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CuCl/air-mediated oxidative coupling reaction of imidazoheterocycles with *N*-aryl glycine esters†

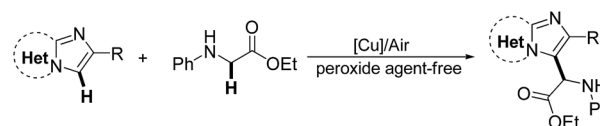
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A copper/air mediated oxidative coupling reaction of imidazoheterocycles with *N*-aryl glycine esters is here described. The reaction proceeded effectively under an air atmosphere without the use of peroxide agents. This simple protocol allows for the preparation of a wide range of imidazoheterocycles with a glycine ester motif, which are of great interest in the field of medicinal chemistry. Interestingly, the coupling of imidazo[1,2-*a*]pyridine with secondary or tertiary α -amino phenylethanone selectively affords the imidazo[1,2-*a*]pyridin-3-yl imine or imidazo[1,2-*a*]pyridin-3-yl diketone in the presence of CuCl and TBHP (tertbutyl hydroperoxide).

Introduction

Glycine is a major protein component and one of the most important natural amino acids in living organisms. It has a wide range of biological and physiological properties.¹ Glycine esters are particularly useful building blocks for the construction of a variety of biological molecules.² We envisioned that the coupling of glycine ester with imidazoheterocycles can produce intriguing molecules for drug screening because imidazoheterocycles are promising drug skeletons with a broad spectrum of biological activity, including antitumor, antiviral, antifungal, and antibacterial activity.^{3,4} Considerable effort has been devoted to the introduction of many different pharmacophores (such as thiol,⁵ thiocyanate,⁶ dithiocarbamyl,⁷ phosphonyl,⁸ trifluoromethyl,⁹ trifluoromethylthiol,¹⁰ and esters¹¹) onto imidazoheterocycles. The coupling of imidazoheterocycles to glycine ester not only affords useful biological applications but also contributes to synthetic chemistry. However, the coupling of imidazole heterocycles to glycine esters has not yet been studied.

The C-H oxidative cross-coupling strategy is an ideal route for the coupling of imidazole heterocycles with glycine esters. In recent years, there has been more interest in the study of the oxidative cross-coupling reaction in organic chemistry.¹² Increasing attention has been paid to the oxidative C-H functionalization at the α -position of *N*-arylglycine ester.^{13,14} The oxidative cross-coupling of glycine esters under oxidant-free conditions and the use of oxygen rather than stoichiometric



Scheme 1 Oxidative coupling of imidazoheterocycles with glycine esters.

peroxide agent is desirable.¹⁴ For example, in 2014, Huo and coauthors reported an auto-oxidative cross-coupling reaction of glycine derivatives and short peptides in a simple mixed organic solvent under mild reaction conditions.^{14c} Wu *et al.* reported a visible light catalysis-assisted coupling reaction of α -amino acids with β -keto esters or indole derivatives in the absence of oxidant.^{14b} Huang *et al.* developed a novel cross-coupling reaction between methylquinoline derivatives and *N*-arylglycine esters by a cooperative catalysis of copper salt and Brønsted acid.^{14d} It has been demonstrated that imidazoheterocycles can capture a trifluoromethyl free radical initiated by TBHP.⁹ It is here reasoned that the coupling of imidazoheterocycles to glycine esters may be carried out *via* an oxidative free radical process. However, imidazopyridines may encounter an oxidative ring opening in the presence of TBHP at 120 °C.¹⁵ In this way, the development of a TBHP-free protocol for the coupling of imidazoheterocycles with glycine esters under mild conditions is desirable. Herein, we report a copper/air-mediated oxidative coupling of imidazoheterocycles to glycine esters in the absence of peroxide agent (Scheme 1).

Results and discussion

The current investigation began with the coupling of imidazopyridine **1a** with glycine ester **2a** for the optimization of reaction conditions (Table 1). Several copper catalysts such as CuI, CuBr,

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† Electronic supplementary information (ESI) available: Copies of ¹H and ¹³C spectra for all compounds. See DOI: 10.1039/c7ra05303g



Table 1 Screening of optimal conditions^a

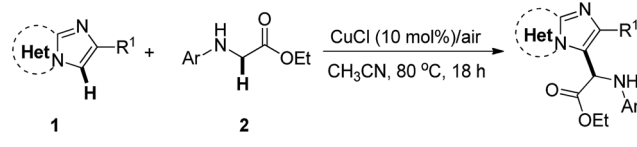

Entry	[Cu]	Oxidant	Solvent	T (°C)	Isolated yield (%)
1	CuI	—	CH ₃ CN	80	40
2	CuBr	—	CH ₃ CN	80	51
3	CuCl	—	CH ₃ CN	80	78
4	Cu(OAc) ₂	—	CH ₃ CN	80	0
5	CuCl	—	DCE	80	65
6	CuCl	—	EtOH	80	46
7	CuCl	—	DMF	80	43
8	CuCl	—	1,4-Dioxane	80	8
9	CuCl	—	Toluene	80	24
10 ^b	CuCl	—	CH ₃ CN	80	76
11 ^c	CuCl	—	CH ₃ CN	80	56
12	—	—	CH ₃ CN	80	0
13	CuCl	—	CH ₃ CN	60	52
14	CuCl	—	CH ₃ CN	100	67
15 ^d	CuCl	—	CH ₃ CN	80	NR
16 ^e	CuCl	O ₂	CH ₃ CN	80	75
17 ^f	CuCl	TBHP	CH ₃ CN	80	78
18	CuCl	H ₂ O ₂	CH ₃ CN	80	0
19	CuCl	K ₂ S ₂ O ₈	CH ₃ CN	80	Trace
20	CuCl	Oxone	CH ₃ CN	80	40

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Cu] (10 mol%), oxidant (2 equiv.), solvent (2 mL), reaction for 18 h under air atmosphere. ^b CuCl (5 mol%). ^c CuCl (1 mol%). ^d Under N₂ (1 atm). ^e Under O₂ (1 atm). ^f TBHP (5.5 mol L⁻¹ in decane).

CuCl, and Cu(OAc)₂ were evaluated in CH₃CN at 80 °C (entries 1–4). The reactivity sequence of copper halides is CuCl > CuBr > CuI. The reaction with 10 mol% of CuCl proceeded well in air, giving product **3** in 78% yield (entry 3). Unexpectedly, Cu(OAc)₂ did not work and no product **3** was observed, though some of substrate **2a** was converted into ethyl 2-oxo-2-(phenylamino) acetate (entry 4). Next, several other solvents including EtOH, DMF, 1,4-dioxane, and toluene were examined. All of these solvents also worked, but were less effective than CH₃CN (entries 5–9). It was shown that the reduction of CuCl loading to 5 mol% led to a slight decrease in the yield of product **3** (76% yield, entry 10). The reaction with 1 mol% of CuCl was still carried out to give product **3** in 56% yield (entry 11). In the absence of CuCl, the reaction could not be carried out (entry 12). The results showed that either decreasing or elevating the temperature led to a decrease in the yield to some extent, e.g. 52% yield at 60 °C and 67% yield at 100 °C (entries 13 and 14). The reaction could not take place in an N₂ atmosphere, suggesting that the O₂ in the air is crucial to the transformation (entry 15). Encouraged by this result, an attempt was made to increase the product yield of the reaction that took place under O₂. However, the product yield was not increased (entry 16). These results suggest that the O₂ in the air is sufficient to induce

the transformation. Next, several oxidants such as TBHP, H₂O₂, K₂S₂O₈, and oxone (2KHSO₅·KHSO₄·K₂SO₄) were investigated with 10 mol% of CuCl in CH₃CN at 80 °C (entries 17–20). The reaction with TBHP and CuCl gave product **3** in 78% yield (entry 17). Other oxidants inhibited this reaction, leading to a decrease in the yield or inhibition of the reaction entirely (entries 18–20).

The scope for the reaction of imidazoheterocycles with *N*-arylglycine esters **2** was investigated with these optimized reaction conditions (Table 1, entry 3; Table 2). Results showed that the current oxidative coupling reaction was suitable to a wide range of imidazopyridines and imidazothiazoles (products **3–26**). The synthetically valuable functional groups on the pyridine ring (such as halo and methoxy groups) were well tolerated. For example, the substrate with a bromo group on the pyridine ring underwent the reaction smoothly and produced the desired product **7** at a yield of 84%. The hydroxyl group

Table 2 The scope of reaction^a


1	3, 78%	4, 76%	5, 75%	6, 74%
7, 84%	8, 80%	9, 82%	10, 65%	
11, 68%	12, 84%	13, 80%	14, 65%	
15, 88%	16, 42%	17, 75%	18, 56%	
19, 34%	20, 73%	21, 68%	22, 61%	
23, 63%	24, 85%	25, 63%	26, 56%	

^a Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol, 1.5 equiv.), CuCl (10 mol%), and CH₃CN (2 mL) at 80 °C for 18 h under air.



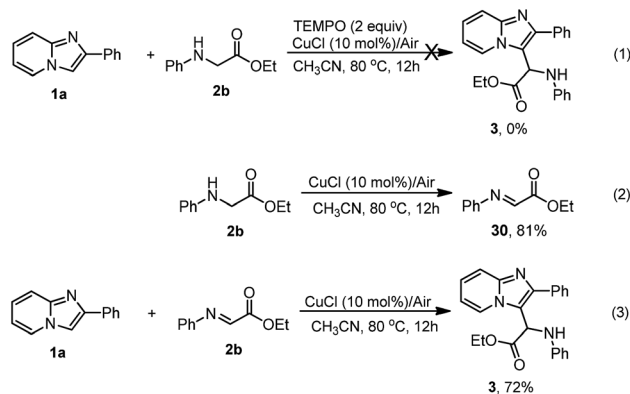
turned out to have strong tolerance under standard conditions, producing product **8** at a yield of 80%.

Next, the effect of various substituents on the benzene ring of imidazoheterocycles was examined. Both electron-donating and electron-withdrawing groups were well tolerated, producing the corresponding products in synthetically useful yields (65–84% yield, products **9–14**). The reaction proceeded well with a diphenyl substituted imidazopyridine, giving product **15** at a yield of 88%. The ethyl substituted imidazopyridine has poorer reactivity than these aryl groups, giving product **16** at a yield of 42%. Subsequently, *N*-arylglycine esters with a substituent (for example, methyl, chloro, or bromo) on the benzene ring were also examined (products **17–19**). Both chloro and bromo groups reduced the reactivity of *N*-phenyl glycine esters, leading to poor yields (products **18** and **19**). Encouragingly, imidazothiazoles were also compatible with the standard conditions (product **20–25**). For example, the reaction of 2-phenylimidazothiazoles with a methoxy or fluoro group on the benzene ring proceeded well to produce the corresponding products **23** and **24** in 63% and 85% yields, respectively. The fused benzo[*d*]imidazo[2,1-*b*]thiazole also performed well, producing product **25** at a yield of 63%. 2-Phenylimidazo[1,2-*a*]pyrimidine was also found to be a suitable substrate for this transformation, affording product **26** at a yield of 56%. However, the reaction did not proceed with *N*-Boc, *N*-Bz or *N*-methyl protected glycine esters under the reaction conditions. *N*-Unprotected glycine ester and glycine were not suitable substrates for this reaction. These substrates may not be oxidized to the corresponding imine cation for the nucleophilic addition with imidazoheterocycles (Scheme 5). Unfortunately, the reaction of *N*-phenyl alanine ester did not occur, which may result from the steric hindrance of the tertiary carbon center.

The coupling reaction between α -amino phenylethanone and imidazopyridine **1a** was also investigated. As shown in Scheme 2, both 1-phenyl-2-(phenylamino)ethanone **2b** and 2-(methyl(phenyl)amino)-1-phenylethanone **2c** were unable to react with imidazopyridine **1a** to produce the desired product under the standard conditions. Imidazopyridine **1a** was quantitatively recovered, and most of substrate **2b** (or **2c**) was decomposed by the C–N bond cleavage and was oxidized to the corresponding 2-oxo-acetamide. Interestingly, the reaction of **1a** with **2b** was able to take place in the presence of TBHP and



Scheme 3 Hydrolysis of compound **3**.



Scheme 4 Control experiments.

selectively afforded a 1-phenyl-2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-(phenylimino)ethanone **27** in 85% yield (eqn (1)). Replacing **2b** with tertiary amine **2c** caused the coupling reaction of **1a** to **2c** to selectively produce a diketone product **28** in 70% yield (eqn (2)).¹⁶ These results are similar to those obtained from the coupling of indole to **2b** reported by Li *et al.*¹⁷

Imidazoheterocycles with glycine motifs are of considerable interest to researchers and may have applications in biochemistry. Compound **3** was hydrolyzed to amino acid **29** (Scheme 3). The hydrolysis proceeded smoothly in the presence of LiOH at 0 °C. After treatment with HCl aqueous solution, a 91% yield of product **29** was obtained.

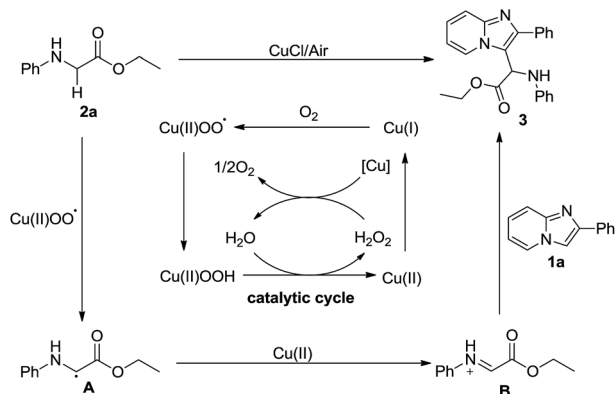
To better understand the reaction pathway, several control experiments were conducted as shown in Scheme 4. The reaction could not take place in the presence of two equivalents of TEMPO (2,2,6,6-tetramethylpiperidinoxy, a free radical trapping agent), suggesting that this reaction may undergo a radical process (Scheme 4, eqn (1)). Under standard conditions, *N*-phenyl glycine ester was oxidized to ethyl 2-(phenylimino)acetate at a yield of 81% (Scheme 4, eqn (2)). Interestingly, imidazopyridine **1a** underwent a Friedel–Crafts reaction with ethyl 2-(phenylimino)acetate (**30**) to produce the desired product **3** at a yield of 72% (Scheme 4, eqn (3)). The results demonstrated that transformation of *N*-phenyl glycine ester into certain active species was crucial to the coupling reaction.

Based on the results of previous reports,¹⁴ a plausible mechanism was proposed and is outlined in Scheme 5. Initially, the oxygen reacts with Cu(I) to produce Cu(II) peroxide radicals, which might abstract an α -hydrogen atom of glycine ester **2a** to form radical **A**, followed by an oxidation with Cu(II) to form imine cation **B**. Subsequently, imidazopyridine **1a** undergoes the Friedel–Crafts reaction with imine cation **B** to produce the desired product **3**.^{14e,18}



Scheme 2 Selective coupling of imidazopyridine **1a** with α -amino phenylethanone.





Scheme 5 A possible mechanism.

Conclusions

In summary, a novel CuCl/air-mediated oxidative cross-coupling of imidazoheterocycles with glycine ester motifs was here developed for the synthesis of imidazoheterocycles with glycine ester motifs. These novel compounds are of great interest in medicinal chemistry. This copper-catalyzed coupling reaction can be carried out in air. Interestingly, in the presence of TBHP and CuCl, the coupling reaction of imidazopyridine **1a** with secondary α -aminophenylethanone selectively produced imidazo[1,2-*a*]pyridin-3-yl imine **27**, whereas the reaction with tertiary α -aminophenylethanone selectively provided imidazo[1,2-*a*]pyridin-3-yl diketone **28** at a good yield.

Experimental section

General remarks

^1H and ^{13}C NMR spectra were measured on a Bruker Avance-III 500 instrument (500 MHz for ^1H , 125 MHz for ^{13}C NMR spectroscopy) using CDCl_3 or DMSO-d_6 as the solvent. Chemical shifts for ^1H and ^{13}C NMR were evaluated by reference to internal Me_4Si (0 ppm) as the standard. The following abbreviations (and combinations thereof) are here used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were measured on a Shimadzu GC-MS-QP2010 Plus spectrometer (EI). HRMS (ESI) analysis was performed on a Bruker micrOTOF-Q II instrument. IR analysis was measured on a Nicolet IS10 spectrometer (ATR).

General procedure for the oxidative coupling reaction of imidazoheterocycles with glycine esters

A 15 mL tube with a Teflon cap, equipped with a magnetic stirring bar, was charged with substrate **1a** (0.20 mmol), *N*-phenyl glycine ester **2a** (0.30 mmol), CuCl (10 mol%) in air, CH_3CN (2 mL) was then added sequentially. The tube was then capped and stirred at 80 °C for 18 h, the crude mixture was diluted with AcOEt, and washed with saturated brine. The organic phase was collected and dried over Na_2SO_4 , filtered through a Celite pad, and washed with AcOEt. The filtrate was concentrated *in vacuo*, and the resulting residue was purified

using column chromatography (petroleum–EtOAc) to produce product **3** as a yellow solid.

Experimental procedure for the hydrolysis of compound 3

A 50 mL round-bottom flask equipped with a magnetic stirring bar was charged with compound **3** (2.0 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (2.0 equiv.), THF (10 mL), and water (5 mL) were then added sequentially at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Next, the reaction mixture was acidified (pH = 3–4) using HCl aq. solution (2 N). The precipitate was filtered and dried to afford product **29** as a white solid.

Typical procedure for the oxidative coupling reaction of imidazopyridine 1a with α -amino phenylethanone 2b or 2c

A 15 mL tube with a Teflon cap, equipped with a magnetic stirring bar, was charged with substrate **1a** (0.20 mmol), α -amino phenylethanone **2b** (or **2c** for product **28**) (0.30 mmol), CuCl (10 mol%), CH_3CN (2 mL) in air, TBHP (5.5 mol L^{-1} in decane, 2 equiv.) was then added sequentially. The tube was then capped and stirred at 80 °C for 12 h. The crude mixture was diluted with AcOEt and washed with saturated brine. The organic phase was collected and dried over Na_2SO_4 , filtered through a Celite pad, and washed with AcOEt. The filtrate was concentrated *in vacuo*, and the resulting residue was purified using column chromatography (petroleum–EtOAc) to produce product **27** as a yellow solid.

Ethyl 2-(phenylamino)-2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)acetate (3). Yield 57.9 mg (78%); yellow solid. Mp: 124.6–126.1 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.42 (d, J = 7.0 Hz, 1H), 7.90 (d, J = 7.0 Hz, 2H), 7.64 (d, J = 9.0 Hz, 1H), 7.53 (t, J = 7.5 Hz, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.20–7.17 (m, 1H), 6.96 (t, J = 8.0 Hz, 2H), 6.79 (t, J = 7.0 Hz, 1H), 6.62 (t, J = 7.5 Hz, 1H), 6.34 (d, J = 8.0 Hz, 2H), 5.75 (d, J = 3.0 Hz, 1H), 4.96 (d, J = 2.5 Hz, 1H), 4.37 (dq, J = 11.0, 7.0 Hz, 1H), 4.22 (dq, J = 11.0, 7.0 Hz, 1H), 1.26 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.7, 146.3, 145.6, 145.4, 134.5, 129.3, 129.1, 128.7, 128.5, 125.4, 124.9, 118.7, 117.8, 115.2, 113.7, 112.5, 62.8, 53.1, 14.1. IR (ATR, cm^{-1}): 2385, 1719, 1686, 1509, 1455, 1006, 876, 747. HRMS (ESI) for $\text{C}_{23}\text{H}_{22}\text{N}_3\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: calcd 372.1707, found 372.1704.

Ethyl 2-(6-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-(phenylamino)acetate (4). Yield 58.5 mg (76%); yellow solid. Mp: 189.5–191.3 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.09 (s, 1H), 7.80 (d, J = 7.7 Hz, 2H), 7.43 (dd, J = 16.5, 7.5 Hz, 3H), 7.34 (t, J = 7.3 Hz, 1H), 6.95 (d, J = 9.5 Hz, 1H), 6.88 (t, J = 7.7 Hz, 2H), 6.54 (t, J = 7.3 Hz, 1H), 6.27 (d, J = 8.5 Hz, 2H), 5.64 (d, J = 3.0 Hz, 1H), 4.88 (d, J = 3.0 Hz, 1H), 4.28 (dq, J = 11.0, 7.0 Hz, 1H), 4.13 (dq, J = 11.0, 7.0 Hz, 1H), 2.23 (s, 3H), 1.18 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.8, 146.1, 145.8, 144.5, 134.3, 129.3, 129.1, 128.7, 128.3, 128.1, 123.0, 122.1, 118.7, 117.01, 114.9, 113.7, 62.8, 53.2, 18.5, 14.1. IR (ATR, cm^{-1}): 2352, 1716, 1540, 1504, 1457, 1219, 804, 695. HRMS (ESI) for $\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: calcd 386.1863, found 386.1868.

Ethyl 2-(6-fluoro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-(phenylamino)acetate (5). Yield 58.4 mg (75%); yellow solid, Mp: 106.7–108.2 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.42 (s, 1H), 7.89 (d, J = 7.5 Hz, 2H), 7.62 (dd, J = 9.5, 5.0 Hz, 1H), 7.53 (t, J =



7.5 Hz, 2H), 7.47 (t, $J = 7.3$ Hz, 1H), 7.13 (t, $J = 8.8$ Hz, 1H), 6.96 (t, $J = 7.6$ Hz, 2H), 6.64 (t, $J = 7.3$ Hz, 1H), 6.34 (d, $J = 8.0$ Hz, 2H), 5.73 (s, 1H), 4.94 (s, 1H), 4.40 (dq, $J = 10.5, 7.0$ Hz, 1H), 4.25 (dq, $J = 10.5, 7.0$ Hz, 1H), 1.29 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.3, 153.1 (d, $J_{\text{C-F}} = 235.5$ Hz), 147.4, 145.4, 143.0, 133.6, 129.2 (d, $J_{\text{C-F}} = 2.3$ Hz), 128.7 (d, $J_{\text{C-F}} = 14.8$ Hz), 119.0, 118.0 (d, $J_{\text{C-F}} = 9.1$ Hz), 117.2, 117.0, 116.6, 113.8, 112.6, 112.2, 63.0, 53.1, 14.1. IR (ATR, cm^{-1}): 2352, 1743, 1507, 1321, 1152, 1013, 809, 730, 693. HRMS (ESI) for $\text{C}_{23}\text{H}_{21}\text{FN}_3\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: calcd 390.1613, found 390.1612.

Ethyl 2-(8-chloro-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-(phenylamino)acetate (6). Yield 59.9 mg (74%); yellow solid. Mp: 200.5–202.1 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.38 (d, $J = 6.5$ Hz, 1H), 7.91 (d, $J = 7.0$ Hz, 2H), 7.52 (d, $J = 7.0$ Hz, 2H), 7.47 (d, $J = 6.5$ Hz, 1H), 7.31–7.25 (m, 1H), 6.95 (t, $J = 7.0$ Hz, 2H), 6.74 (t, $J = 6.5$ Hz, 1H), 6.63 (t, $J = 7.0$ Hz, 1H), 6.32 (d, $J = 7.5$ Hz, 2H), 5.72 (s, 1H), 4.93 (s, 1H), 4.40–4.35 (m, 1H), 4.25–4.21 (m, 1H), 1.27 (t, $J = 6.5$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.5, 147.0, 145.4, 142.8, 133.6, 129.5, 129.2, 128.7, 124.1, 123.9, 123.5, 118.9, 117.1, 113.8, 112.1, 63.0, 53.2, 14.1. IR (ATR, cm^{-1}): 2339, 1733, 1507, 1209, 1007, 872, 741, 688. HRMS (ESI) for $\text{C}_{23}\text{H}_{21}\text{ClN}_3\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: calcd 406.1317, found 406.1321.

Ethyl 2-(8-bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-(phenylamino)acetate (7). Yield 76.3 mg (84%); yellow solid. Mp: 205.9–207.4 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.34 (d, $J = 6.5$ Hz, 1H), 7.83 (d, $J = 7.5$ Hz, 2H), 7.44 (t, $J = 7.5$ Hz, 2H), 7.38 (t, $J = 6.5$ Hz, 2H), 6.87 (t, $J = 7.8$ Hz, 2H), 6.60 (t, $J = 7.0$ Hz, 1H), 6.55 (t, $J = 7.0$ Hz, 1H), 6.24 (d, $J = 8.0$ Hz, 2H), 5.63 (s, 1H), 4.86 (s, 1H), 4.29 (dq, $J = 10.5, 7.0$ Hz, 1H), 4.15 (dq, $J = 10.5, 7.0$ Hz, 1H), 1.19 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.5, 147.0, 145.4, 143.3, 133.6, 129.6, 129.2, 128.7, 127.4, 124.7, 119.8, 118.9, 117.1, 113.8, 112.5, 111.8, 63.0, 53.2, 14.1. IR (ATR, cm^{-1}): 2357, 1728, 1503, 1309, 1214, 920, 740, 689. HRMS (ESI) for $\text{C}_{23}\text{H}_{21}\text{BrN}_3\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: calcd 450.0812, found 450.0821.

Ethyl 2-(8-(hydroxymethyl)-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-(phenylamino)acetate (8). Yield 64.2 mg (80%); yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 8.28 (d, $J = 7.0$ Hz, 1H), 7.81 (d, $J = 7.0$ Hz, 2H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.38 (t, $J = 7.4$ Hz, 1H), 7.05 (d, $J = 6.5$ Hz, 1H), 6.88 (t, $J = 7.8$ Hz, 2H), 6.71 (t, $J = 6.9$ Hz, 1H), 6.56 (t, $J = 7.3$ Hz, 1H), 6.25 (d, $J = 8.5$ Hz, 2H), 5.66 (d, $J = 3.0$ Hz, 1H), 4.95 (dd, $J = 22.0, 13.5$ Hz, 2H), 4.87 (d, $J = 2.5$ Hz, 1H), 4.31 (dq, $J = 10.5, 7.0$ Hz, 1H), 4.15 (dq, $J = 10.5, 7.0$ Hz, 1H), 1.20 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 145.5, 145.4, 144.3, 133.6, 129.8, 129.3, 129.2, 128.7, 128.6, 124.5, 122.0, 118.8, 115.6, 113.7, 112.6, 62.9, 62.4, 53.0, 14.1. IR (ATR, cm^{-1}): 2357, 1715, 1504, 1325, 1250, 917, 753, 688. HRMS (ESI) for $\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}_3^+$ ($\text{M} + \text{H}$) $^+$: calcd 402.1812, found 402.1813.

Ethyl 2-(phenylamino)-2-(2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)acetate (9). Yield 63.1 mg (82%); white solid. Mp: 97.8–99.2 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.34 (d, $J = 7.0$ Hz, 1H), 7.71 (d, $J = 7.5$ Hz, 2H), 7.56 (d, $J = 9.0$ Hz, 1H), 7.25 (d, $J = 7.5$ Hz, 2H), 7.11 (t, $J = 7.8$ Hz, 1H), 6.89 (t, $J = 7.4$ Hz, 2H), 6.71 (t, $J = 6.7$ Hz, 1H), 6.55 (t, $J = 7.3$ Hz, 1H), 6.27 (d, $J = 8.0$ Hz, 2H), 5.67 (s, 1H), 4.86 (s, 1H), 4.32–4.26 (m, 1H), 4.18–4.11 (m, 1H), 2.36 (s, 3H), 1.18 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.7, 146.3, 145.6, 145.3, 138.3, 131.0, 129.4, 129.1, 125.4, 124.9, 118.7, 117.6, 115.0, 113.7, 112.4, 62.8, 53.2, 21.4,

14.0. IR (ATR, cm^{-1}): 2359, 1739, 1600, 1507, 1308, 1013, 823, 746, 692. HRMS (ESI) for $\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: calcd 386.1863, found 386.1868.

Ethyl 2-(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)-2-(phenylamino)acetate (10). Yield 52.1 mg (65%); yellow solid. Mp: 82.3–84.1 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.41 (d, $J = 6.5$ Hz, 1H), 7.84 (d, $J = 8.5$ Hz, 2H), 7.61 (d, $J = 9.0$ Hz, 1H), 7.19–7.15 (m, 1H), 7.06 (d, $J = 8.5$ Hz, 2H), 6.97 (t, $J = 7.7$ Hz, 2H), 6.77 (t, $J = 6.8$ Hz, 1H), 6.62 (t, $J = 7.3$ Hz, 1H), 6.35 (d, $J = 8.0$ Hz, 2H), 5.73 (d, $J = 3.0$ Hz, 1H), 4.97 (d, $J = 2.5$ Hz, 1H), 4.36 (dq, $J = 10.5, 7.0$ Hz, 1H), 4.22 (dq, $J = 10.5, 7.0$ Hz, 1H), 3.87 (s, 3H), 1.26 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.8, 159.9, 146.2, 145.6, 145.3, 130.5, 129.1, 126.5, 125.4, 124.8, 118.7, 117.6, 114.7, 114.2, 113.7, 112.3, 62.8, 55.3, 53.2, 14.1. IR (ATR, cm^{-1}): 2352, 1739, 1600, 1497, 1249, 1119, 836, 753, 692. HRMS (ESI) for $\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}_3^+$ ($\text{M} + \text{H}$) $^+$: calcd 402.1812, found 402.1816.

Ethyl 2-(2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)-2-(phenylamino)acetate (11). Yield 52.9 mg (68%); yellow solid. Mp: 138.7–140.2 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.42 (d, $J = 7.0$ Hz, 1H), 7.90–7.87 (m, 2H), 7.62 (d, $J = 9.0$ Hz, 1H), 7.25–7.18 (m, 3H), 6.97 (t, $J = 7.9$ Hz, 2H), 6.80 (t, $J = 6.7$ Hz, 1H), 6.64 (t, $J = 7.5$ Hz, 1H), 6.33 (d, $J = 8.0$ Hz, 2H), 5.69 (d, $J = 3.0$ Hz, 1H), 4.97 (d, $J = 2.5$ Hz, 1H), 4.37 (dq, $J = 10.5, 7.0$ Hz, 1H), 4.22 (dq, $J = 10.5, 7.0$ Hz, 1H), 1.25 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.5, 163.0 (d, $J_{\text{C-F}} = 246.3$ Hz), 145.5, 145.4, 145.3, 131.0 (d, $J_{\text{C-F}} = 5.8$ Hz), 130.2, 129.1, 125.2 (d, $J_{\text{C-F}} = 43.8$ Hz), 118.8, 117.7, 115.7 (d, $J_{\text{C-F}} = 19.9$ Hz), 115.1, 113.6, 112.6, 62.9, 53.1, 14.0. IR (ATR, cm^{-1}): 2346, 1719, 1540, 1252, 1013, 815, 746, 688. HRMS (ESI) for $\text{C}_{23}\text{H}_{21}\text{FN}_3\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: calcd 390.1613, found 390.1611.

Ethyl 2-(2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)-2-(phenylamino)acetate (12). Yield 68.0 mg (84%); yellow solid. Mp: 159.6–161.3 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.35 (d, $J = 6.5$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 2H), 7.54 (d, $J = 9.0$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.12 (t, $J = 7.7$ Hz, 1H), 6.89 (t, $J = 7.5$ Hz, 2H), 6.72 (t, $J = 6.5$ Hz, 1H), 6.56 (t, $J = 7.2$ Hz, 1H), 6.25 (d, $J = 8.0$ Hz, 2H), 5.61 (s, 1H), 4.88 (s, 1H), 4.28 (dq, $J = 10.5, 7.0$ Hz, 1H), 4.14 (dq, $J = 10.5, 7.0$ Hz, 1H), 1.18 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.4, 145.5, 145.0, 134.6, 132.6, 130.5, 129.2, 128.9, 125.5, 125.2, 118.9, 117.8, 115.3, 113.6, 112.6, 62.9, 53.2, 14.1. IR (ATR, cm^{-1}): 2372, 1716, 1507, 1454, 1003, 834, 745, 695. HRMS (ESI) for $\text{C}_{23}\text{H}_{21}\text{ClN}_3\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: calcd 406.1317, found 406.1319.

Ethyl 2-(2-(4-bromophenyl)imidazo[1,2-*a*]pyridin-3-yl)-2-(phenylamino)acetate (13). Yield 71.8 mg (80%); yellow solid. Mp: 165.5–167.1 °C. ^1H NMR (500 MHz, CDCl_3) δ 8.44 (d, $J = 7.0$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 2H), 7.68–7.62 (m, 3H), 7.21 (t, $J = 7.8$ Hz, 1H), 6.98 (t, $J = 7.6$ Hz, 2H), 6.81 (t, $J = 6.8$ Hz, 1H), 6.65 (t, $J = 7.3$ Hz, 1H), 6.33 (d, $J = 7.5$ Hz, 2H), 5.69 (s, 1H), 4.94 (s, 1H), 4.37 (dq, $J = 10.5, 7.0$ Hz, 1H), 4.22 (dq, $J = 10.5, 7.0$ Hz, 1H), 1.27 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 170.4, 145.5, 145.0, 133.0, 131.9, 130.8, 129.2, 125.5, 125.3, 122.9, 118.9, 117.8, 115.4, 113.7, 112.7, 62.9, 53.2, 14.1. IR (ATR, cm^{-1}): 2352, 1716, 1511, 1457, 1010, 834, 746, 690. HRMS (ESI) for $\text{C}_{23}\text{H}_{21}\text{BrN}_3\text{O}_2^+$ ($\text{M} + \text{H}$) $^+$: calcd 450.0812, found 450.0823.



Ethyl 2-(2-(4-cyanophenyl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)-2-(phenylamino)acetate (14). Yield 53.3 mg (65%); yellow solid. Mp: 146.4–148.3 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.35 (d, *J* = 7.5 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.39 (s, 1H), 6.97 (t, *J* = 7.8 Hz, 2H), 6.69–6.64 (m, 2H), 6.30 (d, *J* = 8.5 Hz, 2H), 5.66 (s, 1H), 4.94 (s, 1H), 4.38 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.24 (dq, *J* = 10.5, 7.0 Hz, 1H), 2.39 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.2, 146.1, 145.4, 143.7, 138.9, 136.8, 132.4, 129.6, 129.2, 126.31 (s), 124.7, 119.0, 118.9, 116.2, 115.7, 113.6, 111.8, 63.0, 53.2, 21.3, 14.1. IR (ATR, cm⁻¹): 2915, 2213, 1713, 1501, 1219, 1017, 852, 775, 692. HRMS (ESI) for C₂₅H₂₃N₄O₂⁺ (M + H)⁺: calcd 411.1816, found 411.1809.

Ethyl 2-(2-([1,1'-biphenyl]-4-yl)imidazo[1,2-*a*]pyridin-3-yl)-2-(phenylamino)acetate (15). Yield 78.7 mg (88%); yellow solid. Mp: 122.6–124.0 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.36 (d, *J* = 7.0 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.68 (d, *J* = 7.0 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 9.0 Hz, 1H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.88 (t, *J* = 7.3 Hz, 2H), 6.70 (t, *J* = 6.8 Hz, 1H), 6.54 (t, *J* = 7.3 Hz, 1H), 6.29 (d, *J* = 7.5 Hz, 2H), 5.72 (s, 1H), 4.90 (s, 1H), 4.29 (dt, *J* = 10.5, 7.0 Hz, 1H), 4.14 (dq, *J* = 10.5, 7.0 Hz, 1H), 1.18 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 169.6, 144.9, 144.6, 144.5, 140.0, 139.6, 132.0, 128.6, 128.1, 127.8, 126.5, 126.3, 126.1, 124.4, 123.9, 117.7, 116.7, 114.2, 112.7, 111.4, 61.8, 52.2, 13.0. IR (ATR, cm⁻¹): 2352, 1736, 1504, 1312, 1013, 846, 751, 692. HRMS (ESI) for C₂₅H₂₃N₄O₂⁺ (M + H)⁺: calcd 448.2020, found 448.2015.

Ethyl 2-(2-ethylimidazo[1,2-*a*]pyridin-3-yl)-2-(phenylamino)acetate (16). Yield 27.1 mg (42%); white solid. Mp: 136.7–138.2 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.38 (d, *J* = 7.0 Hz, 1H), 7.55 (d, *J* = 9.0 Hz, 1H), 7.15–7.11 (m, 3H), 6.75–6.72 (m, 2H), 6.60 (d, *J* = 8.0 Hz, 2H), 5.49 (d, *J* = 3.0 Hz, 1H), 4.88 (s, 1H), 4.26 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.11 (dq, *J* = 10.5, 7.0 Hz, 1H), 2.96 (ddd, *J* = 14.9, 7.4, 5.0 Hz, 2H), 1.41 (t, *J* = 7.5 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.3, 147.9, 146.0, 145.2, 129.3, 124.9, 124.3, 119.0, 117.1, 114.1, 113.6, 112.1, 62.5, 53.1, 21.2, 14.1, 13.9. IR (ATR, cm⁻¹): 2374, 1717, 1506, 1452, 1337, 1014, 838, 755. HRMS (ESI) for C₁₉H₂₂N₃O₂⁺ (M + H)⁺: calcd 324.1707, found 324.1711.

Ethyl 2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-(*p*-tolylamino)acetate (17). Yield 57.8 mg (75%); yellow solid. Mp: 157.8–159.5 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.44 (d, *J* = 7.0 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.80–6.76 (m, 3H), 6.26 (d, *J* = 7.5 Hz, 2H), 5.72 (s, 1H), 4.82 (s, 1H), 4.40–4.31 (m, 1H), 4.25–4.18 (m, 1H), 2.11 (s, 3H), 1.25 (t, *J* = 6.9 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.7, 146.1, 145.3, 143.3, 134.0, 129.6, 129.3, 128.7, 128.4, 128.0, 125.5, 125.0, 117.7, 115.4, 113.8, 112.5, 62.7, 53.4, 20.2, 14.1. IR (ATR, cm⁻¹): 2352, 1736, 1517, 1295, 1017, 804, 741, 698. HRMS (ESI) for C₂₄H₂₄N₃O₂⁺ (M + H)⁺: calcd 386.1863, found 386.1869.

Ethyl 2-((4-chlorophenyl)amino)-2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)acetate (18). Yield 45.4 mg (56%); yellow solid. Mp: 153.2–154.7 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.36 (d, *J* = 6.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 2H), 7.46 (t, *J* = 7.0 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.81 (t, *J* = 6.6 Hz, 1H), 6.23 (d, *J* = 8.0 Hz, 2H),

5.70 (s, 1H), 4.99 (s, 1H), 4.38 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.24 (dq, *J* = 10.5, 7.0 Hz, 1H), 1.28 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.5, 146.5, 145.5, 144.0, 133.9, 129.3, 129.0, 128.8, 128.6, 125.2, 125.0, 123.5, 117.9, 114.8, 114.7, 112.6, 63.0, 53.0, 14.1. IR (ATR, cm⁻¹): 2376, 1717, 1507, 1451, 1007, 836, 753, 692. HRMS (ESI) for C₂₃H₂₁ClN₃O₂⁺ (M + H)⁺: calcd 406.1317, found 406.1320.

Ethyl 2-((4-bromophenyl)amino)-2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)acetate (19). Yield 30.5 mg (34%); yellow solid. Mp: 166.6–168.1 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.35 (d, *J* = 6.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.82 (t, *J* = 6.8 Hz, 1H), 6.18 (d, *J* = 8.5 Hz, 2H), 5.70 (d, *J* = 3.0 Hz, 1H), 5.01 (s, 1H), 4.39 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.24 (dq, *J* = 10.5, 7.0 Hz, 1H), 1.28 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.4, 146.4, 145.4, 144.4, 133.8, 131.8, 129.2, 128.8, 128.6, 125.2, 125.1, 117.8, 115.3, 114.7, 112.7, 110.6, 63.0, 53.0, 14.1. IR (ATR, cm⁻¹): 2357, 1729, 1507, 1308, 1216, 924, 746, 695. HRMS (ESI) for C₂₃H₂₁BrN₃O₂⁺ (M + H)⁺: calcd 450.0812, found 450.0818.

Ethyl 2-(phenylamino)-2-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)acetate (20). Yield 55.0 mg (73%); yellow solid. Mp: 155.7–157.3 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.85 (d, *J* = 7.5 Hz, 2H), 7.71 (d, *J* = 4.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 2H), 6.77 (d, *J* = 4.5 Hz, 1H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.37 (d, *J* = 8.0 Hz, 2H), 5.57 (s, 1H), 4.88 (s, 1H), 4.37 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.23 (dq, *J* = 10.5, 7.0 Hz, 1H), 1.29 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.5, 150.2, 147.0, 145.4, 134.04, 129.2, 128.7, 128.5, 128.0, 119.0, 118.8, 117.6, 113.5, 112.5, 62.7, 53.1, 14.1. IR (ATR, cm⁻¹): 2313, 1716, 1504, 1457, 1016, 920, 746, 690. HRMS (ESI) for C₂₁H₂₀N₃O₂S⁺ (M + H)⁺: calcd 378.1271, found 378.1275.

Ethyl 2-(2-methyl-6-phenylimidazo[2,1-*b*]thiazol-5-yl)-2-(phenylamino)acetate (21). Yield 51.6 mg (66%); yellow solid. Mp: 152.5–154.2 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.41–7.37 (m, 2H), 7.00 (t, *J* = 7.7 Hz, 2H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.38 (d, *J* = 8.0 Hz, 2H), 5.53 (d, *J* = 3.0 Hz, 1H), 4.85 (s, 1H), 4.37 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.23 (dq, *J* = 10.5, 7.0 Hz, 1H), 2.38 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.7, 149.7, 145.8, 145.5, 134.2, 129.2, 128.6, 128.4, 127.9, 126.5, 118.8, 117.3, 115.5, 113.5, 62.7, 53.1, 14.1. IR (ATR, cm⁻¹): 2313, 1713, 1504, 1451, 1013, 917, 751, 692. HRMS (ESI) for C₂₂H₂₂N₃O₂S⁺ (M + H)⁺: calcd 392.1427, found 392.1436.

Ethyl 2-(phenylamino)-2-(6-(*p*-tolyl)imidazo[2,1-*b*]thiazol-5-yl)acetate (22). Yield 47.7 mg (61%); yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 7.73 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 4.5 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.00 (t, *J* = 7.6 Hz, 2H), 6.77 (d, *J* = 4.5 Hz, 1H), 6.66 (t, *J* = 7.3 Hz, 1H), 6.38 (d, *J* = 8.0 Hz, 2H), 5.56 (s, 1H), 4.86 (s, 1H), 4.37 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.22 (dq, *J* = 10.5, 7.0 Hz, 1H), 2.42 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.6, 150.1, 147.1, 145.4, 137.8, 131.1, 129.4, 129.2, 128.4, 119.1, 118.8, 117.3, 113.5, 112.4, 62.7, 53.2, 21.3, 14.1. IR (ATR, cm⁻¹): 2385, 1633, 1514, 1375, 1249, 968, 753, 695. HRMS (ESI) for C₂₂H₂₂N₃O₂S⁺ (M + H)⁺: calcd 392.1427, found 392.1433.



Ethyl 2-(6-(4-methoxyphenyl)imidazo[2,1-*b*]thiazol-5-yl)-2-(phenylamino)acetate (23). Yield 51.3 mg (63%); yellow solid. Mp: 165.8–167.3 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 4.5 Hz, 1H), 7.01 (dd, *J* = 16.4, 8.3 Hz, 4H), 6.76 (d, *J* = 4.5 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.38 (d, *J* = 8.0 Hz, 2H), 5.53 (s, 1H), 4.87 (s, 1H), 4.36 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.23 (dq, *J* = 10.5, 7.0 Hz, 1H), 3.87 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.6, 159.6, 150.1, 146.9, 145.4, 129.8, 129.2, 126.6, 119.0, 118.8, 117.0, 114.2, 113.5, 112.3, 62.7, 55.3, 53.2, 14.1. IR (ATR, cm⁻¹): 2352, 1733, 1507, 1325, 1250, 852, 746, 693. HRMS (ESI) for C₂₂H₂₂N₃O₃S⁺ (M + H)⁺: calcd 408.1377, found 408.1380.

Ethyl 2-(6-(4-fluorophenyl)imidazo[2,1-*b*]thiazol-5-yl)-2-(phenylamino)acetate (24). Yield 67.2 mg (85%); white solid. Mp: 163.6–165.4 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.82 (s, 2H), 7.71 (s, 1H), 7.19 (t, *J* = 7.6 Hz, 2H), 7.01 (t, *J* = 7.0 Hz, 2H), 6.78 (s, 1H), 6.67 (t, *J* = 6.5 Hz, 1H), 6.36 (d, *J* = 7.5 Hz, 2H), 5.50 (s, 1H), 4.90 (s, 1H), 4.37 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.24 (dq, *J* = 10.5, 7.0 Hz, 1H), 1.29 (t, *J* = 6.3 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.3, 162.7 (d, *J*_{C-F} = 246 Hz), 150.2, 146.0, 145.3, 130.2 (d, *J*_{C-F} = 7.9 Hz), 129.2, 119.0 (d, *J*_{C-F} = 8.7 Hz), 117.5, 115.7 (d, *J*_{C-F} = 21.5 Hz), 113.5, 112.6, 62.8, 53.1, 14.0. IR (ATR, cm⁻¹): 2346, 1719, 1540, 1375, 1252, 1013, 851, 746, 688. HRMS (ESI) for C₂₁H₁₉FN₃O₂S⁺ (M + H)⁺: calcd 396.1178, found 396.1175.

Ethyl 2-(7-methyl-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)-2-(phenylamino)acetate (25). Yield 55.6 mg (63%); yellow solid. Mp: 155.7–157.6 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.30 (d, *J* = 7.0 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.38 (s, 1H), 6.95 (t, *J* = 7.8 Hz, 2H), 6.62 (t, *J* = 7.2 Hz, 2H), 6.33 (d, *J* = 8.0 Hz, 2H), 5.71 (d, *J* = 3.0 Hz, 1H), 4.92 (s, 1H), 4.36 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.22 (dq, *J* = 10.5, 7.0 Hz, 1H), 2.37 (s, 3H), 1.26 (d, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.8, 146.0, 145.9, 145.6, 136.0, 134.1, 129.2, 129.1, 128.7, 128.3, 124.6, 118.7, 116.1, 115.1, 114.6, 113.7, 62.8, 53.1, 21.3, 14.1. IR (ATR, cm⁻¹): 2352, 1733, 1514, 1245, 1019, 868, 745, 692. HRMS (ESI) for C₂₆H₂₄N₃O₂S⁺ (M + H)⁺: calcd 442.1584, found 442.1585.

Ethyl 2-(phenylamino)-2-(2-phenylimidazo[1,2-*a*]pyrimidin-3-yl)acetate (26). Yield 41.7 mg (56%); yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 8.83 (d, *J* = 5.5 Hz, 1H), 8.55 (s, 1H), 7.99 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 6.96 (t, *J* = 7.8 Hz, 2H), 6.86 (dd, *J* = 7.0, 4.0 Hz, 1H), 6.65 (t, *J* = 7.3 Hz, 1H), 6.33 (d, *J* = 8.0 Hz, 2H), 5.78 (s, 1H), 4.92 (s, 1H), 4.41 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.25 (dq, *J* = 10.5, 7.0 Hz, 1H), 1.29 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 170.4, 150.2, 148.2, 147.4, 145.3, 133.4, 133.1, 129.4, 129.2, 128.9, 128.8, 119.2, 113.8, 108.7, 100.0, 63.1, 53.3, 14.0. IR (ATR, cm⁻¹): 2365, 1729, 1507, 1454, 1222, 1023, 754, 692. HRMS (ESI) for C₂₂H₂₁N₄O₂⁺ (M + H)⁺: calcd 373.1659, found 373.1664.

(Z)-1-Phenyl-2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)-2-(phenylimino)ethanone (27). Yield 68.2 mg (85%); yellow solid. Mp: 157.6–159.1 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.97–9.95 (m, 1H), 7.74–7.66 (m, 1H), 7.44–7.36 (m, 1H), 7.26–7.21 (m, 3H), 7.05–6.95 (m, 8H), 6.90–6.87 (m, 2H), 6.81–6.77 (m, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 192.8, 158.3, 154.1, 148.8, 147.2, 135.1, 133.6,

133.3, 130.5, 129.4, 129.0, 128.9, 128.6, 128.4, 128.1, 127.3, 124.3, 120.7, 117.8, 117.3, 114.3. IR (ATR, cm⁻¹): 2352, 1666, 1564, 1467, 1348, 920, 876, 713. HRMS (ESI) for C₂₇H₂₀N₃O⁺ (M + H)⁺: calcd 402.1601, found 402.1603.

Phenyl-2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)ethane-1,2-dione (28). Yield 45.6 mg (70%); yellow solid. Mp: 148.8–150.2 °C. ¹H NMR (500 MHz, CDCl₃) δ 9.76 (d, *J* = 7.0 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.20–7.15 (m, 2H), 7.02 (t, *J* = 7.5 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ 191.4, 184.6, 158.7, 148.4, 134.1, 133.4, 132.9, 131.0, 130.1, 129.6, 129.4, 129.3, 128.6, 127.9, 119.0, 117.7, 115.8. IR (ATR, cm⁻¹): 2359, 1676, 1590, 1401, 1255, 917, 758, 625. HRMS (ESI) for C₂₁H₁₅N₂O₂⁺ (M + H)⁺: calcd 327.1128, found 327.1130.

2-(phenylamino)-2-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)acetic acid (29). Yield 62.4 mg (91%); white solid. Mp: 152.5–154.4 °C. ¹H NMR (500 MHz, CDCl₃) δ 8.75 (d, *J* = 6.5 Hz, 1H), 8.00 (s, 2H), 7.93 (s, 1H), 7.43–7.30 (m, 4H), 6.90–6.87 (m, 4H), 6.56 (t, *J* = 7.2 Hz, 1H), 6.21 (d, *J* = 8.0 Hz, 2H), 5.45 (s, 1H), 4.74 (s, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 171.7, 146.3, 140.2, 136.5, 130.6, 130.3, 129.7, 129.1, 127.7, 127.4, 121.1, 118.2, 115.6, 113.5, 113.4, 53.4. IR (ATR, cm⁻¹): 2363, 1717, 1652, 1509, 1360, 993, 750, 695. HRMS (ESI) for C₂₁H₁₈N₃O₂⁺ (M + H)⁺: calcd 344.1394, found 344.1397.

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Notes and references

- (a) G. E. Barrett and D. T. Elmore, *Amino Acids and Peptides*, Cambridge University, Cambridge, 1998; (b) M. Calmes and J. Daunis, *Amino Acids*, 1999, **16**, 215.
- (a) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013; (b) M. Castanho and N. Santos, *Peptide Drug Discovery and Development: Translational Research in Academia and Industry*, Wiley-VCH, Weinheim, 2011; (c) S. Baktharaman, R. Hili and A. K. Yudin, *Aldrichimica Acta*, 2008, **41**, 109; (d) R. L. Polt, in *Amino Acid Derivatives: A Practical Approach*, ed. G. C. Barrett, Oxford University Press, Oxford, UK, 1999, pp. 101–114; (e) F. D. Klingler, *Acc. Chem. Res.*, 2007, **40**, 1367; J. W. Grate and G. C. Frye, in *Sensors Update*, ed. H. Baltes, W. Göpel and J. Hesse, Wiley-VCH, Weinheim, 1996, vol. 2, pp. 10–20.
- (a) C. Enguehard-Gueiffier and A. Gueiffier, *Mini-Rev. Med. Chem.*, 2007, **7**, 888; (b) F. Couty and G. Evano, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier Science, Oxford, 2008, vol. 11, pp. 409–492, and references therein.
- (a) A. Andreani, S. Burnelli, M. Granaiola, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, L. Varoli, N. Calonghi, C. Cappadone, G. Farruggia, M. Zini, C. Stefanelli,



- L. Masotti, N. S. Radin and R. H. Shoemaker, *J. Med. Chem.*, 2008, **51**, 809; (b) J.-H. Park, M. I. El-Gamal, Y. S. Lee and C.-H. Oh, *Eur. J. Med. Chem.*, 2011, **46**, 5769; (c) A. R. Ali, E. R. El-Bendary, M. A. Ghaly and I. A. Shehata, *Eur. J. Med. Chem.*, 2014, **75**, 492.
- 5 (a) C. Ravi, D. Chandra Mohan and S. Adimurthy, *Org. Biomol. Chem.*, 2016, **14**, 2282; (b) Y. Ding, W. Wu, W. Zhao, Y. Li, P. Xie, Y. Huang, Y. Liu and A. Zhou, *Org. Biomol. Chem.*, 2016, **14**, 1428; (c) A. K. Bagdi, S. Mitra, M. Ghosh and A. Hajra, *Org. Biomol. Chem.*, 2015, **13**, 3314; (d) X.-M. Ji, S.-J. Zhou, F. Chen, X.-G. Zhang and R.-Y. Tang, *Synthesis*, 2015, **47**, 659; (e) M.-A. Hiebel and S. Berteina-Raboin, *Green Chem.*, 2015, **17**, 937; (f) C. Ravi, D. Chandra Mohan and S. Adimurthy, *Org. Lett.*, 2014, **16**, 2978.
- 6 (a) D. Yang, K. Yan, W. Wei, G. Li, S. Lu, C. Zhao, L. Tian and H. Wang, *J. Org. Chem.*, 2015, **80**, 11073; (b) S. Mitra, M. Ghosh, S. Mishra and A. Hajra, *J. Org. Chem.*, 2015, **80**, 8275.
- 7 J. Jiao, L. Wei, X.-M. Ji, M.-L. Hu and R.-Y. Tang, *Adv. Synth. Catal.*, 2016, **358**, 268.
- 8 M. Yadav, S. Dara, V. Saikam, M. Kumar, S. K. Aithagani, S. Paul, R. A. Vishwakarma and P. P. Singh, *Eur. J. Org. Chem.*, 2015, **2015**, 6526.
- 9 (a) K. Monir, A. K. Bagdi, M. Ghosh and A. Hajra, *J. Org. Chem.*, 2015, **80**, 1332; (b) X.-M. Ji, L. Wei, F. Chen and R.-Y. Tang, *RSC Adv.*, 2015, **5**, 29766.
- 10 Q. Wang, Z. Qi, F. Xie and X. Li, *Adv. Synth. Catal.*, 2015, **357**, 355.
- 11 (a) S. Wang, X. Huang, Z. Ge, X. Wang and R. Li, *RSC Adv.*, 2016, **6**, 63532; (b) S. Mishra, P. Mondal, M. Ghosh, S. Mondal and A. Hajra, *Org. Biomol. Chem.*, 2016, **14**, 1432; (c) K. Li, X.-M. Zhao, F.-L. Yang, X.-H. Hou, Y. Xu, Y.-C. Guo, X.-Q. Hao and M.-P. Song, *RSC Adv.*, 2015, **5**, 90478.
- 12 (a) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74; (b) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (c) M. Klusmann and D. Sureshkumar, *Synthesis*, 2011, 353; (d) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335.
- 13 (a) Z.-Q. Zhu and Z.-Z. Huang, *Org. Lett.*, 2016, **18**, 1526; (b) K. Li, Q. Wu, J. Lan and J. You, *Nat. Commun.*, 2015, **6**, 8404; (c) H. Peng, J.-T. Yu, Y. Jiang, H. Yang and J. Cheng, *J. Org. Chem.*, 2014, **79**, 9847; (d) W.-T. Wei, R.-J. Song and J.-H. Li, *Adv. Synth. Catal.*, 2014, **356**, 1703; (e) J. Xie and Z.-Z. Huang, *Angew. Chem., Int. Ed.*, 2010, **49**, 10181; (f) L. Zhao and C.-J. Li, *Angew. Chem., Int. Ed.*, 2008, **47**, 7075; (g) G. Zhang, Y. Zhang and R. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 10429; (h) Y. Zhang, M. Nia and B. Feng, *Org. Biomol. Chem.*, 2016, **14**, 1550; (i) L. Zhao, O. Baslé and C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**, 4106.
- 14 (a) Y. Tan, W. Yuan, L. Gong and E. Meggers, *Angew. Chem., Int. Ed.*, 2015, **54**, 13045; (b) X.-W. Gao, Q.-Y. Meng, J.-X. Li, J.-J. Zhong, T. Lei, X.-B. Li, C.-H. Tung and L.-Z. Wu, *ACS Catal.*, 2015, **5**, 2391; (c) C. Huo, Y. Yuan, M. Wu, X. Jia, X. Wang, F. Chen and J. Tang, *Angew. Chem., Int. Ed.*, 2014, **53**, 13544; (d) Z.-Q. Zhu, P. Bai and Z.-Z. Huang, *Org. Lett.*, 2014, **16**, 4881; (e) C. Huo, C. Wang, M. Wu, X. Jia, H. Xie and Y. Yuan, *Adv. Synth. Catal.*, 2014, **356**, 411; (f) X.-W. Gao, Q.-Y. Meng, M. Xiang, B. Chen, K. Feng, C.-H. Tung and L.-Z. Wu, *Adv. Synth. Catal.*, 2013, **355**, 2158; (g) S. Zhu and M. Rueping, *Chem. Commun.*, 2012, **48**, 11960; (h) Z.-Q. Wang, M. Hu, X.-C. Huang, L.-B. Gong, Y.-X. Xie and J.-H. Li, *J. Org. Chem.*, 2012, **77**, 8705.
- 15 K. Yan, D. Yang, W. Wei, G. Li, M. Sun, Q. Zhang, L. Tian and H. Wang, *RSC Adv.*, 2015, **5**, 100102.
- 16 R.-Y. Tang, X.-K. Guo, J.-N. Xiang and J.-H. Li, *J. Org. Chem.*, 2013, **78**, 11163.
- 17 J.-C. Wu, R.-J. Song, Z.-Q. Wang, X.-C. Huang, Y.-X. Xie and J.-H. Li, *Angew. Chem., Int. Ed.*, 2012, **51**, 3453.
- 18 G. Desimoni, G. Faita, M. Mella, M. Toscanini and M. Boiocchi, *Eur. J. Org. Chem.*, 2008, 6232.

