Multistep Continuous-Flow Synthesis of Condensed Benzothiazoles

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In medicinal chemistry, the development of synthetic procedures for the access of new heterocyclic systems as potential scaffolds is elementary. Herein, we report our results on the formation of small drug-like heterocycles, utilizing flow chemistry. This approach enables the extension of the reaction parameter window, including high-pressure/high-temperature or hazardous chemistry. In our work, various novel condensed tricyclic benzothiazoles fused with furo- and thieno-rings were synthesized applying a multistep continuous-flow protocol. The process includes two ring closure steps and a nitro group reduction step. Batch and telescoped continuous-flow syntheses were also designed and performed.

Keywords: flow chemistry, benzothiazoles, catalytic hydrogenation, ring formation, condensed heterocycles

1. Introduction

The synthesis of building blocks in the field of drug discovery is elementary for designing new lead molecules. Although the classic synthetic procedures are widely used, due to the complexity and time consumption of multistep batch syntheses, the development and utilization of new synthetic approaches are highly desired. In addition, the benchtop synthesis has its limits, including the available temperature and pressure ranges as well as hazardous reaction conditions [1]. Application of continuous-flow microreactors could mean a practical solution to overcome these drawbacks and give new opportunities for small molecule drug discovery: (1) the reaction takes place in microcapillaries which results in the rapid mixing of the reagents within seconds due to the occurring laminar flow and radial diffusion, (2) the temperature and the pressure can be controlled fast and accurately, (3) solvents can be overheated using overpressure which allows to increase the reaction speed dramatically, (4) use of small reagent quantities which allows faster reaction optimization, (5) the stereochemistry can be controlled, (6) telescoped multistep flow reactions can be performed, (7) clean products are obtainable, (8) safe handling of the reagents, and (9) easy scale-up [2].

In pharmaceutical research, sulfur- and nitrogen-containing heterocyclic ring systems, such as benzothiazoles, are potential pharmacophores of many biologically active drug molecules [3]. Although the benzothiazole ring system is relatively rare in natural compounds, it is part of some antibiotics and dyes (Figure 1a and b); furthermore, some of its derivatives show antibacterial, antiviral, and antitumor properties [4]. FLT3 kinase inhibitor AC220 [5] (quizartinib, Figure 1c), for example, is a fused benzothiazole derivative, which has been selected as clinical candidate for the treatment of AML (acute myeloid leukemia) patients and is in phase III trials (MV4-11 cell proliferation IC_{50} = 0.56 Nm). Several compounds containing benzothiazole moiety show activity in the central nervous system and are under further development or in clinical investigations [6]. Riluzole (Figure 1d), a 2-aminobenzothiazole, is a marketed drug used to treat ALS (amyotrophic lateral sclerosis).

In recent years, benzothiazole-based structures have provided great interest in drug research due to their versatility and diverse biological activity. A number of new molecules have been patented for the development of new drug molecules for various diseases [7].

During our researches on this field, we faced some challenges within the synthesis of condensed benzothiazoles, which we designed as new building blocks (Figure 2). First, we aimed to achieve their condensation with five-membered rings, such as furan, thiophene, and pyrrole via two possible cyclization approaches to form the desired tricycles: angular and linear ring systems can be obtained, although the formation of the latter is not favorable according to Hammond's law. In addition, only a few synthetic approaches are reported in the literature [8]; hence, there is still a need for a reliable technology for their preparation. Considering the advantages of microreactors listed above, our goal was to find a suitable robust and effective multistep continuous-flow method to the regioselective synthesis of the molecules based on the structures depicted in Figure 2.

2. Results and Discussion

First, we decided to synthesize ethyl 2-amino-8-methylfuro[2,3-*g*][1, 3]benzothiazole-7-carboxylate, compound **I**. The retrosynthetic analysis for its preparation is shown in Figure 3. This molecule can be obtained in two ways: (1) from the corresponding benzothiazole by forming a furan ring, according to Route 1, or (2) by cyclization of the benzofuran, bearing an amino group on the benzene ring, with ammonium thiocyanate (Route 2).

The classic batch synthesis of the furobenzothiazole **I** was among our primary goals. We wished to examine all parameters of the reaction steps for designing the flow protocol.

2.1. Batch Methods for the Synthesis of Compound I. According to Route 1, 2-chloro-1,3-benzothiazol-6-yl acetate (**2**) was prepared [9] from the corresponding phenol derivative (**1**) with acetyl chloride in the presence of $AlCl_3$ (Scheme 1).

This was followed by a Fries rearrangement reaction (Scheme 2), in which we have isolated the 7-acetyl isomer **3a** with poor yield (17%). The regioselectivity of this step was crucial for the subsequent ring closure. Theoretically, the entering position of the acetyl group (the 7- or the 5-position of the corresponding benzothiazole, resulting compounds **3a** and **3b**, respectively) can be controlled by the reaction temperature [10]. Screening the temperature range of 80–200 °C (neat and in toluene) and the reaction times between 5 min and 24 h, we have only isolated the **3a** isomer but the yields remained poor (<10%). In most cases, we regained the phenol compound 1; therefore, we turned to Route 2.

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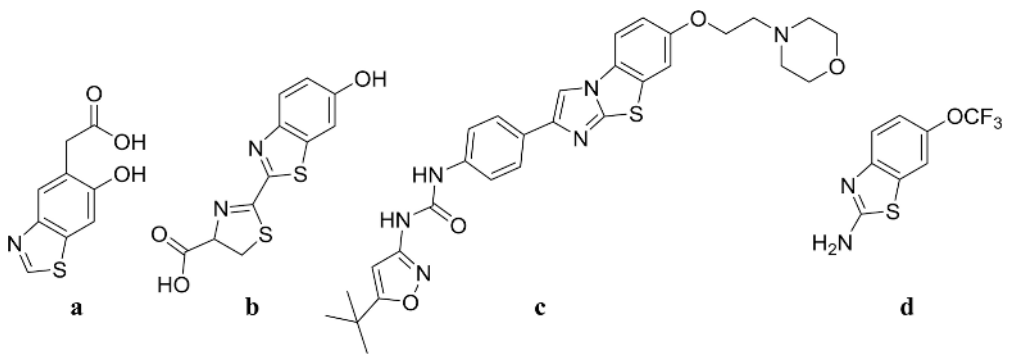


Figure 1. Naturally occurring benzothiazoles antibiotic C304A (a) and firefly luciferin (b), drug candidate AC220 (c), and marketed drug riluzole (d)

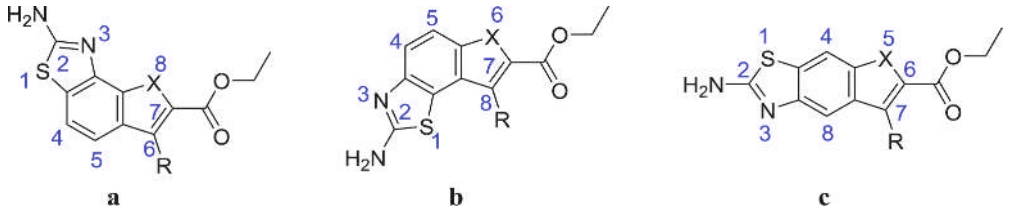


Figure 2. Tricyclic condensed benzothiazoles: (a) (furo/thieno/pyrrolo)[2,3-*e*][1,3]benzothiazole, (b) (furo/thieno/pyrrolo)[2,3-*g*][1,3]benzothiazole, and (c) (furo/thieno/pyrrolo)[3,2-*f*][1,3]benzothiazole ring systems (X = O, S, NH; R = H, CH_3)

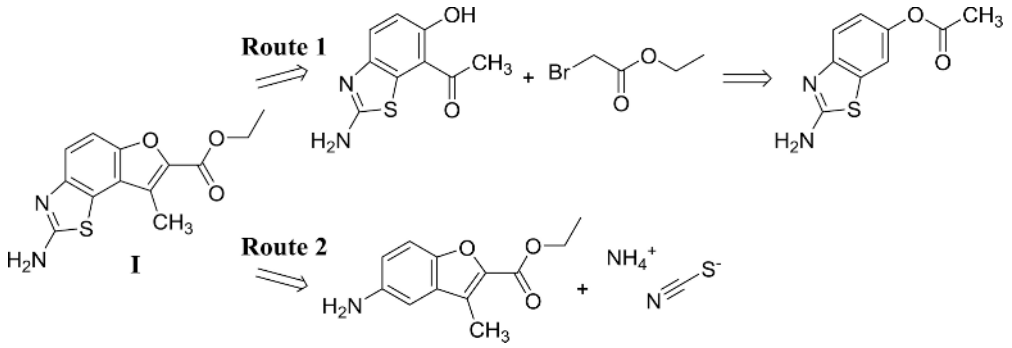
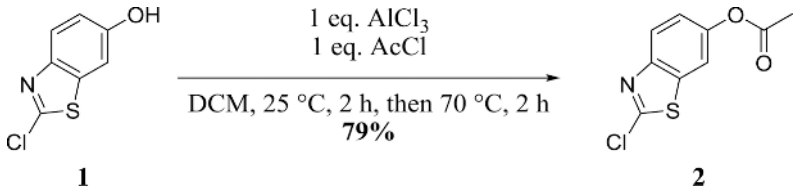
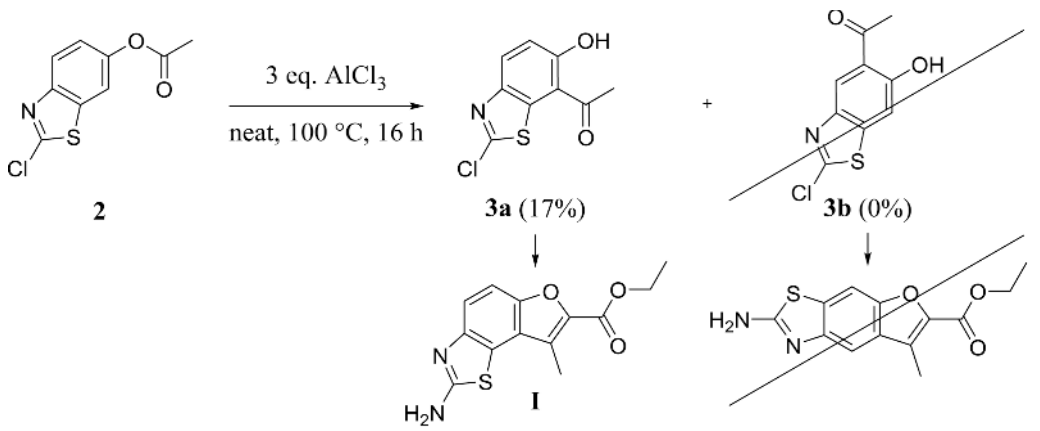


Figure 3. Retrosynthetic analysis for compound **I**

Scheme 1. The preparation of the intermediate **2**



Scheme 2. The preparation of furobenzothiazole **I** based on Route 1



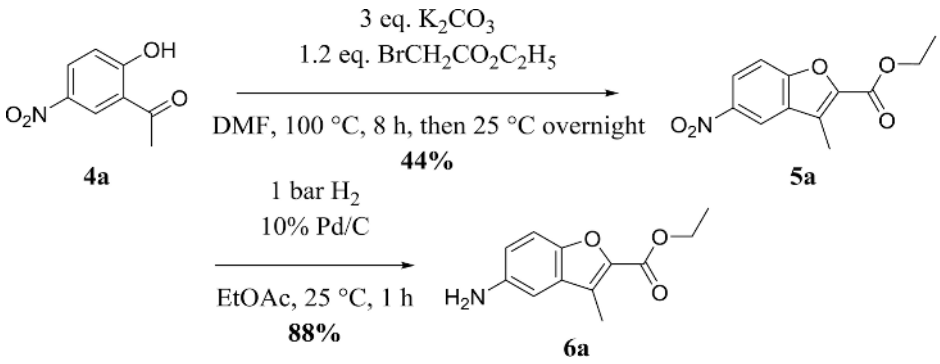
The developed method for the synthesis of **I**, based on Route 2 is shown in Schemes 3 and 4. In the first step, ethyl 3-methyl-5-nitro-1-benzofuran-2-carboxylate (**5a**) was prepared (Scheme 3). Modifying the reactions reported by Korthals et al. [11] and Aboraia et al. [12], 2-hydroxy-5-nitroacetophenone (**4a**) was treated with ethyl bromoacetate in *N*,*N*-dimethylformamide (DMF), in the presence of K_2CO_3. Then, the nitro group of **5a** was reduced with 10% Pd/C catalyst to obtain the amine **6a**, which was used directly in the subsequent ring closure reaction.

For the thiazole ring formation, we have tested two methods. According to van Snick et al. [13] (Scheme 4, Method A), **6a** was treated with ammonium thiocyanate in the presence of bromine, in glacial acetic acid. With this method, we obtained compound **I** with 57% yield (22% overall yield). In the case of Method B (Kuznetsova et al. [14]), bromine was dissolved in methanol saturated with ammonium bromide. This solution was added to **6a** and ammonium thiocyanate, and methanol was used as solvent. The yield was 19% (7% overall yield). In both cases, we have only isolated the angular isomer, and the formation of the linear ring system was not detected.

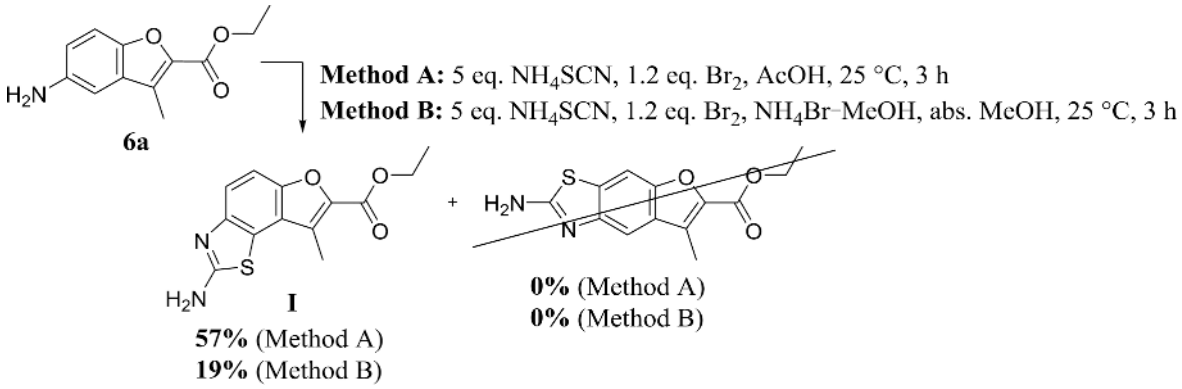
For batch syntheses, we have found Method A more suitable, according to the higher yield. We have used this procedure for the preparation of other reference compounds to the flow protocol. However, for the flow syntheses, Method B is more advantageous considering that compound **I** precipitates from acetic acid. When designing the flow protocol, we have decided to use this method to avoid plugging in the microreactor in the subsequent reactions.

2.2. Flow Procedures for the Synthesis of Compounds I–V. When the batch conditions of Route 2 were translated to a flow protocol, we decided to use *N*,*N*-diisopropylethylamine (DIPEA) instead of K_2CO_3 and DMF as solvent to avoid plugging in the microreactor in the first step. With this alteration, the desired benzofuran (**5a**) was obtainable in two separate steps (shown in Figures 4 and 5). To achieve the best yield in the first step, we have screened the temperature range of 120–160 °C and applied residence times from 5 to 25 min (100- to 20-μL/min flow rates for the 1-mL glass chip reactor). The optimized parameters are shown in Figure 4. The O-alkylation reaction was followed by the ring closure in accordance with the batch method reported by D'Sa et al. [15], applying $P(CH_3NCH_2CH_2)_3$ N (Verkade's base) as catalyst in the second step. Examining the temperature from 70 to 140 °C, we found that full conversion was available at 100 °C within 5 min. This reaction sequence was applied also for the synthesis of other

Scheme 3. Synthetic method for the preparation of **6a** (Route 2, step 1–2)



Scheme 4. The preparation of compound **I** (Route 2, step 3)



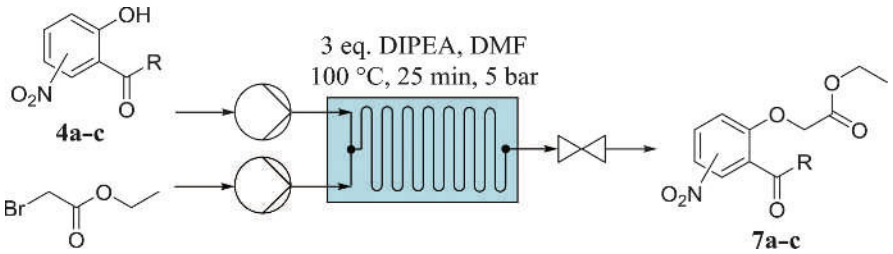


Figure 4. Continuous-flow synthesis of compounds **7a**–**c** (R = H, CH_3)

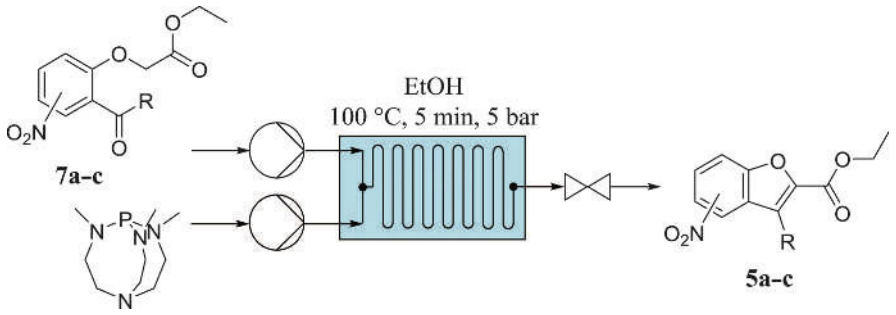


Figure 5. Continuous-flow synthesis of compounds **5a**–**c** (R = H, CH_3)

benzofuran analogues (**5b** and **5c**, for details see Table 1, entries 2 and 3, in comparison with the batch method described in Section 2.1) (Figure 6).

Benzothiophene analogues (**9a**–**c**) were also prepared from 2-fluoro-5-nitroacetophenone (**8a**), 2-fluoro-5-nitrobenzaldehyde (**8b**), and 2-fluoro-3-nitroacetophenone (**8c**) with ethyl thioglycolate (for results, see Table 1, entries 4–6, in comparison with batch reactions [16]). We found that compounds **9a**–**c** can be obtained under flow conditions with DIPEA in one step (Figure 6).

Table 1. Synthesis of various benzofurans and benzothiophenes

Entry	Compound	*n*-NO_2[a]	R	Batch yield (%)	Flow yield (%)
1	**5a**	5-NO_2	CH_3	44[b]	47[d]
2	**5b**	5-NO_2	H	26[b]	69[d]
3	**5c**	3-NO_2	H	57[b]	4[d]
4	**9a**	5-NO_2	CH_3	85[c]	35[e]
5	**9b**	5-NO_2	H	78[c]	66[e]
6	**9c**	3-NO_2	CH_3	84[c]	56[e]
7	**9d**	4-NO_2	H	0[c]	0[e]
8	**9e**	6-NO_2	H	0[c]	0[e]

[a] In the starting compounds.
[b] Reaction conditions: 1.2 equiv. ethyl bromoacetate, 3 equiv. K_2CO_3, DMF, 100 °C, 8 h, then 25 °C, overnight.
[c] Reaction conditions: 1.2 equiv. ethyl thioglycolate, 3 equiv. K_2CO_3, DMF, 100 °C, 8 h, then 25 °C, overnight.
[d] Reaction conditions: 1.2 equiv. ethyl bromoacetate, 3 equiv. DIPEA, DMF, 100 °C, 20–20-μL/min flow rates, 25 min, 5 bar, then 0.4 equiv. P$(CH_3NCH_2CH_2)_3$ N, EtOH, 100 °C, 100–100-μL/min flow rates, 5 min, 5 bar, the yields are overall yields.
[e] Reaction conditions: 1.2 equiv. ethyl thioglycolate, 3 equiv. DIPEA, DMF, 100 °C, 20–20-μL/min flow rates, 25 min, 5 bar.

The yields depend in both cases on the position of the nitro group: using 2-hydroxy-3-nitrobenzaldehyde, the ring closure was less favorable than in the case of the 5-nitro isomer. We have tested both methods on 2-fluoro-4-nitrobenzaldehyde and 2-fluoro-6-nitrobenzaldehyde (Table 1, entries 7 and 8). Unfortunately, the formation of compounds **9d** and **9e** was not detected. Other difficulties were in both conditions: the hydrolysis of the ester groups, the decomposition of the starting materials, and, in the case of benzaldehydes, the formation of the corresponding alcohols and carboxylic acid salts in the Cannizzaro reaction [15, 17].

The hydrogenation of compounds **5a**–**c** and **9a**–**c** and the indoles **10a**,**b** (purchased from Apollo Scientific) to the corresponding amines was performed directly under continuous-flow conditions with an H-Cube® reactor [18], using 10% Pd/C cartridges as catalyst (Figure 7).

We found that, using 0.01-0.05-M stock solutions of the starting compounds (**5a**–**c**, **9a**–**c**, **10a**,**b**), full conversion can be achieved at 40–60 °C in every reaction (for details, see Table 2). To avoid plugging, we used methanol as cosolvent in the noted reactions.

The third step was the formation of the thiazole ring. First, we wished to prepare the furo-, thieno-, and pyrrolo[2,3-*e*][1, 3]benzothiazoles (shown in Figure 2a). Considering the tested batch methods, when designing our flow protocol, we decided to use Kuznetsova's method [14] with some modifications (Figure 8).

Applying DMF as solvent and methanol saturated with ammonium bromide as cosolvent in our flow reactions, we could eliminate the solubility problems and the difficulties of the work-up. Unfortunately, our attempts to synthesize these ring systems were

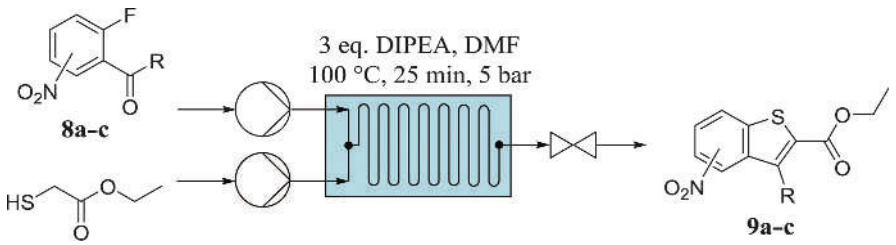


Figure 6. Continuous-flow synthesis of compounds **9a**–**c**

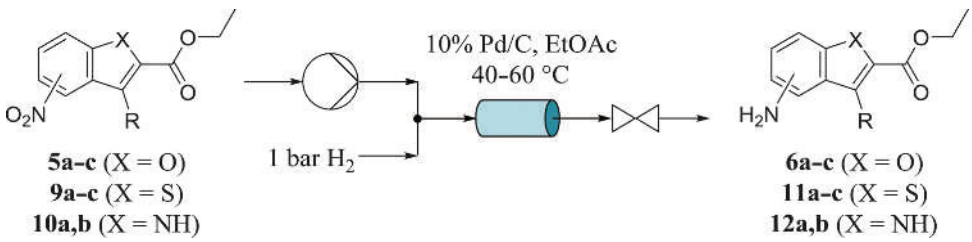


Figure 7. Hydrogenation reactions with H-Cube® (R = H, CH_3)

Table 2. Hydrogenation reactions

Entry	Compound	*n*-NO_2[a]	X	R	Temperature	Yield[b] (%)
1	**6a**	5-NO_2	O	CH_3	40 °C	98
2	**6b**	5-NO_2	O	H	40 °C	98
3	**6c**	7-NO_2	O	H	40 °C	95
4	**11a**	5-NO_2	S	CH_3	40 °C	99[c]
5	**11b**	5-NO_2	S	H	40 °C	96[c]
6	**11c**	7-NO_2	S	CH_3	40 °C	98
7	**12a**	5-NO_2	NH	H	60 °C	99[c]
8	**12b**	7-NO_2	NH	H	60 °C	88[c]

[a] In the starting compounds.
[b] Reaction conditions: 1 bar H_2 (full H_2 mode), 10% Pd/C cartridge, ethyl acetate, 0.5–1.0-mL/min flow rates, 40–60 °C.
[c] Methanol was used as cosolvent.

unsuccessful. The applied reaction conditions yielded the molecules depicted in Figure 9 in every case.

When applying this flow procedure for the synthesis of furo-, thieno-, and pyrrolo[2,3-*g*][1,3]benzothiazoles (shown in Figure 2b), we have successfully isolated compounds **I**–**V** with good or moderate yields (33–82%, in comparison with the batch methods, for more details, see Figure 10 and Table 3). The reactions were regioselective, and the formation of the linear tricycles was not detected.

2.3. Telescoped Continuous-Flow Synthesis of Compound V. The reduction and thiazole ring formation steps can be coupled in flow with some alterations (an overview of the procedure is shown in Figure 11). We have applied this protocol for the synthesis of compound **V**.

Starting with the **10a** indole, the hydrogenation reaction takes place in the H-Cube® reactor with 10% Pd/C catalyst. With the application of DMF as solvent, we can avoid the solvent exchange between the two reaction steps and the plugging in the second step. Using 10-mL stock solution of 0.05-M concentration and 0.2-mL/min flow rate (on the high-performance liquid chromatography [HPLC] pump of the H-Cube®), full conversion can be achieved at 60 °C and atmospheric pressure (full H_2 mode). The reaction mixture, containing the **12a** amine, is collected in the buffer vessel (which also has degasser function) and injected through the second pump with 83-μL/min flow rate. The solution of 5 equiv. ammonium thiocyanate in 10 mL DMF is pumped through the third pump with 83-μL/min flow rate. The two streams mix in the first polytetrafluoroethylene (PTFE) coil reactor (5-mL volume) at room temperature and atmospheric pressure. The reaction mixture enters the second PTFE coil reactor (10-mL volume) after 30 min. Simultaneously, the solution of 1.2 equiv. bromine in 20 mL of the 1:1 mixture of DMF and methanol saturated with ammonium bromide is pumped through the fourth pump with 166-μL/min flow rate into the second coil reactor. The ring closure reaction takes place at 25 °C and atmospheric pressure. After work-up, we can obtain compound **V** with this method in a telescoped way, without the isolation of the intermediates with 33% overall yield and 24 mg/h productivity.

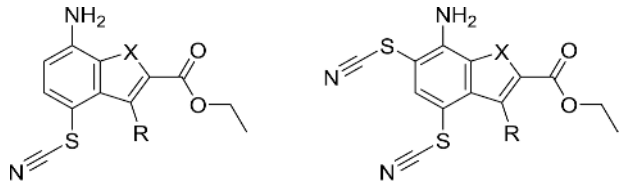


Figure 9. The structures of the isolated compounds (X = O, S, NH; R = H, CH_3)

3. Conclusions

In conclusion, we have developed a multistep synthetic approach for the preparation of angular condensed benzothiazoles (**I**–**V**, Figure 12) in batch and also in a continuous-flow protocol.

Although the yields are moderate to good (33–86%, Table 3) in both methods, the flow procedure has more advantages: considering the safe handling of the reagents, the low time consumption of the optimization, and also the ease of the scale-up, the continuous-flow synthesis is more suitable. With the application of multistep flow protocol, the desired products are obtainable without the isolation of the sensible amine intermediates, which helps to prevent losses during the work-up, in comparison with the batch methods. The reduction of the reaction times is also essential. Applying the flow protocol, we can isolate the products of each step within 1–2 h (compared with the 1–2-day-long batch syntheses). The automatization of the multistep flow syntheses and the use of in-line extraction and structure analysis mean further advantages.

4. Experimental

4.1. General Methods. All solvents and reagents were purchased from commercial vendors and were used without additional purification. Hydrogenation reactions were carried out in an H-Cube® continuous-flow reactor (ThalesNano, Budapest, Hungary). The reactions of the multistep flow protocol were carried out using Azura P 2.1S pumps (Knauer, Berlin, Germany) and PTFE tubing (with 1/16″ and 1/8″ outer diameters). Flangeless PEEK fittings with PEEK ferrules and PEEK T-adapters (0.020″ inner diameter) were used in conjunctions. All other continuous-flow reactions were performed in an Asia® microreactor system (Syrris, Royston, UK), employing two-feed glass chip microreactors (1-mL volume). High-resolution mass spectrometry (HRMS) analyses were performed on a LTQ FT Ultra (Thermo Fisher Scientific, Bremen, Germany) system. The ionization method was electrospray ionization (ESI) and operated in positive ion mode. The protonated molecular ion peaks were fragmented by collision-induced dissociation (CID) at a normalized collision energy of 35–65%. The samples were dissolved in methanol. Data acquisition and analysis were accomplished with Xcalibur software version 2.0 (Thermo Fisher Scientific). Nuclear

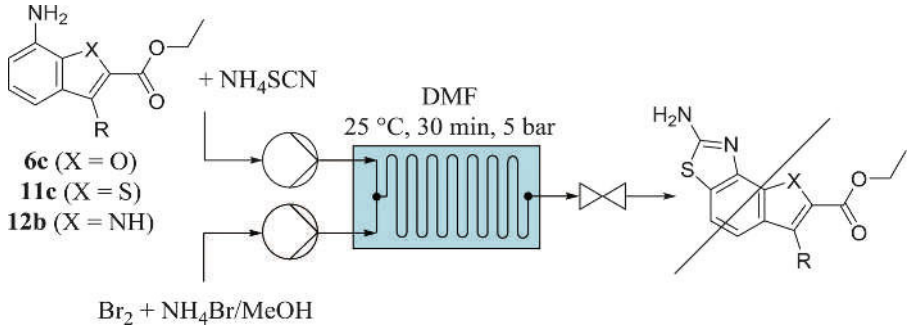


Figure 8. The planned synthesis of (furo/thieno/pyrrolo)[2,3-*e*][1,3]benzothiazoles (R = H, CH_3)

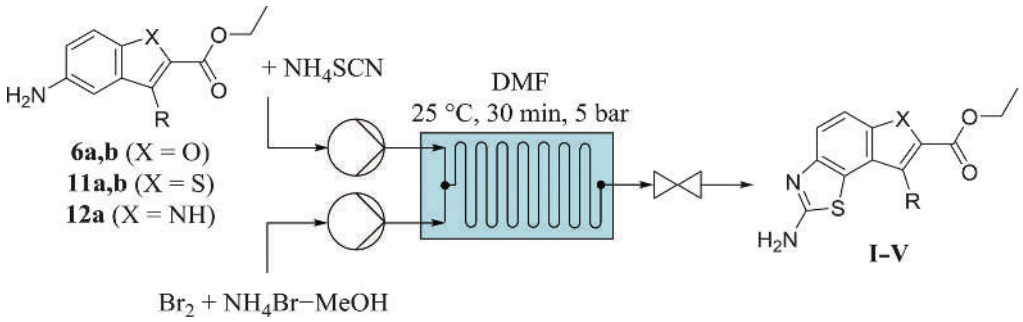


Figure 10. The synthesis of (furo/thieno/pyrrolo)[2,3-*g*][1,3]benzothiazoles in flow (R = H, CH_3)

Table 3. Ring closing reactions

Entry	Compound	X	R	Batch yield[a] (%)	Flow yield[b] (%)
1	**I**	O	CH_3	57	55
2	**II**	S	CH_3	76	62
3	**III**	O	H	51	33
4	**IV**	S	H	86	82
5	**V**	NH	H	56	45

[a] Reaction conditions: 5 equiv. NH_4SCN, 1.2 equiv. Br_2, AcOH, 25 °C, 3 h.
[b] Reaction conditions: 5 equiv. NH_4SCN, 1.2 equiv. Br_2, NH_4Br–MeOH, DMF, 25 °C, 17–17-μL/min flow rates, 30 min, 5 bar.

magnetic resonance (NMR) spectra were recorded at 25 °C on an Agilent (Varian) NMRS-500 equipped with an HCN 5-mm PFG Triple Resonance ^{13}C Enhanced Cold Probe operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C using DMSO-d_6 as solvent. The chemical shifts were referenced to tetramethylsilane (TMS) (for ^{1}H, ^{13}C). HPLC analyses were carried out on a C18 reverse-phase analytical column (Chromolit RP18e 100 × 3 mm) at 40 °C using mobile phases A (water + 0.1% trifluoroacetic acid [TFA]) and B (acetonitrile + 0.1% TFA) at 1.7-mL/min flow rate. The applied gradient was the following: a linear increase of eluent B from 0% to 90% for 9.7 min, and hold at 90% B for 2.8 min. Detection was 220 nm.

Compounds **I**–**V** are new compounds; all other substances are known. These were characterized by comparison with authentic samples or literature data.

4.2. General Procedures for the Synthesis of Benzofurans 5a–c

4.2.1. Batch Procedure. To a solution of the starting compound (**4a**–**c**, 3 mmol) in dry DMF (30 mL), K_2CO_3 (3 equiv., 9.0 mmol) and ethyl bromoacetate (1.2 equiv., 3.6 mmol) at room temperature were added. After stirring the reaction mixture at 100 °C for 8 h and then at 25 °C overnight, the resulting suspension was added to 300 mL ice water and the precipitate formed was filtered off and dried in vacuum. The residual solution was extracted with ethyl acetate. The organic phase was washed with 1-M HCl solution, dried on $MgSO_4$, and concentrated. The combined crude product was purified by recrystallization from ethanol to give pure product.

4.2.2. Flow Procedure. To a solution of the starting compound (**4a**–**c**, 1.0 mmol) in dry DMF (5 mL), DIPEA (3 equiv., 3.0 mmol) was added. Ethyl bromoacetate (1.2 equiv., 1.2 mmol) was dissolved in dry DMF (5 mL) at room temperature. Both solutions were loaded into the 5-mL PTFE double-loop injection module. Pumping pure DMF through the loops with 20–20-μL/min flow rate, the reagents were mixed in the 1-mL glass chip reactor at 100 °C, 5 bar. The reaction mixture left the reactor after 25 min and was collected, poured on ice water, and extracted with ethyl acetate. The organic phase was washed with 1-M HCl solution, dried ($MgSO_4$), and concentrated. The crude product was purified by recrystallization from ethanol. The isolated intermediate was then dissolved in ethanol (5 mL) and loaded into the first injection loop. The solution of $P(CH_3NCH_2CH_2)_3$ N (0.4 equiv.)

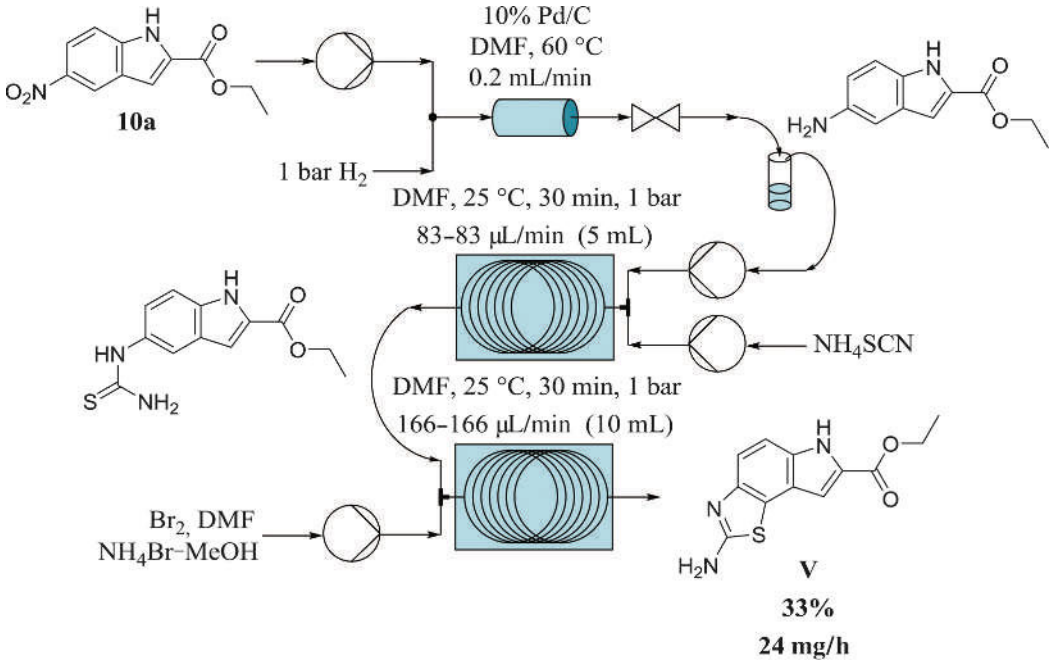


Figure 11. The developed multistep flow protocol for the synthesis of **V**

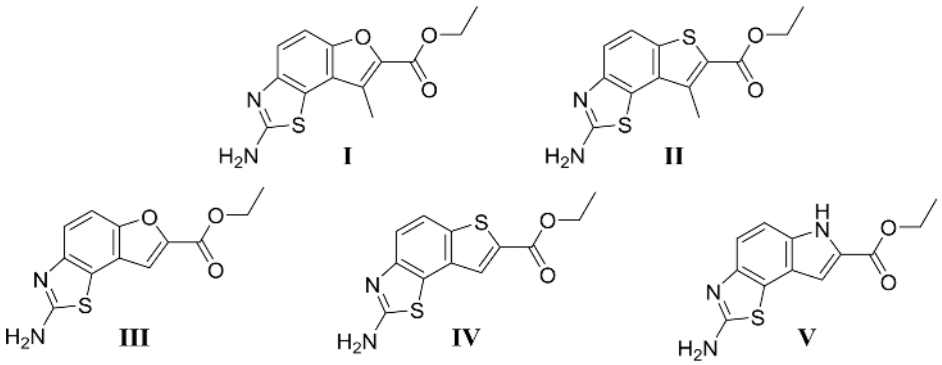


Figure 12. Scope of the new heterocycles **I**–**V**

in 5 mL ethanol was loaded into the second loop. The reagents were pumped through the reactor (100 °C, 5 bar, 100–100-μL/min flow rate for the 1-mL chip reactor) and left it after 5 min. The collected reaction mixture was concentrated, taken up in ethyl acetate, and washed with brine. The organic phase was dried ($MgSO_4$) and concentrated. The product was purified by recrystallization from ethanol.

*4.2.2.1. Ethyl 3-methyl-5-nitro-1-benzofuran-2-carboxylate (***5a***).* Utilizing the general flow procedure, **5a** was isolated with 47% overall yield as pale yellow solid.

*4.2.2.2. Ethyl 5-nitro-1-benzofuran-2-carboxylate (***5b***).* Utilizing the general flow procedure, **5b** was isolated with 69% overall yield as pale yellow solid.

*4.2.2.3. Ethyl 7-nitro-1-benzofuran-2-carboxylate (***5c***).* Utilizing the general flow procedure, **5c** was isolated with 4% overall yield as yellow solid.

4.3. General Procedures for the Synthesis of Benzothiophenes 9a–c

4.3.1. Batch Procedure. To a stirred solution of the starting compound (**8a**–**c**, 3.0 mmol) in dry DMF (30 mL), K_2CO_3 (3 equiv., 9.0 mmol) was added. The reaction mixture was cooled with ice bath under 10 °C. A solution of ethyl thioglycolate (1.2 equiv., 3.6 mmol) in dry DMF (5 mL) was slowly added to the reaction mixture. After stirring at 100 °C for 8 h and then 25 °C overnight, the resulting suspension was added to 300 mL ice water and extracted with ethyl acetate. The organic phase was washed with 1-M HCl solution, dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane.

4.3.2. Flow Procedure. To a solution of the starting compound (**8a**–**c**, 1.0 mmol) in dry DMF (5 mL), DIPEA (3 equiv., 3.0 mmol) was added. Ethyl thioglycolate (1.2 equiv., 1.2 mmol) was dissolved in dry DMF (5 mL) at room temperature. Both solutions were loaded into the injection module. Pumping pure DMF through the loops with 20–20-μL/min flow rate, the reagents were mixed in the 1-mL chip reactor at 100 °C, 5 bar. The reaction mixture left the reactor after 25 min, was collected, poured into water, and extracted with ethyl acetate. The organic phase was washed with 1-M HCl solution, dried ($MgSO_4$), and concentrated. The crude product was purified by recrystallization from ethanol or by flash column chromatography on silica gel eluting with dichloromethane.

*4.3.2.1. Ethyl 5-nitro-1-benzothiophene-2-carboxylate (***9a***).* Utilizing the general flow procedure, **9a** was isolated with 35% yield as pale-yellow solid.

*4.3.2.2. Ethyl 3-methyl-5-nitro-1-benzothiophene-2-carboxylate (***9b***).* Utilizing the general flow procedure, **9b** was isolated with 66% yield as pale-brown solid.

*4.3.2.3. Ethyl 3-methyl-7-nitro-1-benzothiophene-2-carboxylate (***9c***).* Utilizing the general flow procedure, **9c** was isolated with 56% yield as yellow solid.

4.4. Hydrogenation Reactions (Synthesis of Amines 6a–c, 11a–c, and 12a,b)

4.4.1. Batch Procedure. The starting nitro-compound (1 equiv.) was dissolved in 5 mL ethyl acetate. 10-mol% Pd/C (10%) catalyst was added to the solution. The reaction mixture was stirred for 1 h at room temperature, in the continuous stream of hydrogen at atmospheric pressure. The catalyst was then filtered out, and the residual solution was concentrated under reduced pressure. The resulting solid phase was dissolved in 2.5 mL ethyl acetate saturated with HCl and stirred for another 1 h. The formed HCl salt of the desired amine was filtered out, dried under reduced pressure, and was used without further purification.

4.4.2. Flow Procedure. All continuous-flow hydrogenation reactions were performed on the H-Cube®, using 10% Pd/C cartridges (30 × 4 mm) at atmospheric pressure (full H_2 mode), at 40–60 °C and with 0.5–1.0-mL/min flow rates. The catalyst was activated at these parameters by pumping pure solvent through the H-Cube®. After the system had stabilized, the solution of the corresponding nitro-benzofuran, benzothiophene, or -indole (0.01–0.05 M ethyl acetate or using methanol as cosolvent, depending on the solubility) was pumped into the reactor. The outlet collection started with the injection and lasted until the inlet solution had finished. The obtained solution was concentrated to give the crude product, which was used without further purification.

4.5. General Procedures for the Synthesis of Benzothiazoles I–V

4.5.1. Batch Procedure. To a solution of the starting amine (1 equiv.) in glacial acetic acid (10 mL), NH_4SCN (5 equiv.) was added, and the mixture was stirred at room temperature for 1 h. Bromine (1.2 equiv.) was dissolved in glacial acetic acid (10 mL). The reaction mixture was cooled with ice bath under 10 °C while bromine was added, and then stirred at room temperature for 2 h. Acetic acid was evaporated, and the resulting solid was suspended in ammonium hydroxide solution (25%). The precipitate formed was filtered off, dried in vacuum, and recrystallized from methanol.

4.5.2. Flow Procedure. The starting amine (1 equiv.) and NH_4SCN (5 equiv.) were dissolved in 5 mL DMF and loaded into the loop. Bromine (1.2 equiv.) was dissolved in the mixture of 2.5 mL DMF and 2.5 mL methanol saturated with NH_4Br, and loaded into the second loop. The reagents were mixed in the 1-mL chip reactor (25 °C, 5 bar, 17–17-μL/min flow rate) and left it after 30 min. The collected mixture was concentrated then suspended in ammonium hydroxide solution (25%). The precipitate formed was filtered off, dried in vacuum, and recrystallized from methanol.

*4.5.2.1. Ethyl 2-amino-8-methylfuro[2,3-g][1,3]benzothiazole-7-carboxylate (***I***).* Utilizing the general flow procedure, compound **I** was isolated with 55% yield as pale-yellow powder;

mp. 284–285 °C; ^{1}H NMR: δ 1.35 (t, 3H, J 7.1 Hz, CH_3), 2.60 (s, 3H, $ArCH_3$), 4.35 (q, 2H, J 7.1 Hz, CH_2), 7.50 (s, 2H, NH_2), 7.52 (s, 2H, ArH); ^{13}C NMR: δ 10.1 ($ArCH_3$), 14.1 (CH_3), 60.8 (CH_2), 109.3 (C-5), 118.7 (C-4), 121.2 and 122.4 (C-8a, C-8b), 123.8 (C-8), 140.5 (C-7), 149.4 and 149.5 (C-3a, C-5a), 159.4 (COO), 166.0 (CNH_2) ppm; HRMS: 277.06396 ($C_{13}H_{13}O_3N_2S$; calc. 277.06414). ESI–MS–MS (rel. int. %): 249(100).

*4.5.2.2. Ethyl 2-amino-8-methylthieno[2,3-g][1,3]benzothiazole-7-carboxylate (***II***).* Utilizing the general flow procedure, compound **II** was isolated with 62% yield as pale-yellow powder; mp. 255–258 °C; ^{1}H NMR: δ 1.33 (t, 3H, J 7.1 Hz, CH_3), 2.84 (s, 3H, $ArCH_3$), 4.33 (q, 2H, J 7.1 Hz, CH_2), 7.55 (s, 2H, NH_2), 7.59 (d, 1H, J_{orto} 8.6 Hz, H-4), 7.82 (d, 1H, J_{orto} 8.6 Hz, H-5); ^{13}C NMR: δ 14.1 (CH_3), 14.5 ($ArCH_3$), 61.0 (CH_2), 119.2 (C-4), 119.9 (C-5), 124.1 (C-5a), 126.7 (C-8), 132.9 (C-8b), 133.7 (C-8a), 138.8 (C-7), 150.8 (C-3a), 162.5 (COO), 166.3 (CNH_2) ppm; HRMS: 293.04154 ($C_{13}H_{13}O_2N_2S_2$; calc. 293.04130). ESI–MS–MS (rel. int. %): 265(100).

*4.5.2.3. Ethyl 2-aminofuro[2,3-g][1,3]benzothiazole-7-carboxylate (***III***).* Utilizing the general flow procedure, compound **III** was isolated with 33% yield as yellow powder; mp. 234–236 °C; ^{1}H NMR: δ 1.34 (t, 3H, J 7.1 Hz, CH_3), 4.36 (q, 2H, J 7.1 Hz, CH_2), 7.47 (s, 2H, NH_2), 7.52 (d, 1H, J_{orto} 8.9 Hz, H-4), 7.57 (dd, 1H, J_{orto} 8.9 Hz, ^5J 0.9 Hz, H-5), 7.89 (d, 1H, ^5J 0.9 Hz, H-8); ^{13}C NMR: δ 14.1 (CH_3), 61.2 (CH_2), 109.2 (C-5), 112.7 (C-8), 118.4 (C-4), 120.3 (C-8a), 122.1 (C-8b), 145.2 (C-7), 149.5 (C-3a), 151.0 (C-5a), 158.5 (COO), 166.1 (CNH_2) ppm; HRMS: 263.04836 ($C_{12}H_{11}O_3N_2S$; calc. 263.04849). ESI–MS–MS (rel. int. %): 235(100).

*4.5.2.4. Ethyl 2-aminothieno[2,3-g][1,3]benzothiazole-7-carboxylate (***IV***).* Utilizing the general flow procedure, compound **IV** was isolated with 82% yield as pale yellow powder; mp. 255–257 °C; ^{1}H NMR: δ 1.34 (t, 3H, J 7.1 Hz, CH_3), 4.36 (q, 2H, J 7.1 Hz, CH_2), 7.58 (s, 2H, NH_2), 7.57 (d, 1H, J_{orto} 8.7 Hz, H-4), 7.87 (d, 1H, J_{orto} 8.7 Hz, H-5), 8.12 (s, 1H, H-8); ^{13}C NMR: δ 14.1 (CH_3), 61.4 (CH_2), 118.8 (C-4), 119.9 (C-5), 125.1 (C-5a), 128.0 (C-8), 131.5 (C-8a), 134.0 (C-7), 134.8 (C-8b), 150.7 (C-3a), 161.8 (COO), 166.4 (CNH_2) ppm; HRMS: 279.02553 ($C_{12}H_{11}O_2N_2S_2$; calc. 279.02565). ESI–MS–MS (rel. int. %): 251(100).

*4.5.2.5. Ethyl 2-amino-6H-[1,3]thiazolo[5,4-e]indole-7-carboxylate (***V***).* Utilizing the general flow procedure, compound **V** was isolated with 45% yield as pale-brown powder; mp. 197 °C, with decomposition; ^{1}H NMR: δ 1.34 (t, 3H, J 7.1 Hz, CH_3), 4.34 (q, 2H, J 7.1 Hz, CH_2), 7.08 (dd, 1H, ^5J 0.9 Hz, $J_{H\text{-}8,NH}$ 2.3 Hz, H-8), 7.19 (s, 2H, NH_2), 7.32 (dd, 1H, J_{orto} 8.7 Hz, ^5J 0.9 Hz, H-5), 7.35 (d, 1H, J_{orto} 8.7 Hz, H-4), 11.99 (brm, 1H, NH); ^{13}C NMR: δ 14.2 (CH_3), 60.3 (CH_2), 105.1 (C-8), 110.2 (C-5), 116.9 (C-4), 120.2 (C-8a), 120.6 (C-8b), 127.2 (C-7), 133.6 (C-5a), 146.6 (C-3a), 161.0 (COO), 164.4 (CNH_2) ppm; HRMS: 262.06429 ($C_{12}H_{12}O_2N_3S$; calc. 262.06447). ESI–MS–MS (rel. int. %): 234(16); 216(100).

Supporting Information

Electronic Supplementary Material (ESM) with supplementary data of compounds **5a**–**c**, **9a**–**c**, and **I**–**V** associated with this article is available in the online version at doi:10.1556/1046.2015.00004.

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