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Article

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Synthesis of Imidazo[2,1-b]thiazoles *via* Copper-Catalyzed A^3-Coupling in Batch and Continuous-Flow

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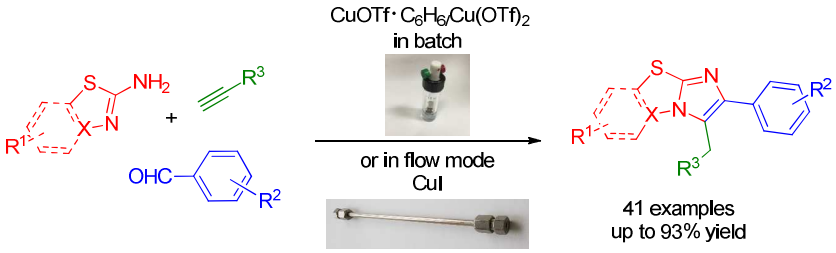
Abstract



A straightforward method for the synthesis of functionalized imidazo[2,1-b]thiazoles starting from benzaldehydes, 2-aminothiazoles and alkynes under copper(I,II) catalysis was developed. The protocol allows the construction of a variety of aryl-substituted imidazo[2,1-b]benzothiazoles, -[2,1-b]thiazoles and -[2,1-b][1,3,4]thiadiazoles. Reactions are easy to perform affording most of the desired products in yields of 33 to 93%. The intensification of the process in a continuous flow reactor increases the products yields up to quantitative.

Keywords: imidazo[2,1-b]thiazoles; imidazo[2,1-b]benzothiazoles; copper catalysis; A^3-Coupling.

INTRODUCTION

Imidazo[2,1-b]thiazole is one of the most important fused sulfur-containing heterocycle widely found in a variety of biologically active agents (Figure 1),[1] including a number of drugs and drug candidates (e.g., anthelmintic levamisole,[1d] potent anticancer agent Quizartinib,[2] p53 inhibitor anti-neoplastic drug pifithrin-β,[3] anti-aging agent SRT2140,[4] anxiolytic agent WAY-181,187[5]). The prevalence of the imidazo[2,1-b]thiazole motif in medicinally relevant compounds,[6] catalysts,[7] phosphorescent emitting[8] and electronic[9] materials has inspired the development of many novel methods for their preparation.[10] However, there are only limited protocols for the one-pot assembly of polyfunctionalized imidazothiazole derivatives.[11] Traditional methods include heterocyclizations of 2-aminothiazoles with α-bromoketones.[12] Recently, Singh et al. reported a visible light-triggered procedure in a green medium for condensation of arylacyl bromides with 2-aminothiazole towards imidazo[2,1-b]thiazoles.[13] Hajra and co-workers reported an elegant Fe/Zn-cocatalyzed aerobic oxidative cyclization of 2-aminobenzothiazole and chalcones.[14] In another report, Zhu et al. demonstrated copper(II) acetate-promoted cycloaddition of α-methylenyl isocyanides with 2-methylbenzothiazole.[15] The metal-free condensation of 2-aminothiazole with β-nitroacrylates to form imidazo[2,1-b][1,3]benzothiazoles in a ionic liquid was reported by Meshram.[16] Despite the impressive progress made in this area, synthesis of functionalized imidazo[2,1-b]thiazoles from readily available and easily varied starting materials using a simple procedure still remains a great challenge. The known methods suffer from the necessity of using prefunctionalized, commercially unavailable reacting substances and limited substrate scope.

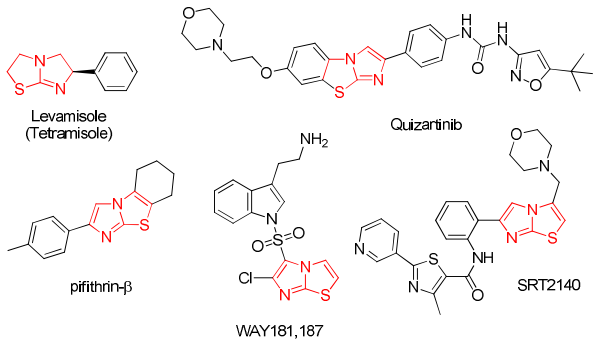
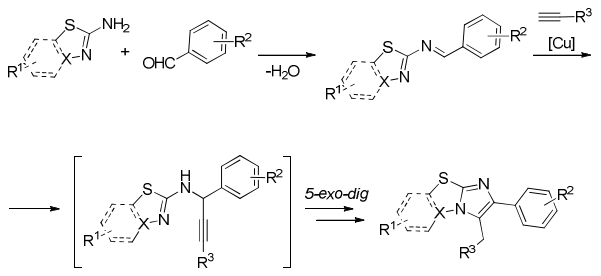


Figure 1. Representative drug or drug candidates containing imidazo[2,1-b]thiazole moieties.

Recently, transition metal-catalyzed three-component coupling of aldehyde, alkyne and amine, commonly called A^3-coupling, has been established as a practical tool in modern organic synthesis.[17] Since the initial reports in 1998 the A^3-coupling[18] has emerged as the most convenient and general approach for the *in situ* generation of labile propargylamine intermediates for cascade heterocyclization.[17,19] Numerous protocols using transition-metal catalysis were developed for functionalized five- and six-membered N,O-heterocycles, e.g. quinolines,[20] imidazopyridines,[21] furans,[22] benzofurans,[23] 1,4-dihydropyridines,[24] pyrroles[25] and oxazoles.[26] However, the use of A^3-coupling in constructing sulfur-containing heterocyclic compounds remains strictly limited.[27] Only two solitary examples of the synthesis of 2-(4-chlorophenyl)-4-phenylthiazolopyrimidine[27a] and 5-benzyl-6-phenylimidazo[2,1-b][1,3]thiazole[27b] were reported. As part of our ongoing synthetic efforts toward imidazoheterocycles,[28] herein we report a general and efficient synthesis of the imidazo[2,1-b]thiazole scaffold by the copper-catalyzed three-component coupling reaction of 2-aminothiazoles with aryl aldehydes and alkynes involving *5-exo-dig* cyclization of an *in situ* generated propargylamine intermediate (Scheme 1). We also demonstrate that the use of continuous-flow technique allows for the full implementation of this transformation, thus providing a more convenient and scalable method.

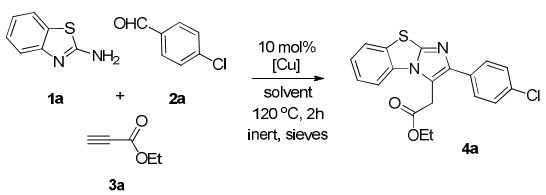
Scheme 1. Proposed approach towards the imidazo[2,1-b]thiazole scaffold



RESULTS AND DISCUSSION

We started our study by optimizing the reaction of 2-aminobenzothiazole (**1a**) with p-chlorobenzaldehyde (**2a**) and ethyl propiolate (**3a**) to prepare imidazo[2,1-b]benzothiazole **4a** (Table 1). In the absence of additives in toluene at 120 ^{o}C, the desired transformation did not occur (Table 1, entry 1). Screening of the *d*-metal catalytic systems (see SI), which hold promise for the heterocyclization to **4a**, revealed superior activity of copper salts (Table 1, entries 2-7). Among others, CuCl, CuOTf•C_6H_6 and $Cu(OTf)_2$ showed promising results, providing the desired product **4a** in 61%, 67%, and 55% yield, respectively (Table 1, entries 2-4). However, the best results were achieved by performing the reaction with the homogeneous catalytic system CuOTf•C_6H_6 (10 mol %)/$Cu(OTf)_2$ (10 mol %) in toluene under an inert atmosphere at 120 ^{o}C. Compound **4a** was obtained in 75% yield in 2 h (Table 1, entry 8). A sharp decrease in the yield was observed in other solvents tested and at a lower temperature (Table 1, entries 10-12), as well as under aerobic conditions (Table 1, entry 9). The structure of imidazo[2,1-b]thiazole **4a** was confirmed by single-crystal X-ray diffraction (see Supporting Information, Figure S1).

Table 1. Optimization of the reaction conditions[a]



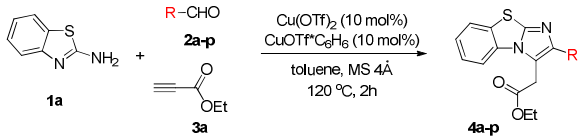
Entry	[Cu]	Solvent	T, ^{o}C	Yield

				4a,%[b]
1	-	Toluene	120	-
2	CuCl	Toluene	120	61
3	$CuOTf{\cdot}C_6H_6$	Toluene	120	67
4	$Cu(OTf)_2$	Toluene	120	55
5	$Cu(OAc)_2{\cdot}H_2O$	Toluene	120	<10
6	$CuI/Cu(OTf)_2$	Toluene	120	56
7	$CuCl/Cu(OTf)_2$	Toluene	120	71
8	**$CuOTf{\cdot}C_6H_6/Cu(OTf)_2$**	**Toluene**	**120**	**75**
9	$CuOTf{\cdot}C_6H_6/Cu(OTf)_2$	Toluene	120	33[c]
10	$CuOTf{\cdot}C_6H_6/Cu(OTf)_2$	Anisole	110	49
11	$CuOTf{\cdot}C_6H_6/Cu(OTf)_2$	MeCN	82	<10
12	$CuOTf{\cdot}C_6H_6/Cu(OTf)_2$	DMSO	120	50

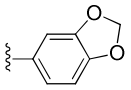
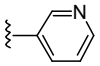
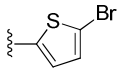
[a)] *Reaction conditions*: amine **1a** (0.20 mmol), aldehyde **2a** (0.22 mmol), ethyl propiolate **2a** (0.4 mmol), Cu salt (10 mol %), 4Å molecular sieves and solvent (1 mL) in a V-shaped vial under an inert atmosphere. [b)] Yield after chromatography. [c)] Reaction was performed in air.

With the optimized conditions in hand, the substrate scope was explored with a variety of aldehydes (Table 2), alkynes (Table 3) and amines (Table 4). It was found that functionally diverse benzaldehydes worked well in the reaction (Table 2, entries 1-14). Both electron-withdrawing groups (2-Cl, 3-Cl, 4-Cl, 2,4-Cl_2, 3,4-Cl_2, 4-F, 4-NO_2, 3-NO_2) and electron-donating groups (3-Me, 4-OMe, 2-OMe, 2,4-$(OMe)_2$) were tolerated under the reaction conditions. Products **4a-n** were isolated in moderate to good yields. Non-functionalized product **4i** was obtained from benzaldehyde in 46% yield (Table 2, entry 9). In addition, a 3-pyridinecarboxaldehyde, as well as 2-thiophenecarboxaldehyde, were tolerated under these reaction conditions (Table 2, entries 15 and 16). Corresponding polyheterocyclic products **4o** and **4p** were obtained in 38% and 61% yields, respectively. Aliphatic aldehydes did not produce the desired products under optimized conditions, which was attributed to side decomposition processes.

Table 2. Scope of aldehydes[a]



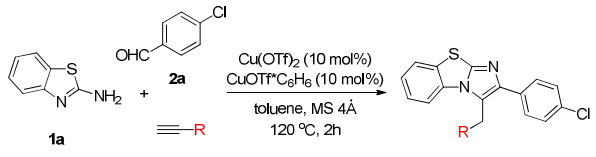
Entry	Compd	R	Yield **4**, %[b]
1	**4a**	4-Cl-C_6H_4	75
2	**4b**	3-Cl-C_6H_4	59
3	**4c**	2-Cl-C_6H_4	60
4	**4d**	2,4-Cl_2-C_6H_3	72
5	**4e**	3,4-Cl_2-C_6H_3	55
6	**4f**	4-F-C_6H_4	48

7	**4g**	4-NO_2-C_6H_4	54
8	**4h**	3-NO_2-C_6H_4	48
9	**4i**	Ph	46
10	**4j**	Tol	52
11	**4k**	4-MeO-C_6H_4	45
12	**4l**	2-MeO-C_6H_4	42
13	**4m**	2,4-$(MeO)_2$-C_6H_3	33
14	**4n**		50
15	**4o**		38
16	**4p**		61

[a)] *Reaction conditions*: amine **1a** (0.2 mmol, 1 equiv), aldehyde **2** (1.1 equiv), alkyne **2a** (2 equiv), CuOTf•C_6H_6 (10 mol %), $Cu(OTf)_2$ (10 mol %), 4Å molecular sieves and toluene (1 mL) in a V-shaped vial under an inert atmosphere for 2 h at 120 °C. [b)] Yield after chromatography.

Furthermore, a number of propiolic acid esters and amides were successfully reacted to yield methylenecarbonyl-substituted imidazo[2,1-b]benzothiazoles **4a,q-s** (Table 3, entries 1-4). Ethynyl isopropyl ketone underwent the reaction giving product **4t** in 65% yield (Table 3, entry 5). 3-(Sulfonylmethyl)imidazo[2,1-b]benzothiazoles **4u-w** were synthesized using alkyl- and aryl-substituted ethynyl sulfones in moderate yields (Table 3, entries 6-8). Aliphatic and aryl alkynes were found to be inefficient for the elaborated transformation under optimized batch conditions. The trace amounts of the products derived from n-butyl- and phenylacetylenes were detected (yields ≤ 5-7%).

Table 3. Scope of alkynes[a]



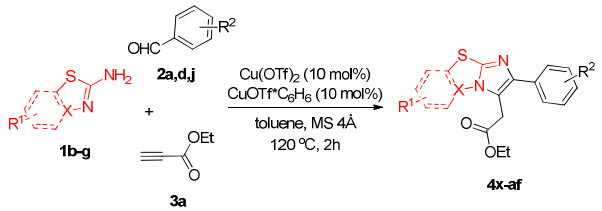
Entry	Compd	R	Yield **4**, %[b]
1	**4a**	CO_2Et	75
2	**4q**	CO_2Me	72
3	**4r**	$CONMe_2$	61
4	**4s**	$CONPr_2$	75
5	**4t**	$COPr^i$	65
6	**4u**	SO_2Me	45
7	**4v**	$SO_2C_6H_4Bu^t$	45

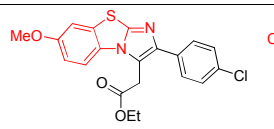
8	**4w**	SO_2Tol	53

[a] *Reaction conditions*: amine **1a** (0.2 mmol, 1 equiv), aldehyde **2a** (1.1 equiv), alkyne **3** (2 equiv), $CuOTf•C_6H_6$ (10 mol %), $Cu(OTf)_2$ (10 mol %), 4Å molecular sieves and toluene (1 mL) in a V-shaped vial under an inert atmosphere for 2 h at 120 °C. [b] Yield after chromatography.

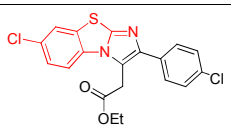
In addition, we were delighted to find that versatile thioamidines including functionalized 2-aminobenzothiazoles, 2-aminothiazole and 2-amino-1,3,4-thiadiazoles underwent smooth reactions (Table 4). Parent imidazo[2,1-b]benzothiazoles **4x** and **4y,** imidazo[2,1-b]thiazoles **4z** and **4aa**, as well as several imidazo[2,1-b][1,3,4]thiadiazoles **4ab-ad**, were obtained in 35-77% yields. However, attempts to perform the reaction of tolyl aldehyde or 4-nitrobenzaldehyde with 2-aminothiazole accompanied by the condensation with ethyl propiolate failed (Table 4, compounds **4ae** and **4af**), as complex mixtures of products were obtained.

Table 4. Scope of heterocyclic thioamidines[a,b]

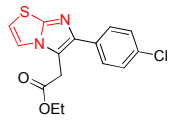




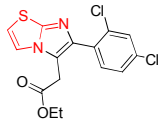
4x, 77%



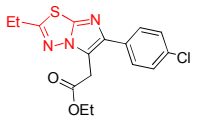
4y, 40%



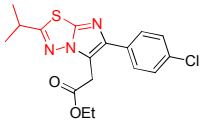
4z, 46%



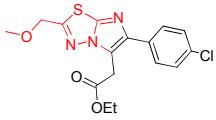
4aa, 60%



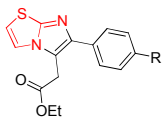
4ab, 55%



4ac, 41%



4ad, 35%



4ae, R = Me, --%
4af, R = NO_2, --%

[a] *Reaction conditions*: amine **1** (0.2 mmol, 1 equiv), aldehyde **2** (1.1 equiv), alkyne **3a** (2 equiv), $CuOTf•C_6H_6$ (10 mol %), $Cu(OTf)_2$ (10 mol %), 4Å molecular sieves and toluene (1 mL) in a V-shaped vial under an inert atmosphere for 2 h at 120 °C. [b] Yield after chromatography.

Therefore, the reaction scope was found to be quite general, and the functional group tolerance is quite good. Conversely, the elaborated batch procedure gives most products **4** in 45-65%

yields. In some cases, the batch protocol proved to be fully inefficient (Table 4, compounds **4ae** and **4af**). These limitations can be overcome by means of intensification of the process. Therefore, we turned to continuous-flow synthesis in the presence of heterogeneous copper(I,II) catalysts, which may overcome disadvantages of the batch synthesis.[29] The improved heat transfer under continuous-flow conditions reduces the effect of side reactions, whereas the back-pressure regulation technology can be used to eliminate solvent boiling, resulting in substantial enhancement of reaction kinetics.[30]

It should be noted that the continuous-flow synthesis of propargylamines *via* A^3-coupling was pioneered by Organ, Li and co-workers.[31] Several examples demonstrated the successful transition from batch to continuous-flow conditions for the heterocyclization of propargylamines, resulting in an increase in the of yield and functional-group compatibility.[32] Meanwhile, the direct formation of imidazoheterocycles *via* A^3-coupling strategy using continuous-flow conditions is still unknown.

The continuous-flow study of the efficient and scalable production of imidazo[2,1-b]thiazoles **4** was performed using pregenerated imines **6** and propiolate **3** (Tables 5,6). The continuous-flow setup is represented in Figure 2 and is fully illustrated in the Supporting Information. A steel column 4.6 mm in diameter and 200 mm in length with steel frits filled with CuI granules (10-100 μm particle size) or a catalyst system consisting of commercially available finely divided CuI (1-4 μm particle size) and 50 μm spherical silica gel in a 1 : 1 ratio was used (see Supporting Information, Figures S2,S3). A mixture of substrates **6** and **3b** in anisole was fed to the column heated up to 200 ^{o}C by a piston pump at a rate of 0.55-1.0 mL min^{-1} and at 15 atm to prevent alkyne external leak using a back-pressure regulator.

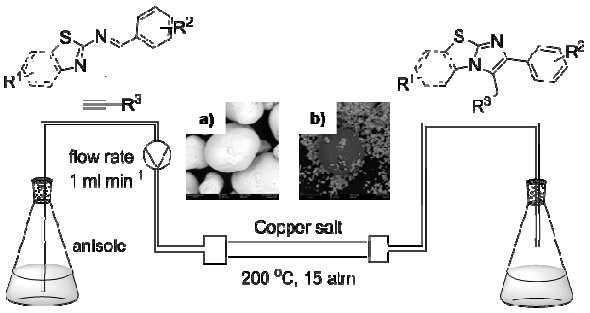
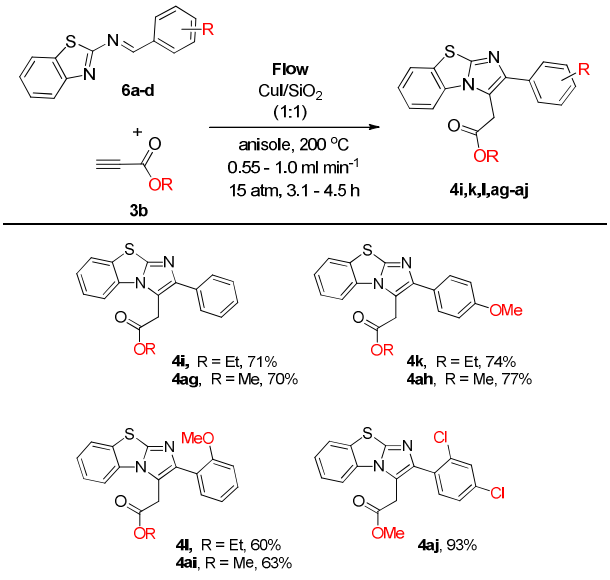


Figure 2. Continuous-flow experimental setup. a) SEM image (20 μm) for granular CuI (10-100 μm particle size), b) SEM image (20 μm) 1 : 1 CuI/SiO_2 mixture (finely-divided CuI 1-4 μm particle size; silica gel particle size 50 μm).

Imidazo[2,1-b]benzothiazoles were synthesized under continuous-flow conditions in the presence of the CuI/SiO_2 catalyst in higher yields compared to the batch mode. Thus, coupling products **4i**, **4k**, and **4l** were isolated in 71%, 74%, and 60% yields, respectively (*continuous-flow*, Table 4) *versus* 46%, 45%, and 42% yields (*batch*, Table 2, entries 9, 11, 12). Additionally, scope of the continuous-flow protocol towards imidazo[2,1-b]benzothiazoles was extended using methyl propiolate **3b** and imines **6a-d** derived from benzaldehyde and its *p*-OMe-, *o*-OMe-, and o,*p*-di-Cl-substituted derivatives. Corresponding products **4ag-4aj** functionalized at the aryl moiety were isolated in 63-93% yields.

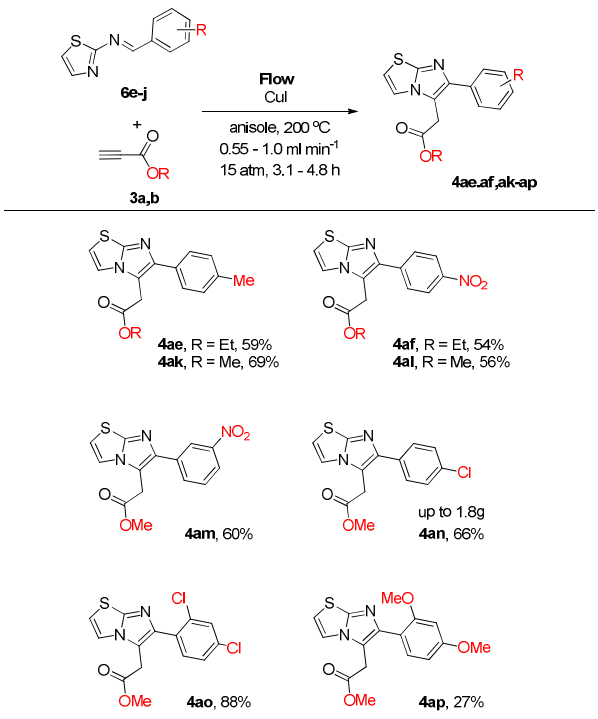
Table 5. Continuous-flow synthesis of imidazo[2,1-b]benzothiazoles[a-c]



[a] *Reaction conditions*: imine **6** (1.0 mmol, 1 equiv), propiolate **3a,b** (3.0 mmol, 3 equiv), CuI/SiO_2 (1:1 ratio, 2.8 g), and anisole (20 mL) at 200 °C at a total flow rate of 0.55-1.0 mL min^{-1} under inert atmosphere. [b] Isolated yield. [c] Product **4aj** was obtained using CuI catalyst.

Moreover, the continuous-flow mode proved to be efficient for imidazo[2,1-b]thiazoles **4ae** and **4af** that are not available under batch conditions (Tables 4,6). The products **4ae** and **4af** were obtained under continuous-flow conditions using CuI granules as the catalyst in 59% and 54% yields, respectively. Closely related imidazo[2,1-b]thiazoles **4ak** and **4al** derived from methyl propiolate **3b** were isolated in 69% and 56% yields. To enhance the diversity of available imidazo[2,1-b]thiazoles, imines **6e-j** derived from 2-aminothiazole and aryl aldehydes containing electron-donating and -withdrawing groups were subjected to the reaction with methyl propiolate **3b** (Table 6). The electron-withdrawing substituents in ortho and para positions, such as Cl and NO_2, provided good/high product yields (56-88% for **4al-ao**). Electron-donating methoxy groups attached to the aryl moiety decreased the yield to 27% (**4ap**). All of these reactions were carried out on a 1.0 mmol scale, but they can easily be scaled-up. Indeed, imidazo[1,2-a]thiazole **4an** was prepared in a yield of 1.8 g on the 9 mmol scale without remarkable reduction in the yield.

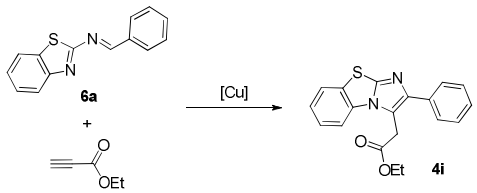
Table 6. Continuous-flow synthesis of imidazo[2,1-b]thiazoles[a,b]



[a] *Reaction conditions*: imine **6** (1.0 mmol, 1 equiv), propiolate **3a,b** (3.0 mmol, 3 equiv), CuI granules (4.2 g), and anisole (20 mL) at 200 °C at a total flow rate of 0.55-1.0 mL min^{-1} under inert atmosphere. [b] Yield after chromatography.

Finally, a direct comparison of the efficiency of the continuous-flow and batch protocols was performed using model condensation of imine **6a** and ethyl propiolate **3a** (Table 7). The yield of the coupling product - imidazo[2,1-b]benzothiazole **4i** - in 2h under batch conditions using $Cu(OTf)_2$ (10 mol%)/$CuOTf{\cdot}C_6H_6$ (10 mol%) and MS 4Å at 120 °C in toluene was equal to the yield of **4i** in the three-component batch protocol (46%, Table 2, entry 9). Attempts to perform the reaction under the same conditions in a continuous-flow experimental setup by passing a mixture of **6a**, **3a** and $Cu(OTf)_2$ (10 mol%)/$CuOTf{\cdot}C_6H_6$ (10 mol%) in toluene through a steel column filled with MS 4Å and preheated to 120 °C failed because of the system obstruction caused by poor solubility of the starting materials. The use of anisole instead of toluene provided dissolution and resulted in the formation of product **4i** in 64% yield (Table 7, entry 1). Notably, the principal result was the same at 1 atm and 15 atm. Therefore, the pressure is not a crucial factor for the cyclization efficiency. The highest yield of product **4i** was achieved under continuous-flow conditions using a steel column filled with CuI/SiO_2 at 200 °C (71%, Tables 5,7). The complete conversion was achieved in 3.1 h by passing a solution of **6a** and **3a** in anisole through the "catalyst" column at 15 atm to avoid alkyne boiling. On the contrary, the reaction performed under batch conditions in anisole in the presence of CuI/SiO_2 (3 eqiuv, 1:1 mixture) in a sealed microreactor vial at 200 °C gave compound **4i** in ≤10% yield, which can be attributed to the side decomposition processes.

Table 7. Continuous-flow *vs* batch conditions



Entry	Reaction conditions	Yield **4i**, %[c]	
		Batch mode	*Continuous-flow mode*
1[a]	$Cu(OTf)_2$ (10 mol%) $CuOTf{*}C_6H_6$ (10 mol%) toluene, MS 4Å 120 °C, 2 h	46	0 reactions in anisole 64[d] (1 atm) 61[d] (15 atm)
2[b]	CuI/SiO_2 (1:1) anisole, 200 °C, 3.1 h	≤10	71

[a] *Batch protocol*: imine **6a** (50 mg, 0.2 mmol, 1 equiv), ethyl propiolate **3a** (44 mg, 2 equiv), $CuOTf{\cdot}C_6H_6$ (10 mg, 10 mol %), $Cu(OTf)_2$ (7 mg, 10 mol %), 4Å molecular sieves and toluene (1 mL) in a V-shaped vial under an inert atmosphere for 2 h at 120 °C.
Continuous-flow protocol: imine **6a** (240 mg, 1.0 mmol, 1 equiv), ethyl propiolate **3a** (290 mg, 3.0 mmol, 3 equiv), CuI/SiO_2 (1:1 ratio, 2.8 g), and solvent (20 mL) at 120 °C at a total flow rate of 0.55 mL min^{-1} under inert atmosphere.

[b] *Batch protocol*: imine **6a** (50 mg, 0.2 mmol, 1 equiv), ethyl propiolate **3a** (44 mg, 2 equiv), CuI/SiO_2 (1:1 ratio, 230 mg), and anisole (1 mL) in a V-shaped vial under an inert atmosphere for 3.1 h at 200 °C.
Continuous-flow protocol: imine **6a** (240 mg, 1.0 mmol, 1 equiv), ethyl propiolate **3a** (290 mg, 3.0 mmol, 3 equiv), CuI/SiO_2 (1:1 ratio, 2.8 g), and anisole (20 mL) at 15 atm at 200 °C at a total flow rate of 0.55 mL min^{-1} under inert atmosphere.
[c] Yield after chromatography. [d] Yields determined by HPLC analysis.

These experiments clearly indicated that the homogeneous catalytic system $Cu(OTf)_2/CuOTf{\cdot}C_6H_6$ found for the batch mode and heterogeneous CuI-based catalytic systems proposed for the continuous-flow mode are not interchangeable. Moreover, the yields of the target coupling products were increased only in the continuous-flow mode.

CONCLUSION

In conclusion, we investigated the copper-catalyzed three-component coupling reaction of 2-aminothiazoles with aldehydes and alkynes yielding imidazo[2,1-b]thiazoles under batch and continuous-flow conditions. The coupling products were obtained in higher yields in continuous flow. To the best of our knowledge, this is the first application of the continuous-flow technology to the copper-catalyzed condensation of alkynes with imines, derived from heterocyclic thioamidines with aldehydes, allowing for synthesis of a variety of substituted imidazoheterocycles. The reactions are easy to conduct, and the functional group tolerance is quite good. High efficiency, excellent atom economy and a wide availability of reagents imply that an extensive range of substituents can be selectively incorporated into the imidazo[2,1-b]thiazole ring.

EXPERIMENTAL SECTION

General information

NMR spectra were acquired on Bruker Avance 600, 300 spectrometers at room temperature; the chemical shifts δ were measured in ppm relative to the solvent (^{1}H: $CDCl_3$, δ = 7.27 ppm; ^{13}C: $CDCl_3$, δ = 77.00 ppm). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; ddd, double double doublet. The coupling constants (J) are in Hertz. The structures of compounds were established using 1D NMR (^{1}H, ^{13}C, JMOD) and

2D NMR (^{1}H-^{1}H COSY, ^{13}C-^{1}H HSQC) spectroscopy. High-resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) in positive ion mode (interface capillary voltage 4500 V); the mass range was from m/z 50 to 3000 Da; external/internal calibration was performed using an electrospray calibration solution. Syringe injection was used for solutions in CH_3CN (flow rate 3 mL/min). Nitrogen was applied as the dry gas. The interface temperature was set at 180 ^{o}C. Scanning electron microscope (SEM) images were recorded on a Phenom Prox electron microscope (Phenom, Netherlands) operating at 15 kV. The melting points (mp) are uncorrected and were measured on a Boetius capillary melting point apparatus. Analytical thin-layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F254 aluminum supported plates); the visualization was accomplished with an UV lamp (365 nm). All commercial reagents and solvents were used without additional purification. Reactions were performed in 2 mL glass V-shaped vials (Wheaton Scientific) and monitored by TLC with GF 254 silica gel coated plates. Column chromatography was performed on neutral aluminum oxide (Brockmann II, pH 9-10) or silica gel 60 (230-400 mesh) treated with 1% triethylamine solution in petroleum benzene. Flash chromatography was performed using automated flash chromatography system equipped with an HP-Silica 15 μm column. Parent N,N-dipropyl- and N,N-dimethylpropiolamides were prepared according to the published procedure.[33] Ethynyl sulfones[34] and ethynyl isopropyl ketone[35] were prepared by known methods. Schiff bases were prepared by the condensation of 2-aminothiazoles with aldehydes.[36]

Typical experimental procedures

Batch procedure: A screw-capped V-shaped vial (2.0 mL) was charged with 2-aminothiazole (0.2 mmol, 1.0 equiv), aldehyde (0.22 mmol, 1.1 equiv), freshly activated 4Å molecular sieves (150 mg) and dry toluene (1.5 mL). The vial was capped with a pressure cap and stored at 120 ^{o}C for 14-24 h until complete consumption of 2-aminothiazole (monitored by ^{1}H NMR). The resulting mixture containing imine was cooled to room temperature and the solvent was removed under reduced pressure. Under inert atmosphere, the reside was redissolved in dry toluene (1

mL) and then CuOTf·C_6H_6 (10 mg, 0.02 mmol, 10 mol %), $Cu(OTf)_2$ (7 mg, 0.02 mmol, 10 mol %), alkyne (0.4 mmol, 2 equiv) and 4Å molecular sieves (100 mg) were added. The reaction mixture was additionally stirred in the vial capped with a pressure cap at 120 ^oC for 2 h. After the completion of the reaction, the mixture was filtered through a plug of neutral aluminum oxide (eluent – EtOAc). The filtrate was concentrated under reduced pressure to give a crude material, which was purified by column chromatography on silica gel (eluent Et_3N:EtOAc/petroleum ether) or neutral aluminum oxide (eluent EtOAc/petroleum ether) to give product.

Continuous flow procedure: A solution of imine (1.0 mmol, 1 equiv) and methyl propiolate (270 μL, 3.0 mmol, 3 equiv) in dry anisole (20 mL) was delivered to a catalyst cartridge (200 mm length, 4.6 mm diameter) charged with CuI granules (4.2 g) or CuI/SiO_2 (1:1 ratio, 2.8 g) heated at 200 °C at a total flow rate of 0.55-1.0 mL min^{-1}, equating to a residence time of about 100-220 min. A 15 atm back-pressure regulator was applied to the system. The solvent was removed under reduced pressure and the product was purified by silica gel flash column chromatography (eluent hexane/EtOAc).

*Ethyl [2-(4-chlorophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4a**).* Yield 75% (56 mg, batch procedure), yellow solid, mp 100-102 °C; R_f = 0.20 (petroleum ether - EtOAc, 5:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.07 1H), 7.71-7.73 (m, 3H), 7.43-7.48 (m, 3H), 7.37 (dd, *J* = 7.33, 8.07 Hz, 1H), 4.29 (q, *J* = 7.33 Hz, 2H), 4.19 (s, 2H), 1.30 (t, *J* = 7.33 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (CO), 147.7 (C), 144.9 (C), 133.7 (C), 133.0 (C), 132.2 (C), 130.4 (C), 129.2 (2×CH), 128.8 (2×CH), 126.1 (CH), 124.8 (CH), 124.4 (CH), 117.1 (C), 113.1 (CH), 61.9 (CH_2), 31.7 (CH_2), 14.2 (CH_3); IR (KBr) 3433 (w), 1727 (s), 1495 (s), 1366 (s), 1254 (s), 1088 (s), 1030 (s), 828 (s), 743 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}ClN_2O_2S^+$ 371.0616; Found 371.0617.

*Ethyl [2-(3-chlorophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4b**).* Yield 59% (43 mg, batch procedure), yellow solid, mp 86-88 °C; R_f = 0.20 (petroleum ether - EtOAc, 5:1). ^1H

NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.67 Hz, 1H), 7.80 (s, 1H), 7.70 (d, *J* = 7.27 Hz, 1H) 7.64 (dd, *J* = 1.67, 7.32 Hz, 1H), 7.31-7.45 (m, 4H), 4.28 (q, *J* = 7.26 Hz, 2H), 4.18 (s, 2H), 1.29 (t, *J* = 7.26 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (CO), 147.8 (C), 144.7 (C), 135.8 (C), 134.6 (C), 133.0 (C), 130.5 (C), 129.9 (CH), 128.0 (CH), 127.7 (CH), 126.1 (CH), 126.0 (CH), 124.8 (CH), 124.4 (CH), 117.4 (C), 113.2 (CH), 62.0 (CH_2), 31.8 (CH_2), 14.2 (CH_3); IR (KBr) 2981 (s), 1735 (s), 1599 (s), 1495 (s), 1370 (s), 1199 (s), 1094 (s), 1028 (s), 790 (s), 747 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}ClN_2O_2S^+$ 371.0616; Found 371.0609.

*Ethyl [2-(2-chlorophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4c**).* Yield 60% (44 mg, batch procedure), yellow solid, mp 124-126 °C; R_f = 0.20 (petroleum ether - EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.33 Hz, 1H), 7.68 (d, *J* = 8.24 Hz, 1H), 7.55-7.58 (m, 1H), 7.48-7.51 (m, 1H), 7.41 (dd, *J* = 7.33, 8.24 Hz, 1H), 7.31-7.36 (m, 3H), 4.18 (q, *J* = 7.39 Hz, 2H), 4.02 (s, 2H), 1.21 (t, *J* = 7.39 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (CO), 147.5 (C), 143.5 (C), 134.0 (C), 133.1 (C), 132.8 (CH+C), 130.5 (C), 130.0 (CH), 129.6 (CH), 126.8 (CH), 126.0 (CH), 124.7 (CH), 124.4 (CH), 118.7 (C), 113.1 (CH), 61.6 (CH_2), 31.6 (CH_2), 14.2 (CH_3); IR (KBr) 3453 (w), 2974 (s), 1737 (s), 1581 (s), 1492 (s), 1364 (s), 1186 (s), 1027 (s), 768 (s), 746 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}ClN_2O_2S^+$ 371.0616; Found 371.0606.

*Ethyl [2-(2,4-dichlorophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4d**).* Yield 72% (58 mg, batch procedure), yellow solid, mp 114-116 °C; R_f = 0.37 (petroleum ether - EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.33 Hz, 1H), 7.69 (d, *J* = 8.24 Hz, 1H), 7.53 (s, 1H), 7.50 (d, *J* = 8.24 Hz, 1H), 7.35-7.47 (m, 3H), 4.19 (q, *J* = 7.33 Hz, 2H), 4.00 (s, 2H), 1.22 (t, *J* = 7.33 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3 (CO), 147.6 (C), 142.3 (C), 134.8 (C), 134.6 (C), 133.4 (CH), 132.8 (C), 131.3 (C), 130.3 (C), 129.6 (CH), 127.1 (CH), 126.0 (CH), 124.7 (CH), 124.3 (CH), 118.9 (C), 113.0 (CH), 61.6 (CH_2), 31.5 (CH_2), 14.1 (CH_3); IR (KBr) 3426 (w), 2985 (s), 1717 (s), 1552 (s), 1492 (s), 1331 (s), 1210 (s), 1030 (s), 818 (s), 748 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{15}Cl_2N_2O_2S^+$ 405.0226; Found 405.0215.

*Ethyl [2-(3,4-dichlorophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4e**).* Yield 55% (44 mg, batch procedure), yellow solid, mp 132-135 °C; R_f = 0.40 (petroleum ether - EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 1.65 Hz, 1H), 7.87 (d, *J* = 8.20 Hz, 1H), 7.71 (d, *J* = 7.92 Hz, 1H) 7.61 (dd, *J* = 1.65, 8.47 Hz, 1H), 7.50 (d, *J* = 8.47 Hz, 1H) 7.44 (dd, *J* = 8.20 Hz, 1H), 7.35 (dd, *J* = 7.92 Hz, 1H), 4.29 (q, *J* = 7.33 Hz, 2H), 4.17 (s, 2H), 1.31 (t, *J* = 7.33 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4 (CO), 147.9 (C), 143.7 (C), 134.0 (C), 132.8 (C), 132.7 (C), 131.6 (C), 130.5 (CH), 130.4 (C), 129.6 (CH), 127.0 (CH), 126.2 (CH), 125.0 (CH), 124.5 (CH), 117.5 (C), 113.2 (CH), 62.0 (CH_2), 31.7 (CH_2), 14.2 (CH_3); IR (KBr) 3435 (w), 2975 (s), 1726 (s), 1492 (s), 1371 (s), 1245 (s), 1199 (s), 1150 (s) 1026 (s), 737 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{14}Cl_2N_2O_2SNa^+$ 427.0045; Found 427.0035.

*Ethyl [2-(4-fluorophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4f**).* Yield 48% (33 mg, batch procedure), yellow solid, mp 86-87 °C; R_f = 0.22 (petroleum ether - EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68-7.81 (m, 4H), 7.41 (dd, *J* = 7.76 Hz, 1H), 7.32 (dd, *J* = 7.76 Hz, 1H), 7.15 (dd, *J* = 8.52 Hz, 2H), 4.28 (q, *J* = 7.33 Hz, 2H), 4.16 (s, 2H), 1.28 (t, *J* = 7.33 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8 (CO), 162.5 (d, $J_{C\text{-}F}$ = 247.1 Hz, C), 147.5 (C), 145.2 (C), 133.0 (C), 130.3 (C), 130.1 (d, $J_{C\text{-}F}$ = 3.2 Hz, C), 129.7 (d, $J_{C\text{-}F}$ = 8.0 Hz, 2×CH), 126.1 (CH), 124.6 (CH), 124.4 (CH), 116.7 (C), 115.5 (d, $J_{C\text{-}F}$ = 21.4 Hz, 2×CH), 113.0 (CH), 61.8 (CH_2), 31.7 (CH_2), 14.2 (CH_3); IR (KBr) 3435 (w), 2948 (w), 1726 (s), 1504 (s), 1487 (s), 1210 (s), 751 (w) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}FN_2O_2S^+$ 355.0911; Found 355.0912.

*Ethyl [2-(4-nitrophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4g**).* Yield 54% (41 mg, batch procedure), yellow solid, mp 162-164 °C; R_f = 0.20 (petroleum ether - EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J* = 9.16 Hz, 2H), 7.97 (d, *J* = 9.16 Hz, 2H), 7.88 (d, *J* = 8.24 Hz, 1H), 7.74 (d, *J* = 7.33 Hz, 1H), 7.47 (dd, *J* = 7.33, 7.89 Hz, 1H), 7.38 (dd, *J* = 7.89, 8.24 Hz, 1H), 4.30 (q, *J* = 7.32 Hz, 2H), 4.23 (s, 2H), 1.30 (t, *J* = 7.32 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3 (CO), 148.4 (C), 147.0 (C), 143.8 (C), 140.5 (C), 132.8 (C), 130.6 (C),

128.3 (2×CH), 126.3 (CH), 125.2 (CH), 124.6 (CH), 124.0 (2×CH), 118.8 (C), 113.3 (CH), 62.2 (CH_2), 32.0 (CH_2), 14.3 (CH_3); IR (KBr) 3425 (w), 1742 (s), 1515 (s), 1497 (s), 1339 (s), 1190 (w), 1158 (w), 745 (w) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}N_3O_4S^+$ 382.0856; Found 382.0843.

*Ethyl [2-(3-nitrophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4h**).* Yield 48% (37 mg, batch procedure), yellow solid, mp 153-156 °C; R_f = 0.32 (petroleum ether - EtOAc, 5:1). ^1H NMR (300 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.23 (d, *J* = 8.24 Hz, 1H), 8.18 (d, *J* = 8.24 Hz, 1H), 7.95 (d, *J* = 8.24 Hz, 1H), 7.76 (d, *J* = 8.24 Hz, 1H), 7.65 (dd, *J* = 8.24 Hz, 1H), 7.49 (dd, *J* = 8.24 Hz, 1H), 7.40 (dd, *J* = 8.24 Hz, 1H), 4.33 (q, *J* = 7.27 Hz, 2H), 4.23 (s, 2H), 1.34 (t, *J* = 7.27 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4 (CO), 148.7 (C), 148.3 (C), 143.8 (C), 135.8 (C), 134.0 (CH), 133.0 (C), 130.6 (C), 129.7 (CH), 126.4 (CH), 125.2 (CH), 124.6 (CH), 122.6 (CH), 122.4 (CH), 118.1 (C), 113.3 (CH), 62.3 (CH_2), 32.0 (CH_2), 14.2 (CH_3); IR (KBr) 3444 (w), 2922 (s), 1732 (s), 1526 (s), 1493 (s), 1349 (s), 1206 (s), 1152 (s), 748 (w) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}N_3O_4S^+$ 382.0856; Found 382.0851.

*Ethyl (2-phenylimidazo[2,1-b][1,3]benzothiazol-3-yl)acetate (**4i**).* Yield 46% (31 mg, batch procedure); yield 71% (238 mg, continuous flow procedure, residence time 3.5 h, flow rate 0.85 mL min^{-1}, CuI/SiO_2 1:1 mixture), yellow solid, mp 80-82 °C; R_f = 0.20 (petroleum ether - EtOAc, 5:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.70-7.81 (m, 4H), 7.47 (dd, *J* = 7.64 Hz, 3H), 7.31-7.41 (m, 2H), 4.27 (q, *J* = 7.12 Hz, 2H), 4.21 (s, 2H), 1.28 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (CO), 147.6 (C), 146.0 (C), 134.0 (C), 133.2 (C), 130.5 (C), 129.1 (2×CH), 128.7 (2×CH), 127.8 (CH), 126.1 (CH) 124.7 (CH), 124.5 (CH), 117.0 (C), 113.1 (CH), 61.8 (CH_2), 31.8 (CH_2), 14.2 (CH_3); IR (KBr) 3433 (w), 2980 (s), 1721 (s), 1582 (s), 1498 (s), 1198 (s), 1014 (s), 739 (w) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_2S^+$ 337.1005; Found 337.1001.

*Ethyl [2-(4-methylphenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4j**).* Yield 52% (36 mg, batch procedure), yellow solid, mp 74-77 °C; R_f = 0.23 (petroleum ether - EtOAc, 4:1). ^1H

NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.05 Hz, 1H), 7.79 (d, *J* = 7.53 Hz, 1H), 7.86 (d, *J* = 8.05 Hz, 2H), 7.43 (dd, *J* = 7.53 Hz, 1H), 7.36 (dd, *J* = 8.05 Hz, 1H), 7.29 (d, *J* = 8.05 Hz, 2H), 4.28 (q, *J* = 7.29 Hz, 2H), 4.21 (s, 2H), 2.42 (s, 3H), 1.29 (s, *J* = 7.29 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0 (CO), 147.5 (C), 146.2 (C), 137.5 (C), 133.2 (C), 131.1 (C), 130.5 (C), 129.4 (2×CH), 128.0 (2×CH), 126.0 (CH), 124.5 (CH), 124.4 (CH), 116.7 (C), 113.0 (CH), 62.0 (CH_2), 31.9 (CH_2), 21.3 (CH_3), 14.2 (CH_3); IR (KBr) 3386 (w), 2922 (s), 1734 (s), 1509 (s), 1487 (s), 1195 (s), 1195 (w), 1158 (s), 746 (w) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_2S^+$ 351.1162; Found 351.1165.

*Ethyl [2-(4-methoxyphenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4k**).* Yield 45% (37 mg, batch procedure), yield 74% (271 mg, continuous flow procedure, residence time 4.1 h, flow rate 0.55 mL min^{-1}, CuI/SiO_2 1:1 mixture), yellow solid, mp 90-92 °C; R_f = 0.32 (petroleum ether - EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.25 Hz, 1H), 7.75 (d, *J* = 8.25 Hz, 1H), 7.69 (d, *J* = 8.24 Hz, 2H), 7.46 (dd, *J* = 7.33, 8.24 Hz, 1H), 7.27 (dd, *J* = 7.33, 8.24 Hz, 1H), 7.02 (d, *J* = 8.24 Hz, 2H), 4.28 (q, *J* = 7.32 Hz , 2H), 4.19 (s, 2H), 3.87 (s, 3H), 1.28 (t, *J* = 7.32 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (CO), 159.6 (C), 134.9 (C), 133.1 (C), 132.4 (C), 130.5 (C), 129.5 (2×CH), 126.3 (CH),125.6 (C), 124.9 (CH), 124.6 (CH), 116.4 (C), 114.3 (2×CH), 113.1 (CH), 61.9 (CH_2), 55.4 (OCH_3), 31.9 (CH_2), 14.3 (CH_3); IR (KBr) 2980 (w), 1725 (s), 1509 (s), 1487 (s), 1252 (s), 1196 (s), 1170 (s), 1018 (w), 835 (w), 740 (w) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_3S^+$ 367.1111; Found 367.1102.

*Ethyl [2-(2-methoxyphenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4l**).* Yield 42% (31 mg, batch procedure), yield 60% (220 mg, continuous flow procedure, residence time 4.1 h, flow rate 0.55 mL min^{-1}, CuI/SiO_2 1:1 mixture), yellow solid, mp 175-177 °C; R_f = 0.34 (petroleum ether - EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.49 Hz, 1H), 7.62 (d, *J* = 8.49 Hz, 2H), 7.28-7.42 (m, 3H), 7.07 (dd, *J* = 7.36 Hz, 1H), 7.00 (d, *J* = 8.49 Hz, 1H), 4.20 (q, *J* = 7.32 Hz, 2H), 4.04 (s, 2H), 3.79 (s, 3H), 1.22 (t, *J* = 7.32 Hz, 3H); ^{13}C NMR (75

MHz, $CDCl_3$): δ 170.1 (CO), 156.5 (C), 147.3 (C), 142.2 (C), 133.2 (C), 132.0 (CH), 130.5 (C), 129.5 (CH), 126.0 (CH), 124.4 (CH), 124.3 (CH), 123.0 (C), 121.0 (CH), 118.8 (C), 113.0 (CH), 111.3 (CH), 61.3 (CH_2), 55.6 (OCH_3), 31.9 (CH_2), 14.2 (CH_3); IR (KBr) 3436 (w), 1724 (s), 1500 (s), 1366 (s), 1253 (s), 1026 (s), 753 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_3S^+$ 367.1111; 367.1106.

*Ethyl [2-(2,4-dimethoxyphenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4m**).* Yield 33% (26 mg, batch procedure), yellow solid, mp 88-90 °C; R_f = 0.31 (petroleum ether - EtOAc, 4:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.07 Hz, 1H), 7.75 (d, *J* = 7.34 Hz, 1H), 7.47 (dd, *J* = 7.34 Hz, 1H), 7.30-7.40 (m, 3H), 6.98 (d, *J* = 8.07 Hz, 1H), 4.29 (q, *J* = 7.34 Hz, 2H), 4.22 (s, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 1.29 (t, *J* = 7.34 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8 (CO), 149.3 (C), 149.2 (C), 147.3 (C), 144.9 (C), 133.0 (C), 130.4 (C), 126.3 (CH), 125.8 (C), 125.0 (CH), 124.9 (CH), 120.4 (CH), 116.5 (C), 113.3 (CH), 111.5 (CH), 111.3 (CH), 61.9 (CH_2), 56.1 (OCH_3), 56.0 (OCH_3), 31.9 (CH_2), 14.2 (CH_3); IR (KBr) 2978 (w), 1733 (s), 1510 (s), 1487 (s), 1253 (s), 1022 (w), 750 (w) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{21}N_2O_4S^+$ 397.1217; Found 397.1212.

*Ethyl [2-(1,3-benzodioxol-5-yl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4n**).* Yield 50% (37 mg, batch procedure), yellow solid, mp 79-81 °C; R_f = 0.32 (petroleum ether - EtOAc, 4:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.07 Hz, 1H), 7.70 (d, *J* = 7.34 Hz, 1H), 7.42 (dd, *J* = 7.34, 8.07 Hz, 1H), 7.33 (dd, *J* = 7.34, 8.07 Hz, 1H), 7.21-7.28 (m, 2H), 6.90 (d, *J* = 8.07 Hz, 1H), 6.01 (s, 2H), 4.28 (q, *J* = 7.33 Hz, 2H), 4.18 (s, 2H), 1.29 (t, *J* = 7.33 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (CO), 147.9 (C), 147.3 (C), 146.0 (C), 133.1 (C), 130.4 (C), 128.1 (C), 126.0 (CH), 124.5 (CH), 124.4 (CH), 121.8 (CH), 116.4 (C), 112.9 (CH), 110.1 (C), 108.7 (CH), 108.5 (CH), 101.2 (CH_2), 61.8 (CH_2), 31.8 (CH_2), 14.2 (CH_3); IR (KBr) 2978 (w), 2905 (w), 1723 (s), 1496 (s), 1254 (s), 1235 (s), 1036 (s), 752 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{17}N_2O_4S^+$ 381.0904; Found 381.0895.

*Ethyl (2-pyridin-3-ylimidazo[2,1-b][1,3]benzothiazol-3-yl)acetate (**4o**).* Yield 38% (29 mg, batch procedure), yellow solid, mp 84-86 °C; R_f = 0.20 (petroleum ether - EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.62 (d, *J* = 3.88 Hz, 1H), 8.13 (d, *J* = 8.06 Hz, 1H), 7.84 (d, *J* = 8.06 Hz, 1H), 7.74 (d, *J* = 8.06 Hz, 1H), 7.35-7.49 (m, 3H), 4.29 (q, *J* = 7.25 Hz, 2H), 4.21 (s, 2H), 1.30 (t, *J* = 7.25 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4 (CO), 148.6 (2×CH), 148.2 (C), 142.9 (C), 135.6 (CH), 133.0 (C), 130.5 (C), 130.1 (C), 126.3 (CH), 125.0 (CH), 124.5 (CH), 123.7 (C), 117.8 (CH), 113.1 (CH), 62.0 (CH_2), 31.7 (CH_2), 14.2 (CH_3); IR (KBr) 3437 (s), 2926 (w), 1728 (s), 1492 (s), 1299 (s), 1208 (s), 1023 (s), 754 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{16}N_3O_2S^+$ 338.0958; Found 338.0950.

*Ethyl [2-(5-bromo-2-thienyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4p**).* Yield 61% (52 mg, batch procedure), yellow solid, mp 77-79 °C; R_f = 0.30 (petroleum ether - EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.16 Hz, 1H), 7.70 (d, *J* = 7.63 Hz, 1H), 7.44 (dd, *J* = 7.63, 8.16 Hz, 1H), 7.34 (dd, *J* = 7.63 Hz, 1H), 7.15 (d, *J* = 3.86 Hz, 1H), 7.05 (d, *J* = 3.82 Hz, 1H), 4.25 (q, *J* = 7.63 Hz, 2H), 4.21 (s, 2H), 1.27 (t, *J* =7.63 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1 (CO), 147.8 (C), 139.5 (C), 138.4 (C), 132.8 (C), 130.5 (CH), 130.4 (C), 126.2 (CH), 125.0 (CH), 124.5 (CH), 124.4 (CH), 116.5 (C), 113.1 (CH), 112.2 (C), 62.0 (CH_2), 31.8 (CH_2), 14.2 (CH_3); IR (KBr) 2974 (s), 1729 (s), 1487 (s), 1189 (s), 818 (s), 747 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{14}BrN_2O_2S_2^+$ 422.9654; Found 422.9666.

*Methyl [2-(4-chlorophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4q**).* Yield 72% (51 mg, batch procedure), yellow solid, mp 122-124 °C (mp_{lit} 124-126 °C[37]); R_f = 0.35 (petroleum ether - EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.10 Hz, 1H), 7.67-7.63 (m, 3H), 7.42-7.47 (m, 3H), 7.35 (dd, *J* = 7.32, 8.46 Hz, 1H), 4.20 (s , 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1 (CO), 147.7 (C), 144.8 (C), 133.7 (C), 133.0 (C), 132.2 (C), 130.5 (C), 129.2 (2×CH), 128.8 (2×CH), 126.3 (CH), 124.8 (CH), 124.5 (CH), 116.9 (C), 112.9 (CH), 52.9 (CH_2), 31.5 (CH_3); IR (KBr) 3432 (w), 1723 (s), 1496 (s), 1331 (s), 1210 (s), 1092 (s),

1012 (s), 834 (s), 750 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{14}ClN_3OS^+$ 357.0459; Found 357.0459.

2-[2-(4-Chlorophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]-N,N-dimethylacetamide ***(4r)***. Yield 61% (45 mg, batch procedure), yellow solid, mp 229-231 °C; R_f = 0.32 (petroleum ether - EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.12 Hz, 1H), 7.53-7.58 (m, 3H), 7.37-7.42 (m, 3H), 7.31 (dd, *J* = 7.33, 8.12 Hz, 1H), 4.17 (s, 2H), 3.15 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4 (CO), 147.6 (C), 144.5 (C), 133.4 (C), 133.1 (C), 132.8 (C), 130.5 (C), 129.4 (2×CH), 128.8 (2×CH), 126.1 (CH), 124.6 (CH), 124.3 (CH), 118.5 (C), 113.1 (CH), 37.5 (CH_2), 36.1 (CH_3), 30.8 (CH_2); IR (KBr) 3436 (w), 2924 (s), 1655 (s), 1497 (s), 1391 (s), 1128 (s), 1009 (s), 828 (s), 742 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}ClN_3OS^+$ 370.0775; Found 370.0770.

2-[2-(4-Chlorophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]-N,N-dipropylacetamide ***(4s)***. Yield 75% (63 mg, batch procedure), yellow solid, mp 85-87 °C; R_f = 0.32 (petroleum ether - EtOAc, 4:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.34 Hz, 1H), 7.55 (d, *J* = 8.07 Hz, 1H), 7.54 (d, *J* = 8.07 Hz, 2H), 7.40 (d, *J* = 8.07 Hz, 2H), 7.37 (dd, *J* = 8.07 Hz, 1H), 7.29 (dd, *J* = 7.34, 8.07 Hz, 1H), 4.17 (s, 2H), 3.32-3.42 (m, 4H), 1.57-1.71 (m, 4H), 0.90-0.98 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0 (CO), 147.5 (C), 144.5 (C), 133.4 (C), 133.2 (C), 133.0 (C), 130.4 (C), 129.3 (2×CH), 128.7 (2×CH), 125.9 (CH), 124.5 (CH), 124.3 (CH), 118.8 (C), 113.1 (CH), 49.9 (CH_2), 48.1 (CH_2), 30.9 (CH_2), 22.3 (CH_2), 21.0 (CH_2), 11.4 (CH_3), 11.3 (CH_3); IR (KBr) 3435 (w), 2960 (s), 1640 (s), 1497 (s), 1462 (s), 829 (s), 743 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}ClN_3OS^+$ 426.1401; Found 426.1394.

1-[2-(4-Chlorophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]-3-methylbutan-2-one ***(4t)***. Yield 65% (48 mg, batch procedure), yellow solid, mp 153-154 °C; R_f = 0.32 (petroleum ether - EtOAc, 4:1). ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.57 Hz, 1H), 7.47 (d, *J* = 8.44 Hz, 2H), 7.37 (d, *J* = 8.44 Hz, 2H), 7.36-7.38 (m, 1H), 7.32 (dd, *J* = 7.57, 8.07 Hz, 1H),7.28 (dd, *J* = 7.57, 8.07 Hz, 1H), 4.28 (s, 2H), 2.76-2.81 (m, 1H), 1.14 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$): δ 210.1 (CO), 147.7 (C), 144.7 (C), 133.5 (C), 133.0 (C), 132.7 (C), 130.4 (C), 129.1 (2×CH), 128.8 (2×CH), 126.0 (CH), 124.6 (CH), 124.4 (CH), 117.6 (C), 112.6 (CH), 40.2 (CH), 37.8 (CH_2), 18.4 (2×CH_3); IR (KBr) 3408 (w), 2975 (s), 1712 (s), 1495 (s), 1364 (s), 1308 (s), 1086 (s), 1041 (s), 828 (s), 748 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{18}ClN_2OS^+$ 369.0823; Found 369.0818.

2-(4-Chlorophenyl)-3-[(methylsulfonyl)methyl]imidazo[2,1-b][1,3]benzothiazole ***(4u)***. Yield 45% (33 mg, batch procedure), yellow solid, mp 243-245 °C; R_f = 0.32 (petroleum ether - EtOAc, 4:1). ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.24 Hz, 1H), 7.72 (d, *J* = 7.33 Hz, 1H), 7.70 (d, *J* = 9.16 Hz, 2H), 7.46 (d, *J* = 9.16 Hz, 2H), 7.45-7.51 (m, 1H), 7.38 (dd, *J* = 7.33, 8.24 Hz, 1H), 4.95 (s, 2H), 2.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.4 (C), 147.6 (C), 134.6 (C), 133.0 (C), 131.8 (C), 130.3 (C), 129.4 (2×CH), 129.3 (2×CH), 126.3 (CH), 125.4 (CH), 124.4 (CH), 114.4 (CH), 111.8 (C), 51.3 (CH_2), 39.9 (CH_3); IR (KBr) 3426 (w), 2925 (w), 1499 (s), 1461 (s), 1306 (s), 1137 (s), 746 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{14}ClN_2O_2S_2^+$ 377.0180; Found 377.0168.

3-{[(4-Tert-butylphenyl)sulfonyl]methyl}-2-(4-chlorophenyl)imidazo[2,1-b][1,3]benzothiazole ***(4v)***. Yield 45% (44 mg, batch procedure), yellow solid, mp 175-176 °C; R_f = 0.26 (petroleum ether - EtOAc, 5:1). ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.26 Hz, 1H), 7.73 (d, *J* = 8.26 Hz, 1H), 7.49 (d, *J* = 8.81 Hz, 2H), 7.47-7.53 (m, 1H), 7.40 (dd, *J* = 7.33, 8.26 Hz, 1H), 7.22-7.34 (m, 6H), 5.07 (s, 2H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4 (C), 149.9 (C), 147.5 (C), 134.4 (C), 133.9 (C), 133.0 (C), 131.5 (C), 130.2 (C), 128.9 (2×CH), 128.7 (2×CH), 128.3 (2×CH), 126.2 (3×CH), 125.2 (CH), 124.3 (CH), 114.7 (CH), 112.4 (C), 53.0 (CH_2), 35.3 (C), 31.0 (3×CH_3); IR (KBr) 3424 (w), 2965 (s), 1494 (s), 1317 (s), 1154 (s), 1107 (s), 1013 (s), 837 (s), 747 (s) 501 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{24}ClN_2O_2S_2^+$ 495.0962; Found 495.0955.

2-(4-Chlorophenyl)-3-{[(4-methylphenyl)sulfonyl]methyl}imidazo[2,1-b][1,3]benzothiazole ***(4w)***. Yield 53% (48 mg, batch procedure), yellow solid mp 122-125 °C; R_f = 0.20 (petroleum

ether - EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.11 Hz, 1H), 7.72 (d, *J* = 7.34 Hz, 1H), 7.50 (dd, *J* = 7.34, 8.11 Hz, 1H), 7.36-7.42 (m, 3H), 7.20-7.27 (m, 4H), 7.06 (d, *J* = 8.07 Hz, 2H), 5.04 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.7 (C), 147.4 (C), 145.4 (C), 134.3 (C), 133.7 (C), 133.0 (C), 131.5 (C), 130.1 (C), 129.7 (2×CH), 128.9 (2×CH), 128.4 (2×CH), 128.2 (2×CH), 126.2 (CH), 125.2 (CH), 124.2 (CH), 114.6 (CH), 112.4 (C), 52.8 (CH_2), 21.6 (CH_3); IR (film) 3402 (w), 2923 (w), 1596 (s), 1493 (s), 1321 (s), 1166 (s), 1143 (s), 1085 (s), 1011 (s), 886 (s), 754 (s) 547 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{18}ClN_2O_2S_2^+$ 453.0493; Found 453.0486.

*Ethyl [2-(4-chlorophenyl)-7-methoxyimidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4x**).* Yield 77% (62 mg, batch procedure), yellow solid, mp 159-163 °C; R_f = 0.33 (petroleum ether - EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.80 Hz, 1H), 7.70 (d, *J* = 8.07 Hz, 2H), 7.42 (d, *J* = 8.07 Hz, 2H), 7.21 7.06 (d, *J* = 1.47 Hz, 1H), 6.99 (dd, *J* = 1.47, 8.80 Hz, 1H), 4.27 (q, *J* = 7.34 Hz, 2H), 4.13 (s, 2H), 3.86 (s, 3H), 1.28 (t, *J* = 7.34 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (CO), 157.0 (C), 147.0 (C), 144.3 (C), 133.4 (C), 132.5 (C), 131.8 (C), 129.1 (2×CH), 128.8 (2×CH), 127.2 (C), 116.9 (C), 113.6 (CH), 113.2 (CH), 108.9 (CH), 61.9 (CH_2), 56.0 (CH_3), 31.6 (CH_2), 14.2 (CH_3); IR (KBr) 3452 (w), 2914 (w), 1734 (s), 1496 (s), 1372 (s), 1203 (s), 825(s), 797 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{18}ClN_2O_3S^+$ 401.0721; Found 401.0720.

*Ethyl [7-chloro-2-(4-chlorophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4y**).* Yield 40% (32 mg, batch procedure), yellow solid, mp 188-190 °C; R_f = 0.32 (petroleum ether - EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.24 Hz, 1H), 7.68-7.70 (m, 3H), 7.40-7.45 (m, 3H), 4.27 (q, *J* = 7.32 Hz, 2H), 4.14 (s, 2H), 1.29 (t, *J* = 7.32 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5 (CO), 147.5 (C), 145.4 (C), 133.9 (C), 132.2 (C), 131.9 (C), 131.6 (C), 130.4 (CH), 129.2 (2×CH), 128.8 (2×CH), 126.4 (CH), 124.2 (CH), 117.3 (C), 113.9 (CH), 62.0 (CH_2), 31.6 (CH_2), 14.2 (CH_3); IR (KBr) 3430(w), 3430 (w), 2988 (s), 1725 (s), 1498 (s), 1317

(s), 1213 (s), 832 (s), 803 (s); HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{15}Cl_2N_2O_2S^+$ 405.0226; Found 405.0240.

*Ethyl [6-(4-chlorophenyl)imidazo[2,1-b][1,3]thiazol-5-yl]acetate (**4z**).* Yield 46% (29 mg, batch procedure), yellow solid, mp 111-112 °C; R_f = 0.22 (petroleum ether - EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.81 Hz, 2H), 7.53 (d, *J* = 4.41 Hz, 1H), 7.44 (d, *J* = 8.81 Hz, 2H), 6.89 (d, *J* = 4.41 Hz, 1H), 4.23 (q, *J* = 7.33 Hz, 2H), 3.91 (s, 2H), 1.30 (t, *J* = 7.33 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3 (CO), 149.2 (C), 144.4 (C), 133.3 (C), 132.9 (C), 129.0 (2×CH), 128.9 (2×CH), 117.9 (CH), 114.5 (C), 112.6 (CH), 61.7 (CH_2), 31.6 (CH_2), 14.3 (CH_3); IR (KBr) 2982 (w), 1734 (s), 1488 (w), 1468 (w), 1249 (w), 1188 (w), 836 (w), 756 (w) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}ClN_2O_2S^+$ 321.0459; Found 321.0452.

*Ethyl [6-(2,4-dichlorophenyl)imidazo[2,1-b][1,3]thiazol-5-yl]acetate (**4aa**).* Yield 60% (43 mg, batch procedure), yellow solid, mp 80-82 °C; R_f = 0.22 (petroleum ether - EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.50 (m, 3H), 7.32 (dd, *J* = 2.20, 8.76 Hz, 1H), 6.88 (d, *J* = 4.40 Hz, 1H), 4.17 (q, *J* = 7.37 Hz, 2H), 3.76 (s, 2H), 1.25 (t, *J* = 7.37 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1 (CO), 149.2 (C), 141.7 (C), 134.6 (C), 134.3 (C), 133.4 (CH), 131.7 (C), 129.7 (CH), 127.2 (CH), 118.2 (CH), 116.7 (C), 112.7 (CH), 61.5 (CH_2), 31.3 (CH_2), 14.1 (CH_3); IR (KBr) 2981 (w), 1734 (s), 1545 (s), 1476 (s), 1366 (s), 1189 (s), 1100 (s), 826 (s), 763 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{13}Cl_2N_2O_2S$ 355.0069; Found 355.0078.

*Ethyl [6-(4-chlorophenyl)-2-ethylimidazo[2,1-b][1,3,4]thiadiazol-5-yl]acetate (**4ab**).* Yield 55% (38 mg, batch procedure), yellow solid, mp 125-127 °C; R_f = 0.32 (petroleum ether - EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.24 Hz, 2H), 7.38 (d, *J* = 8.24 Hz, 2H), 4.20 (q, *J* = 7.32 Hz, 2H), 4.03 (s, 2H), 3.02 (q, *J* = 7.33 Hz, 2H), 1.41 (t, *J* = 7.32 Hz, 3H), 1.24 (t, *J* = 7.33 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3 (CO), 153.9 (C), 142.5 (C), 133.2 (C), 132.9 (C), 128.7 (2×CH), 128.4 (2×CH), 116.3 (C), 106.7 (C), 61.4 (CH_2), 30.7 (CH_2), 25.7 (CH_2), 14.1 (CH_3), 13.1 (CH_3); IR (KBr) (w), 2936 (w), 1738 (s), 1493 (s), 1253 (w), 1191 (w),

836 (w)cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{17}ClN_3O_2S^+$ 350.0725; Found 350.0719.

*Ethyl [6-(4-chlorophenyl)-2-isopropylimidazo[2,1-b][1,3,4]thiadiazol-5-yl]acetate (**4ac**).* Yield 41% (30 mg, batch procedure), yellow solid, mp 137-138 °C; R_f = 0.32 (petroleum ether - EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.20 Hz, 2H), 7.40 (d, *J* = 8.20 Hz, 2H), 4.22 (q, *J* = 7.24 Hz, 2H), 4.06 (s, 2H), 3.29-3.38 (m,1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.25 (t, *J* = 7.24 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9 (CO), 169.4 (C), 144.0 (C), 142.4 (C), 133.3 (C), 133.0 (C), 128.8 (2×CH), 128.5 (2×CH), 116.3 (CH), 61.5 (CH_2), 32.5 (CH), 30.8 (CH_2), 22.3 (2×CH_3), 14.2 (CH_3); IR (film) 3436 (w), 2977 (s), 1738 (s), 1493 (s), 1192 (s), 1092 (s), `1029 (s), 836 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}ClN_3O_2S^+$ 364.0881; Found 364.0871.

*Ethyl [6-(4-chlorophenyl)-2-(methoxymethyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]acetate (**4ad**).* Yield 35% (26 mg, batch procedure), yellow solid, mp 109-112 °C; R_f = 0.20 (petroleum ether - EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.75 Hz, 2H), 7.41 (d, *J* = 8.75 Hz, 2H), 4.75 (s, 2H), 4.22 (q, *J* = 7.28 Hz, 2H), 4.06 (s, 2H), 3.51 (s, 3H), 1.27 (t, *J* = 7.28 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1 (CO), 162.8 (C), 144.4 (C), 142.8 (C), 133.5 (C), 132.8 (C), 128.8 (2×CH), 128.6 (2×CH), 116.4 (C), 69.4 (CH_2), 61.6 (CH_2), 59.2 (CH_3), 30.6 (CH_2), 14.1 (CH_3); IR (film) 2982 (s), 1731 (s), 1492 (s), 1190 (s), 1095 (s), 1032 (s), 835 (s) 723 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{17}ClN_3O_3S^+$ 368.0645; Found 368.0644.

*Ethyl [6-(4-methylphenyl)imidazo[2,1-b][1,3]thiazol-5-yl]acetate (**4ae**).* Yield 59% (177 mg, continuous flow procedure, residence time 3.6 h, flow rate 1.0 mL min^{-1}, CuI, 10-100μm), yellow solid, mp 60-61 °C; R_f = 0.56 (hexane - EtOAc, 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.95 Hz, 2H), 7.51 (d, *J* = 4.41 Hz, 1H), 7.27 (d, *J* = 7.95 Hz, 2H), 6.83 (d, *J* = 4.41 Hz, 1H), 4.23 (q, *J* = 7.09 Hz, 2H), 3.93 (s, 2H), 2.41 (s, 3H), 1.30 (t, *J* = 7.09 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.9 (CO), 148.4 (C), 144.9 (C), 136.6 (C), 130.7 (C), 128.7

(2×CH), 127.1 (2×CH), 117.3 (CH), 113.5 (C), 111.5 (CH), 60.9 (CH_2), 31.0 (CH_2), 20.6 (CH_3), 13.5 (CH_3); IR (KBr) 3445 (w), 2979 (s), 2917 (s), 1737 (s), 1548 (s), 1465 (s), 1375 (s), 1320 (s), 1179 (s), 1157 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{17}N_2O_2S^+$ 301.1005; Found 301.1007.

*Ethyl [6-(4-nitrophenyl)imidazo[2,1-b][1,3]thiazol-5-yl]acetate (**4af**).* Yield 54% (179 mg, continuous flow procedure, residence time 3.3 h, flow rate 1.0 mL min^{-1}, CuI, 10-100μm), yellow solid, mp 159-160 °C; R_f = 0.58 (hexane - EtOAc, 1:2). ^1H NMR (600 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.92 Hz, 2H), 7.96 (d, *J* = 8.92 Hz, 2H), 7.57 (d, *J* = 4.52 Hz, 1H), 6.95 (d, *J* = 4.52 Hz, 1H), 4.26 (q, *J* = 7.22 Hz, 2H), 3.98 (s, 2H), 1.32 (t, *J* = 7.22 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.8 (CO), 149.9 (C), 146.8 (C), 143.1 (C), 140.8 (C), 128.0 (2×CH), 124.0 (2×CH), 117.8 (CH), 116.3 (C), 113.6 (CH), 62.0 (CH_2), 31.8 (CH_2), 14.2 (CH_3); IR (KBr) 3434 (w), 3118 (s), 1727 (s), 1598 (s), 1507 (s), 1468 (s), 1338 (s), 1314 (s), 1239 (s), 1086 (s), 852 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}N_3O_4S^+$ 332.0700; Found 332.0705.

*Methyl (2-phenylimidazo[2,1-b][1,3]benzothiazol-3-yl)acetate (**4ag**).* Yield 70% (222 mg, continuous flow procedure, residence time 3.5 h, flow rate 0.85 mL min^{-1}, CuI/SiO_2 1:1 mixture), yellow solid, mp 82-83 °C (mp_{lit} 75-76 °C[37] for **7b***H_2O); R_f = 0.43 (hexane - EtOAc, 2:1). ^1H NMR (600 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.12 Hz, 1H), 7.73-7.75 (m, 3H), 7.44-7.50 (m, 3H), 7.35-7.40 (m, 2H), 4.25 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.4 (CO), 147.6 (C), 146.1 (C), 133.9 (C), 133.1 (C), 130.5 (C), 128.7 (2×CH), 128.0 (2×CH), 127.8 (CH), 126.2 (CH) 124.6 (CH), 124.5 (CH), 116.7 (C), 112.9 (CH), 52.8 (CH_2), 31.6 (CH_3); IR (KBr) 3436 (w), 2954 (s), 1728 (s), 1498 (s), 1216 (s), 1156 (s), 738 (s), 701 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O_2S^+$ 323.0849; Found 323.0845.

*Methyl [2-(4-methoxyphenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4ah**).* Yield 77% (271 mg, continuous flow procedure, residence time 4.1 h, flow rate 0.55 mL min^{-1}, CuI/SiO_2 1:1 mixture), yellow solid, mp 134-136 °C (mp_{lit} 130-131 °C[37]); R_f = 0.49 (hexane - EtOAc, 1:1). ^1H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.11 Hz, 1H), 7.72 (d, *J* = 7.33 Hz, 1H), 7.68 (d, *J* =

8.70 Hz, 2H), 7.44 (dd, *J* = 7.33, 8.11 Hz, 1H), 7.34 (dd, *J* = 7.33, 8.11 Hz, 1H), 7.02 (d, , *J* = 8.70 Hz, 2H), 4.21 (s, 2H), 3.87 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.5 (CO), 159.3 (C), 147.4 (C), 146.0 (C), 133.2 (C), 130.4 (C), 129.3 (2×CH), 126.5 (C), 126.1 (CH), 124.5 (CH), 124.4 (CH), 116.0 (C), 114.1 (2×CH), 112.7 (CH), 55.3 (OCH_3), 52.8 (CH_3), 31.6 (CH_2); IR (KBr) 3401 (w), 2951 (s), 1732 (s), 1510 (s), 1490 (s), 1252 (s), 1176 (s), 1028 (s), 833 (s), 745 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_3S^+$ 353.0954; Found 353.0938.

*Methyl [2-(2-methoxyphenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4ai**).* Yield 63% (222 mg, continuous flow procedure, residence time 4.1 h, flow rate 0.55 mL min^{-1}, CuI/SiO_2 1:1 mixture), yellow solid, mp 78-79 °C; R_f = 0.44 (hexane - EtOAc, 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 0.91, 8.01 Hz, 1H), 7.64 (dd, *J* = 1.77, 7.56 Hz, 1H), 7.61 (dd, *J* = 1.15, 8.04 Hz, 1H), 7.42 (ddd, *J* = 0.91, 7.81, 8.04 Hz, 1H), 7.38 (ddd, *J* = 1.77, 7.44, 8.35 Hz, 1H), 7.34 (ddd, *J* = 1.15, 7.81, 8.01 Hz, 1H), 7.09 (ddd, *J* = 0.80, 7.44, 7.56 Hz, 1H), 7.02 (dd, *J* = 0.80, 8.35 Hz, 1H), 4.07 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.7 (CO), 156.4 (C), 147.4 (C), 142.3 (C), 133.2 (C), 131.9 (CH), 130.5 (C), 129.5 (CH), 126.0 (CH), 124.4 (CH), 124.3 (CH), 122.9 (C), 121.0 (CH), 118.6 (C), 112.8 (CH), 111.2 (CH), 55.6 (CH_3), 52.4 (CH_3), 31.7 (CH_2); IR (KBr) 3401 (w), 2950 (s), 1735 (s), 1499 (s), 1483 (s), 1246 (s), 1164 (s), 1020 (s), 750 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_3S^+$ 353.0954; Found 353.0943.

*Methyl [2-(2,4-dichlorophenyl)imidazo[2,1-b][1,3]benzothiazol-3-yl]acetate (**4aj**).* Yield 93% (359 mg, continuous flow procedure, residence time 3.3 h, flow rate 1.0 mL min^{-1}, CuI, 10-100μm), yellow solid, mp 154-155 °C; R_f = 0.41 (hexane - EtOAc, 2:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.07 Hz, 1H), 7.68 (d, *J* = 8.43 Hz, 1H), 7.55 (d, *J* = 1.83 Hz, 1H), 7.50 (d, *J* = 8.43 Hz, 1H), 7.46 (dd, *J* = 7.33, 8.43 Hz, 1H), 7.38 (dd, *J* = 7.33, 8.43 Hz, 1H), 7.36 (dd, *J* = 1.83, 8.07 Hz, 1H), 4.04 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.9 (CO), 147.7 (C), 142.5 (C), 134.9 (C), 134.6 (C), 133.4 (CH), 133.0 (C), 131.3 (C), 130.5 (C),

129.7 (CH), 127.2 (CH), 126.2 (CH), 124.8 (CH), 124.5 (CH), 118.7 (C), 112.9 (CH), 52.6 (CH_3), 31.3 (CH_2); IR (KBr) 3434 (w), 2948 (s), 1721 (s), 1493 (s), 1210 (s), 819 (s), 749 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{13}Cl_2N_2O_2S^+$ 391.0069; Found 391.0061.

*Methyl [6-(4-methylphenyl)imidazo[2,1-b][1,3]thiazol-5-yl]acetate (**4ak**).* Yield 69% (198 mg, continuous flow procedure, residence time 3.6 h, flow rate 1.0 mL min^{-1}, CuI, 10-100μm), yellow solid, mp 67-69 °C; R_f = 0.52 (hexane - EtOAc, 1:1). ^1H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.44 Hz, 2H), 7.52 (d, *J* = 4.32 Hz, 1H), 7.28 (d, *J* = 7.44 Hz, 2H), 6.87 (d, *J* = 4.32 Hz, 1H), 3.96 (s, 2H), 3.78 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.0 (CO), 149.1 (C), 143.7 (C), 137.4 (C), 131.2 (C), 129.4 (2×CH), 127.7 (2×CH), 117.9 (CH), 114.0 (C), 112.4 (CH), 52.6 (CH_3), 31.3 (CH_2), 21.3 (CH_3); IR (KBr) 3401 (w), 2952 (s), 2925 (s), 1721 (s), 1686 (s), 1636 (s), 1373 (s), 1305 (s), 1165 (s), 804 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{15}N_2O_2S^+$ 287.0849; Found 287.0848.

*Methyl [6-(4-nitrophenyl)imidazo[2,1-b][1,3]thiazol-5-yl]acetate (**4al**).* Yield 56% (178 mg, continuous flow procedure, residence time 3.3 h, flow rate 1.0 mL min^{-1}, CuI, 10-100μm), yellow solid, mp 194-195 °C; R_f = 0.54 (hexane - EtOAc, 1:2). ^1H NMR (600 MHz, $CDCl_3$): δ 8.35 (d, *J* = 8.73 Hz, 2H), 7.97 (d, *J* = 8.73 Hz, 2H), 7.64 (d, *J* = 4.51 Hz, 1H), 7.08 (d, *J* = 4.51 Hz, 1H), 4.03 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.9 (CO), 149.6 (C), 147.2 (C), 141.5 (C), 139.0 (C), 128.3 (2×CH), 124.2 (2×CH), 118.1 (CH), 116.3 (CH), 114.8 (C), 53.0 (CH_2), 31.4 (CH_3); IR (KBr) 3438 (w), 3114 (s), 1729 (s), 1600 (s), 1507 (s), 1467 (s), 1342 (s), 1225 (s), 1202 (s), 1088 (s), 996 (s), 860 (s), 852 (s), 725 (s), 667 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{12}N_3O_4S^+$ 318.0543; Found 318.0539.

*Methyl [6-(3-nitrophenyl)imidazo[2,1-b][1,3]thiazol-5-yl]acetate (**4am**).* Yield 60% (190 mg, continuous flow procedure, residence time 3.3 h, flow rate 1.0 mL min^{-1}, CuI, 10-100μm), yellow solid, mp 102-103 °C; R_f = 0.55 (hexane - EtOAc, 1:2). ^1H NMR (600 MHz, $CDCl_3$): δ 8.64 (dd, *J* = 1.84 Hz, 1H), 8.19 (ddd, *J* = 1.84, 2.27, 8.08 Hz, 1H), 8.11 (ddd, *J* = 1.84, 2.27,

8.08 Hz, 1H), 7.63 (dd, *J* = 8.08 Hz, 1H), 7.57 (d, *J* = 4.52 Hz, 1H), 6.96 (d, *J* = 4.52 Hz, 1H), 3.99 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.3 (CO), 149.6 (C), 148.6 (C), 142.8 (C), 135.7 (C), 133.5 (CH), 129.7 (CH), 122.5 (CH), 122.2 (CH), 117.9 (CH), 115.4 (C), 113.6 (CH), 52.8 (CH_3), 31.3 (CH_2); IR (KBr) 3435 (w), 3119 (s), 1733 (s), 1526 (s), 1467 (s), 1349 (s), 1251 (s), 698 (s), 661(s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{12}N_3O_4S^+$ 318.0543; Found 318.0534.

*Methyl [6-(4-chlorophenyl)imidazo[2,1-b][1,3]thiazol-5-yl]acetate (**4an**).* Yield 66% (202 mg, continuous flow procedure, residence time 3.3 h, flow rate 1.0 mL min^{-1}, CuI, 10-100μm), yellow solid, mp 123-124 °C; R_f = 0.68 (hexane - EtOAc, 1:3). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.78 Hz, 2H), 7.53 (d, *J* = 4.53 Hz, 1H), 7.43 (d, *J* = 8.78 Hz, 2H), 6.89 (d, *J* = 4.53 Hz, 1H), 3.94 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.7 (CO), 149.3 (C), 144.4 (C), 133.5 (C), 132.6 (C), 129.0 (2×CH), 128.7 (2×CH), 117.9 (CH), 114.4 (C), 112.8 (CH), 52.7 (CH_2), 31.4 (CH_3); IR (KBr) 3451 (w), 3114 (s), 2955 (s), 1735 (s), 1488 (s), 1465 (s), 1221 (s), 1201 (s), 1130 (s), 1091 (s), 716 (s), 663 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{12}ClN_2O_2S^+$ 307.0303; Found 307.0296.

*Methyl [6-(2,4-dichlorophenyl)imidazo[2,1-b][1,3]thiazol-5-yl]acetate (**4ao**).* Yield 88% (299 mg, continuous flow procedure, residence time 3.3 h, flow rate 1.0 mL min^{-1}, CuI, 10-100μm), yellow solid, mp 142-143 °C; R_f = 0.51 (hexane - EtOAc, 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52 (d, *J* = 2.20 Hz, 1H), 7.50 (d, *J* = 4.52 Hz, 1H) 7.48 (d, *J* = 8.07 Hz, 1H), 7.34 (dd, *J* = 2.20, 8.07 Hz, 1H), 6.91 (d, *J* = 4.52 Hz, 1H), 3.79 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.6 (CO), 149.3 (C), 141.9 (C), 134.7 (C), 134.3 (C), 133.4 (CH), 131.6 (C), 129.7 (CH), 127.2 (CH), 118.1 (CH), 116.4 (C), 112.7 (CH), 52.4 (CH_3), 31.0 (CH_2); IR (KBr) 3449 (w), 3113 (s), 1736 (s), 1549 (s), 1477 (s), 1324 (s), 1204 (s), 824 (s), 762 (s), 654 (s) cm^{-1}; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}Cl_2N_2O_2S^+$ 340.9913; Found 340.9902.

*Methyl [6-(2,4-dimethoxyphenyl)imidazo[2,1-b][1,3]thiazol-5-yl]acetate (**4ap**).* Yield 27% (90 mg, continuous flow procedure, residence time 4.8 h, flow rate 0.55 mL min^{-1}, 80 atm, 140 ^{o}C,

CuI, 10-100μm), yellow solid, mp 91-93 °C; R_f = 0.29 (hexane - EtOAc, 1:2). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50-7.51 (m, 2H), 6.93 (br.s, 1H), 6.63 (dd, *J* = 2.30, 8.36 Hz, 1H), 6.56 (d, *J* = 2.30 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 2H), 3.80 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.1 (CO), 161.3 (C), 157.6 (CH), 153.3 (C), 148.4 (C), 132.3 (CH), 118.2 (CH), 116.0 (C), 113.1 (C), 105.0 (CH), 98.8 (CH), 55.6 (CH_3), 55.5 (CH_3), 52.4 (CH_3), 31.2 (CH_2) (the signal of the one C atom was not observed); HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{17}N_2O_4S^+$ 333.0904; Found 333.0897.

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Notes

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: Optomization of reaction conditions, continuous-flow experimental setup and copies of NMR (^{1}H, ^{13}C, ^{1}H-^{1}H COSY, ^{13}C-^{1}H HSQC) spectra for **4a-ap** (PDF)

X-ray crystallographic data for compound **4a** (CIF)

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