
7	40	0.25/0.25	90	DCM	62
8	40	0.25/0.25	80	DCM	71
9	**60**	**0.17/0.17**	**80**	**DCM**	**81**
10	100	0.1/0.1	80	DCM	72

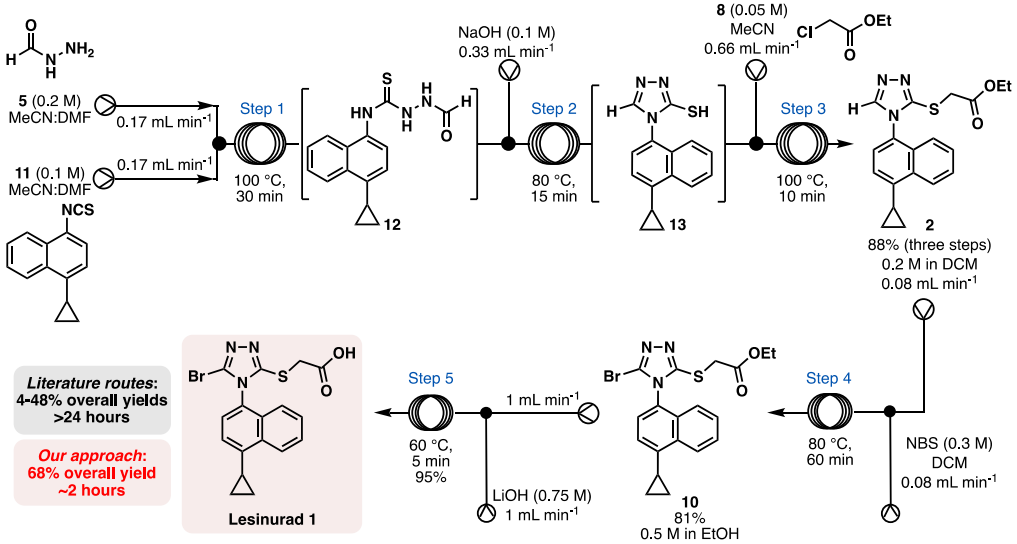
[a]100 psi back-pressure regulator.

The process involved six steps, and we were able to telescope three steps to generate **3** after 20 minutes in 91% yield. The need for work-up and solvent incompatibility prevented us from integrating steps 3 and 4. Suzuki coupling followed by the continuous flow bromination reaction of **2**, and hydrolysis gave lesinurad **1** in 24% overall yield.

Considering the low yield obtained for the Suzuki coupling reaction, we decided to explore a different approach using isothiocyanate **11** as starting material. Compound **11** can be prepared in batch *via* Suzuki coupling and isothiocyanate formation from 1-amino-4-bromo-naphthalene (**Scheme 2S**, Supporting Information), however it is possible to obtain it from commercial sources.

We examined the synthesis of intermediate **12** from isothiocyanate **11** through the same platform used to prepare compound **3**. As previously mentioned, before optimizing flow conditions, we investigated the batch synthesis of lesinurad **1** for this second approach, and it was obtained in 40% yield after 32 hours (for more details, see the Supporting Information).

After minor modifications to the previously optimized flow conditions, synthesis of **2** was achieved (for optimization details, see **Tables S1**, **S2** and **S3**). As we anticipated, the presence of the



Scheme 4. Five-step continuous flow synthesis of Lesinurad **1**.

cyclopropyl group in isothiocyanate **11** decreased its reactivity towards nucleophiles, when compared to isothiocyanate **4**, thus reducing the reaction rate of step 1. Hence, a total of 55 minutes of residence time and temperatures of 100 °C and 80 °C in reactors 1 and 2, respectively, were sufficient for all reactions to reach completion (**Scheme 4**). The three-step sequence afforded compound **2** in 88% yield with a throughput of 0.32 g h^{-1}. After purification, compound **10** was prepared using the same conditions shown in **Table 4** (entry 9). The final hydrolysis reaction to generate lesinurad **1** was performed in reactor 5 by treating a stream of **10** with an aqueous solution of LiOH at 60 °C for 5 min. After acidification, the product was purified by recrystallization and it was isolated in 95% yield. Overall, this approach afforded lesinurad **1** in 68% isolated yield over five steps in *ca.* 2 hours of residence time.

Conclusions

In summary, we have developed a rapid and efficient continuous flow synthesis of lesinurad **1**. In our first approach, we used isothiocyanate **4** as starting material, which involved six steps integrating both batch and flow processes. Suzuki coupling was performed in batch and gave compound **2** in only 34% yield, which encouraged us to explore an alternative route using isothiocyanate **11** as starting point. In our second approach, lesinurad **1** was obtained in 68% overall yield compared to less than 48% in patented and published syntheses.[35,39,40] Condensation, cyclization and *S*-alkylation were conducted in a telescoped process that required no purification of intermediates. Bromination of **2** was also optimized in continuous flow regime, generating bromide **10** in 81% yield in 60 minutes, which is significantly shorter than reported batch procedures (~24 hours). The optimized process involves five steps in three separate flow operations and total residence time of 2 hours. To the best of our knowledge, this is the fastest synthesis and highest reported yield to produce lesinurad **1**. Our approach enables significant reduction of time and waste generation by avoiding purification steps, and consequently, solvent usage.

Experimental Section

General

Starting materials, reagents and solvents were obtained from commercial sources and used as received unless otherwise specified. Reactions were monitored by thin-layer chromatography (TLC) on Silica Gel 60 F254 plates under UV light (254 nm). Flash chromatography was performed using Silica Gel 60 (230-400 mesh, Sigma-Aldrich). Organic solutions were concentrated under reduced pressure on a Büchi or Heidolph rotary evaporator. Column chromatography was mediated on a Biotage Isolera flash chromatography system using SNAP KP-Sil columns. ^{1}H NMR spectra were recorded on either Bruker Avance-400, Bruker Avance-500, or Bruker Avance-600 instruments and are reported relative to residual solvent: $CHCl_3$ (δ 7.26) or DMSO (δ 2.50). ^{13}C NMR spectra were recorded on the same instruments and are reported relative to $CHCl_3$ (δ 77.16) or DMSO (δ 39.52). Data for ^{1}H NMR are reported as follows: chemical shift (multiplicity, coupling constant in Hz, integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, tt = triplet of triplets, q = quartet, quint. = quintet, sext = sextet, dd = doublet of doublets, ddd = doublet of doublets of doublets, m = multiplet, bs = broad signal. NMR spectra were processed using MestReNova NMR Processor version 12.0.4. Melting points were recorded on a Mettler Toledo MP50 benchtop melting point system with a heating rate of 5 °C min^{-1} and are uncorrected. High-resolution mass spectrometry in electrospray ionization mode (HRMS (ESI+)) was performed on a BRUKER Impact II mass spectrometer, and the data processed using the Bruker Compass Data Analysis 4.3 software (Bruker Daltonics). IUPAC names of the compounds were generated using ChemBioDraw Ultra 14.0. In summary, we have developed a rapid and efficient continuous.

General Procedures in Continuous Flow Regime

General Procedure A (Condensation): Hydrazide **5** (12 mg, 0.2 mmol) was taken up in 1 mL of MeCN/DMF (8:2) and filled into loop 1. The isothiocyanate (0.1 mmol) was taken up in 1 mL of MeCN/DMF (8:2) and filled into loop 2. The two loops were simultaneously injected into streams of MeCN/DMF, and the plugs met at a T-piece before passing through a 10 mL coil reactor. The system was pressurized by a 100 psi back pressure regulator. The output was collected, and the solvent was evaporated under reduced pressure. The residue was dissolved in 10 mL of water and extracted with EtOAc (3 × 10 mL). The organic layers were combined and extracted with water (3 × 10 mL), and brine (1 × 10 mL). The crude product was further purified by flash chromatography (DCM/MeOH 2 – 5%) to afford the desired thiosemicarbazide.

General Procedure B (Cyclization): Hydrazide **5** (12 mg, 0.2 mmol) was taken up in 1 mL of MeCN/DMF (8:2) and filled into loop 1. The isothiocyanate (0.1 mmol) was taken up in 1 mL of MeCN/DMF (8:2) and filled into loop 2. The two loops were simultaneously injected into streams of MeCN/DMF, and the plugs met at a T-piece before passing through a coil reactor (10 mL). Separately, a 0.1 M solution of NaOH was pumped, and mixed via a T-piece with the output stream of Reactor 1. The combined mixture entered a second flow coil (10 mL). The system was pressurized by a 100 psi back pressure regulator, and the reactor output was collected and worked up by neutralization with a HCl 1M solution and extraction with EtOAc (3 × 10 mL). The organic layers were combined and extracted with water (3 × 10 mL), and brine (1 × 10 mL). The crude product was further purified by flash chromatography (DCM/MeOH 1 – 5%) to afford the desired thiol.

General Procedure C (*S*-Alkylation): Hydrazide **5** (12 mg, 0.2 mmol) was taken up in 1 mL of MeCN/DMF (8:2) and filled into loop 1. The isothiocyanate (0.1 mmol) was taken up in 1 mL of MeCN/DMF (8:2) and filled into loop 2. The two loops were

simultaneously injected into streams of MeCN/DMF, and the plugs met at a T-piece before passing through a coil reactor (10 mL). Separately, a solution of 0.1 M NaOH was pumped and mixed via a T-piece with the output stream of Reactor 1. The combined mixture entered a second flow coil (10 mL). Subsequently, a solution of ethyl chloroacetate **8** in MeCN (0.1 M) and the output stream of Reactor 2 met at a T-piece before passing through a coil reactor (14 mL). The reactor output was collected and extracted with EtOAc (3 × 10 mL). The organic layers were combined and extracted with water (3 × 10 mL), and brine (1 × 10 mL). The crude product was further purified by flash chromatography (Hexanes/EtOAc 10 – 60%) to afford the desired 3-thio-1,2,4-triazole.

***N*-(4-Bromonaphthalen-1-yl)-2-formylhydrazine carbothioamide (6):** Compound **6** was prepared according to general procedure A, and the flow equipment was set as described in **Table 1** (entry 6). White solid (31 mg, 97% yield). M.p. = 152 – 153 °C. ^{1}H NMR (250 MHz, DMSO- d_6) δ 8.23 – 8.13 (m, 1H), 8.12 (s, 1H), 8.04 – 7.93 (m, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.78 – 7.66 (m, 1H), 7.67 – 7.55 (m, 1H), 7.42 – 7.22 (m, 1H). ^{13}C NMR (63 MHz, DMSO-d_6) δ 182.4, 160.9, 135.9, 132.0, 131.6, 129.5, 128.0, 127.0, 126.5, 124.6, 124.5, 120.2. HRMS (ESI +): *m/z* calculated for $C_{12}H_{11}BrN_3OS^+$ [M + H$^+$] 323.9801, found 323.9812.

4-(4-Bromonaphthalen-1-yl)-4*H*-1,2,4-triazole-3-thiol (7): Compound **7** was prepared according to general procedure B, and the flow equipment was set as described in **Table 2** (entry 4). The product was obtained as a mixture of tautomers (85:15 thiol/thione). White solid (29 mg, 94% yield). M.p. = 160 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6, major tautomer) δ 14.11 (bs, 1H), 8.72 (s, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.81 (ddd, *J* = 8.5, 6.8, 1.2 Hz, 1H), 7.72 (ddd, *J* = 8.5, 6.8, 1.2 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6, major tautomer) δ 167.8, 143.0, 131.7, 130.7, 130.4, 129.7, 128.8, 128.6, 127.6, 127.1, 123.9, 123.4. HRMS (ESI +): *m/z* calculated for $C_{12}H_9BrN_3S^+$ [M + H$^+$] 305.9695, found 305.9685.

Ethyl 2-((4-(4-bromonaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetate (3): Compound **3** was prepared according to general procedure C, and the flow equipment was set as described in **Table 3** (entry 4). Light yellow solid (36 mg, 91% yield). M.p. = 96 – 98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.5 Hz, 1H), 8.29 (s, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.04 (d, *J* = 16.1 Hz, 1H) 4.03 (d, *J* = 16.1 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 151.2, 145.3, 132.6, 130.2, 129.2, 128.9, 128.8, 128.7, 128.0, 125.8, 125.6, 122.2, 62.0, 34.5, 14.0. HRMS (ESI +): *m/z* calculated for $C_{16}H_{15}BrN_3O_2S^+$ [M + H$^+$] 392.0063, found 392.0066.

Scale-up experiment: Solutions of hydrazide **5** (1.08 g, 18 mmol) in 90 mL of MeCN/DMF (8:2) and isothiocyanate **4** (2.38 g, 9 mmol) in 90 mL of MeCN/DMF (8:2) were mixed at a T-piece and pumped through a coil reactor at 70 °C. The output from Reactor 1 was connected to a second T-piece with an incoming aqueous solution of NaOH 0.1 M, and the mixture was pumped into Reactor 2 maintained at 60 °C. The output of Reactor 2 containing thiol **7** was connected to a third T-piece with a solution of **8** in MeCN (0.1 M). The flow stream was allowed to pump into Reactor 3. The system was pressurized by a 100 psi back pressure regulator. After approximately two total residence times, the output flow from Reactor 3 was collected for 180 minutes and extracted with EtOAc (4 × 300 mL). The organic layers were combined and extracted with water (4 × 400 mL), and brine (1 × 400 mL). The crude product was further purified by flash chromatography (Hexanes/EtOAc 10 – 60%) to afford compound **3**.

Ethyl 2-((4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetate (2): Compound **2** was prepared in batch from bromide **3** (for more details, see the Supporting Information), and under continuous flow according to general procedure C. The flow equipment was set as described in **Table 2S** (entry 2). White solid (31 mg, 88% yield). M.p. = 83 – 84 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.4 Hz, 1H), 8.32 (s, 1H), 7.69 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.60 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.40 – 7.31 (m, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.13 (d, *J* = 16.0 Hz, 1H), 4.08 (d, *J* = 16.0 Hz, 1H), 2.45 (tt, *J* = 8.7, 5.4 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.24 – 1.15 (m, 2H), 0.96 – 0.76 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 151.6, 145.9, 143.1, 134.4, 129.4, 127.9, 127.6, 127.3, 125.4, 125.2, 123.2, 122.4, 62.2, 34.7, 14.2, 13.6, 7.1, 7.0. HRMS (ESI +): *m/z* calculated for $C_{19}H_{20}N_3O_2S^+$ [M + H$^+$] 354.1271, found 354.1276.

Scale-up experiment: Solutions of hydrazide **5** (733 mg, 12.2 mmol) in 61 mL of MeCN/DMF (8:2) and isothiocyanate **11** (1.37 g, 6.1 mmol) in 61 mL of MeCN/DMF (8:2) were mixed at a T-piece and pumped through a coil reactor at 100 °C. The output from Reactor 1 was connected to a second T-piece with an incoming aqueous solution of NaOH 0.1 M, and the mixture was pumped into Reactor 2 maintained at 80 °C. The output of Reactor 2 containing thiol **13** was connected to a third T-piece with a solution of **8** in MeCN (0.1 M). The flow stream was allowed to pump into Reactor 3. The system was pressurized by a 100 psi back pressure regulator. After approximately two total residence times, the output flow from Reactor 3 was collected for 240 minutes and extracted with EtOAc (4 × 300 mL). The organic layers were combined and extracted with water (4 × 300 mL), and brine (1 × 300 mL). The crude product was further purified by flash chromatography (Hexanes/EtOAc 10 – 60%) to afford compound **2**.

Ethyl 2-((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetate (10): The flow equipment was set according to **Table 4** (entry 9). Solutions of compound **2** (706 mg, 2 mmol) in 10 mL of DCM and NBS (539 mg, 3 mmol) in 10 mL of DCM were mixed at a T-piece and pumped through a coil reactor at 80 °C (20 mL, 60 min) for 120 minutes. The output was collected, the solvent was evaporated under reduced pressure, and the product was further purified by flash

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chromatography (Hexanes/EtOAc 10 – 50%) to afford compound **10**. Colorless oil (700 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.74 – 7.63 (m, 1H), 7.64 – 7.54 (m, 1H), 7.38 (s, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.07 (d, *J* = 16.2 Hz, 1H), 4.01 (d, *J* = 16.2 Hz, 1H), 2.45 (tt, *J* = 8.4, 5.5 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.23 – 1.14 (m, 2H), 0.97 – 0.84 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 153.9, 143.6, 134.3, 131.3, 129.1, 127.9, 127.2, 126.9, 126.2, 125.3, 123.1, 122.1, 62.1, 34.2, 14.1, 13.5, 7.0, 6.9. HRMS (ESI +): *m/z* calculated for $C_{19}H_{19}BrN_3O_2S^+$ [M + H$^+$] 432.0376, found 432.0379.

***N*-(4-Cyclopropylnaphthalen-1-yl)-2-formylhydrazine carbothioamide (12):** Compound **12** was prepared according to general procedure A and the flow equipment was set as described in **Table S1** (entry 3, Supporting Information). White solid (27 mg, 93% yield). M.p. = 157 – 159 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 9.82 (s, 1H), 9.67 (s, 1H), 8.41 (d, *J* = 7.5 Hz, 1H), 8.10 (s, 1H), 7.91 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.59 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.25 (s, 2H), 2.41 (tt, *J* = 8.4, 5.4 Hz, 1H), 1.15 – 0.99 (m, 2H), 0.85 – 0.66 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 182.5, 161.0, 137.9, 133.4, 130.5, 125.9, 125.7, 125.6, 124.3, 124.2, 122.7, 122.6, 12.8, 6.7. HRMS (ESI +): *m/z* calculated for $C_{15}H_{16}N_3OS^+$ [M + H$^+$] 286.1009, found 286.0999.

4-(4-Cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazole-3-thiol (13): Compound **13** was prepared according to general procedure B and the flow equipment was set as described in **Table S2** (entry 2, Supporting Information). White solid (24 mg, 91% yield). M.p. = 195 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6) δ 14.03 (s, 1H), 8.67 (s, 1H), 8.54 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 2.62 – 2.47 (m, 1H), 1.23 – 1.07 (m, 2H), 0.91 – 0.66 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.9, 143.3, 141.6, 133.4, 129.1, 128.8, 127.2, 126.8, 126.4, 124.8, 122.9, 122.6, 12.9, 7.1, 6.9. HRMS (ESI +): *m/z* calculated for $C_{15}H_{14}N_3S^+$ [M + H$^+$] 268.0903, found 268.0909.

2-((5-Bromo-4-(4-cyclopropylnaphthalen-1-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetic acid (1): The flow equipment was set according to **Scheme 4** (Step 5). Solutions of compound **10** (2.16 g, 5 mmol) in 10 mL of EtOH and LiOH (321 mg, 7.5 mmol) in 10 mL of water were mixed at a T-piece and pumped through a coil reactor at 60 °C (10 mL, 5 min) for 10 minutes. The output was collected, the solvent was evaporated under reduced pressure, and the solution was acidified with HCl 1M. The precipitate was filtered, and the product was purified by recrystallization in EtOAc. White solid (1.92 g, 95% yield). M.p. = 67 – 70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.4 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1H), 7.59 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1H), 7.38 (s, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 4.03 (d, *J* = 15.9 Hz, 1H), 3.97 (d, *J* = 15.9 Hz, 1H), 2.44 (tt, *J* = 8.5, 5.5 Hz, 1H), 1.33 – 1.13 (m, 2H), 0.98 – 0.79 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 155.2, 144.1, 134.5, 131.9, 129.0, 128.3, 127.5, 126.5, 126.4, 125.5, 123.3, 122.0, 34.7, 13.6, 7.2, 7.1.

Conflicts of interest

There are no conflicts to declare.

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