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Synthesis of 5-arylhistidines via a Suzuki–Miyaura cross-coupling

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Abstract—Microwave irradiation efficiently promoted the Suzuki–Miyaura reaction of a 5-bromohistidine with various arylboronic acids in the presence of a palladium catalyst. This methodology allowed the synthesis of histidines substituted at position 5 of the imidazole ring with a phenyl, a substituted phenyl, a pyridyl or a thienyl ring. The corresponding 5-arylhistidines were obtained in moderate to good yields.

1. Introduction

Unnatural amino acids are increasingly becoming important substrates in modern drug design, synthesis, and discovery research. Their incorporation into biologically active peptides may lead to peptidomimetics with restricted conformational flexibility, increased proteolytic stability, and enhanced selectivity and biological activity.[1,2] Among them, biaryl amino acids have been the focus of intense synthetic efforts owing to the broad spectrum of activities shown by peptides containing biaryl motifs.[3,4] In particular, arylhistidines occur naturally in the active site of the heme–copper oxidases and in cytotoxic and antifungal marine peptides.[5–7]

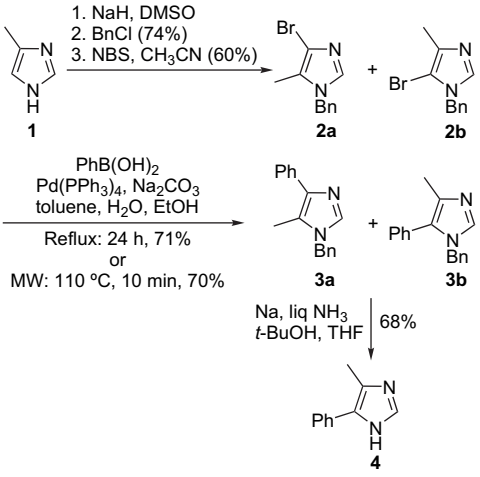
A method of choice for the preparation of unsymmetric biaryl systems is the Suzuki–Miyaura cross-coupling of an aryl halide with an arylboronic acid.[8–13] It has been shown that microwaves significantly enhance this reaction leading to higher overall yields and purities as well as shorter reaction times.[14–18] Although a great variety of biarylic compounds have been prepared following this approach, up to now it has not been applied to the arylation of imidazole rings.

In the course of our synthetic studies on biaryl amino acids, we focused our interest on studying a methodology toward the preparation of 5-arylhistidines. Here we report the arylation of an imidazole derivative via a microwave-assisted Suzuki–Miyaura cross-coupling reaction, and the extension of this methodology to the synthesis of 5-arylhistidines. For comparison purposes, cross-coupling reactions under thermal heating were also studied and will be discussed.

2. Results and discussion

2.1. Microwave-assisted arylation of an imidazole derivative

The feasibility of the microwave-assisted Suzuki–Miyaura reaction for the arylation of position 4(5) of an imidazole ring was investigated using the 4(5)-methylimidazole (**1**) as model system (Scheme 1). For this purpose, the commercially available imidazole **1** was treated with NaH (1.1 equiv) and BnCl (1 equiv),[19] and then brominated



Scheme 1. Synthesis of 4(5)-methyl-5(4)-phenylimidazole (**4**) via a Suzuki–Miyaura cross-coupling.

Keywords: Histidine; Arylation; Suzuki–Miyaura cross-coupling; Microwave; Biaryl compounds.
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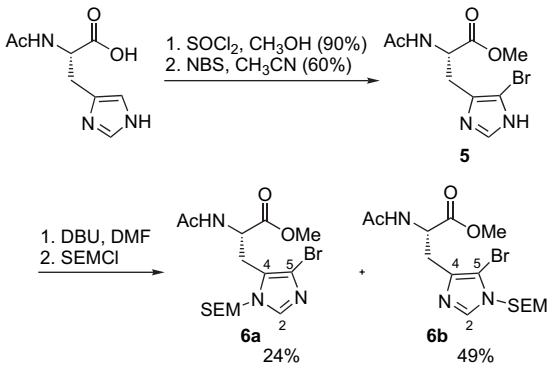
with NBS (1 equiv) to afford bromoimidazoles **2a** and **2b** (Scheme 1).[8] These regioisomers were separated by column chromatography to be fully characterized. ^{1}H and ^{13}C NMR as well as mass spectrometry clearly proved the assumption of regioisomerism, and the unambiguous assignment was achieved by HMBC ($J^{1,3}$) and X-ray analysis. The HMBC spectra of the isomer **2a** showed that the signal of the methylene protons of the benzyl group correlated with the carbon linked to the methyl substituent. In the spectra of the major regioisomer **2b**, the methylene protons of the protecting group correlated with the carbon linked to the Br atom.

The coupling of a regioisomeric mixture of **2a** and **2b** with phenylboronic acid (1.1 equiv) was first attempted employing standard conditions, i.e., 5 mol % $Pd(PPh_3)_4$ as catalyst and aqueous 2 M Na_2CO_3 as base (5 equiv), in toluene/ethanol (Scheme 1). After heating at 110 °C for 24 h, a mixture of phenylimidazoles **3a** and **3b** was obtained in 71% yield. The isomers were characterized by NMR spectroscopy and mass spectrometry. Then, the Suzuki–Miyaura reaction was performed under microwave irradiation employing the above reaction conditions. Even though phenylimidazoles **3a** and **3b** were obtained in similar yield (70%), the reaction time was considerably shortened, from 24 h to just 10 min corresponding to a 144-fold rate increase. Final debenzylation of **3a** and **3b** by sodium in liquid ammonia afforded exclusively 4(5)-methyl-5(4)-phenylimidazole (**4**) in 68% yield.[20]

2.2. Microwave-assisted arylation of a histidine derivative

The above methodology was applied to the synthesis of 5-arylhistidines. The commercially available Ac-His-OH was chosen as the starting material, which was converted to the methyl ester by treatment with $SOCl_2$ in methanol (Scheme 2). The [2-(trimethylsilyl)ethoxy]methyl (SEM) group was selected to protect the imidazole ring because it can be more flexibly removed than the benzyl group, being more suitable for solid-phase peptide synthesis.[21,22] Imidazole deprotonation of Ac-His-OMe with DBU (1.5 equiv) at 0 °C for 1.5 h in DMF under nitrogen, followed by the addition of SEMCl (1 equiv) at 0 °C, and stirring for 1.5 h produced a regioisomeric mixture of Ac-His(π-SEM)-OMe and Ac-His(τ-SEM)-OMe in less than 5% yield. As an alternative, the direct bromination of Ac-His-OMe followed by SEM protection was attempted. Treatment of Ac-His-OMe with



Scheme 2. Synthesis of 5-bromohistidines **6a** and **6b**.

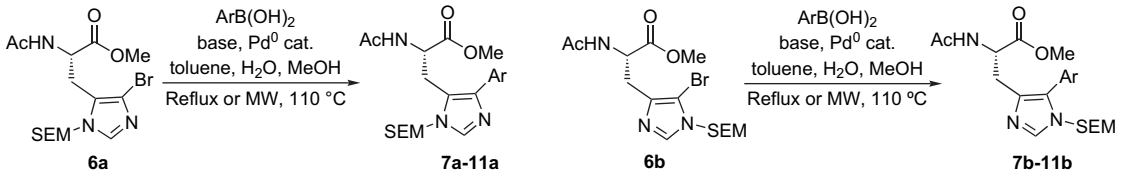
NBS (1.1 equiv) at 0 °C in acetonitrile for 15 min led to the 5-bromohistidine **5** (60% yield) along with the 2,5-dibromohistidine derivative (13% yield).[23] Alkylation of **5** with SEMCl as described above gave a regioisomeric mixture of the SEM-protected 5-bromohistidines **6a** and **6b**, which were easily separated by column chromatography and obtained in 24% and 49% yields, respectively. The unambiguous assignment of each regioisomer was achieved by HMBC ($J^{1,3}$). The spectra of isomer **6a** showed that the signal of the methylene protons of the SEM N–CH_2–O moiety correlated with the imidazole carbon linked to the β-CH_2. By contrast, in the spectra of regioisomer **6b**, the methylene protons of this moiety correlated with the carbon linked to the Br atom.

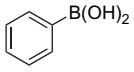
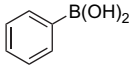
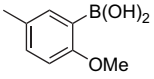
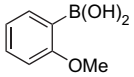
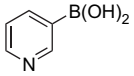
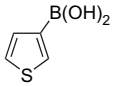
With the properly functionalized 5-bromohistidines **6a** and **6b** in hand, we set out to examine the arylation of position 5 of the imidazole ring via a Suzuki–Miyaura cross-coupling. The reaction conditions were standardized by optimization of the coupling reaction of **6a** and **6b** with phenylboronic acid (Table 1). No reaction took place when either **6a** or **6b** was treated with phenylboronic acid (1.1 equiv), 5 mol % $Pd(PPh_3)_4$, and aqueous 2 M Na_2CO_3 (2 equiv), in toluene/methanol under conventional heating at 110 °C for 24 h (entries 1 and 16). An increase of the catalyst amount to 20 mol % did not lead either to the formation of the 5-phenylhistidine **7b** (entry 2). The use of other palladium catalysts only afforded **7b** in 26% yield (entries 3–5).

The arylation of 5-bromohistidine **6b** was then attempted under microwave heating (Table 1). The coupling was conducted by employing the above reaction conditions using $Pd(PPh_3)_4$ as catalyst (entries 6 and 7). When 20 mol % of $Pd(PPh_3)_4$ was used, the 5-phenylhistidine **7b** was obtained in 63% yield after 30 min irradiation (entry 7). In entries 8–10 we investigated the catalyst. $PdCl_2$(dppf) was not effective for the reaction, producing a low yield of **7b** (20%). In the case of $Pd_2(dba)_3$, **7b** was obtained in similar yield as with $Pd(PPh_3)_4$ (58%) but using a lower amount of catalyst (10 mol %) and in a shorter reaction time (10 min). Based on these conditions we examined the influence of the base (entries 11–15). KF was found to be the most effective, furnishing **7b** in 62% yield. The advantage of using KF as base is clearly evident from the arylation of 5-bromohistidine **6a**, which led to **7a** in 82% after 15 min irradiation (entries 17–20).

Next, we explored the applicability of the Suzuki–Miyaura reaction to the coupling of 5-bromohistidines **6a** and **6b** with other arylboronic acids, possessing substituted benzene, pyridine, and thiophene rings (Table 1, entries 21–28). All reactions went to completion within 1 h giving rise to the desired 5-arylhistidines **8**–**11** in moderate to good yields. In general, the arylation of 5-bromohistidine **6a** proceeded smoother than that of **6b**. These results could be tentatively explained taking into account that in regioisomer **6b** the SEM group is at N(τ), which would increase the steric hindrance, resulting in a more difficult reaction. Similar to previous studies,[24,25] coupling of 3-pyridylboronic acid with **6a** and **6b** was found to be difficult, with a 40 mol % of catalyst being necessary to promote the reaction (entries 25 and 26). The best result was obtained for the reaction of **6a** with 3-thienylboronic acid leading to **11a** with 85% yield (entry 28).

Table 1. Arylation of 5-bromohistidines **6a** and **6b** with various arylboronic acids



Entry	Histidine **5**	$ArB(OH)_2$	$ArB(OH)_2$ (equiv)	Heating[a]	Catalyst	Catalyst (mol %)	Base	Time	Product	Yield[b] (%)
1			1.1	Reflux	$Pd(PPh_3)_4$	5	Na_2CO_3	24 h	**7b**	0
2			2.1	Reflux	$Pd(PPh_3)_4$	20	Na_2CO_3	24 h	**7b**	0
3			2.1	Reflux	$Pd_2(dba)_3$	20	Na_2CO_3	24 h	**7b**	12
4			2.1	Reflux	$PdCl_2(dppf)$	20	Na_2CO_3	24 h	**7b**	26
5			2.1	Reflux	$Pd(OAc)_2$	20	Na_2CO_3	24 h	**7b**	0
6			2.1	MWI	$Pd(PPh_3)_4$	10	Na_2CO_3	30 min	**7b**	22
7			2.1	MWI	$Pd(PPh_3)_4$	20	Na_2CO_3	30 min	**7b**	63
8	**6b**		2.1	MWI	$PdCl_2(dppf)$	20	Na_2CO_3	20 min	**7b**	20
9			2.1	MWI	$Pd_2(dba)_3$	10	Na_2CO_3	10 min	**7b**	58
10			2.1	MWI	$Pd_2(dba)_3$	20	Na_2CO_3	15 min	**7b**	45
11			2.1	MWI	$Pd_2(dba)_3$	10	K_2CO_3	10 min	**7b**	10
12			2.1	MWI	$Pd_2(dba)_3$	10	Cs_2CO_3	10 min	**7b**	27
13			2.1	MWI	$Pd_2(dba)_3$	10	$NaHCO_3$	10 min	**7b**	35
14			2.1	MWI	$Pd_2(dba)_3$	10	K_3PO_4	10 min	**7b**	47
15			2.1	MWI	$Pd_2(dba)_3$	10	KF	10 min	**7b**	62
16			1.1	Reflux	$Pd(PPh_3)_4$	5	Na_2CO_3	24 h	**7a**	0
17			2.1	MWI	$Pd_2(dba)_3$	10	Na_2CO_3	10 min	**7a**	35
18	**6a**		2.1	MWI	$Pd_2(dba)_3$	10	Na_2CO_3	15 min	**7a**	37
19			2.1	MWI	$Pd_2(dba)_3$	15	K_3PO_4	15 min	**7a**	8
20			2.1	MWI	$Pd_2(dba)_3$	10	KF	15 min	**7a**	82
21	**6b**		2.1	MWI	$Pd_2(dba)_3$	10	KF	1 h	**8b**	36
22	**6a**		2.1	MWI	$Pd_2(dba)_3$	10	KF	1 h	**8a**	54
23	**6b**		2.1	MWI	$Pd_2(dba)_3$	40	KF	10 min	**9b**	51
24	**6a**		2.1	MWI	$Pd_2(dba)_3$	20	KF	1 h	**9a**	68
25	**6b**		2.1	MWI	$Pd_2(dba)_3$	40	KF	10 min	**10b**	33
26	**6a**		2.1	MWI	$Pd_2(dba)_3$	40	KF	10 min	**10a**	40
27	**6b**		2.1	MWI	$Pd_2(dba)_3$	20	KF	30 min	**11b**	54
28	**6a**		2.1	MWI	$Pd_2(dba)_3$	20	KF	15 min	**11a**	85

[a] All experiments were performed at 110 °C.
[b] Isolated yields after chromatography.

Finally, the removal of the SEM group of arylhistidines was examined (Table 2). The reaction conditions were first studied with phenylhistidine **7b**. Disappointingly, treatment of **7b** with TBAF (5 equiv) in THF at room temperature led to a complex mixture of unidentified products. When the reaction was performed with PPTS (1 equiv) in MeOH, the starting material was recovered. Removal of the SEM group could be accomplished by treatment with TFA/CH_2Cl_2 (2:1) at room temperature for 1.5 h giving the 5-phenylhistidine **12** in 97% yield (entry 2). These conditions were then applied to the deprotection of histidines **7a** and **8**–**11** affording 5-arylhistidines **12**–**16** in high yields. Chiral HPLC studies were performed in order to analyze the optical integrity of the deprotected 5-arylhistidines. Results showed that no racemization occurred.

3. Conclusion

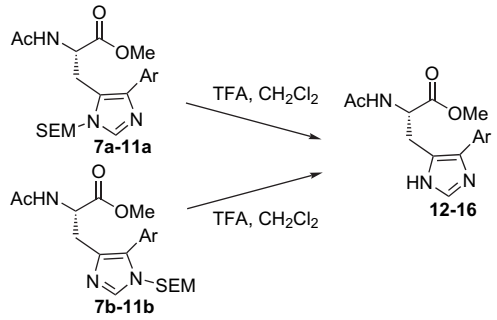
A straightforward approach has been established to the synthesis of 5-arylhistidines. Microwave irradiation facilitates the Suzuki–Miyaura reaction of the corresponding 5-bromohistidine with phenyl, substituted phenyl, pyridyl, and thienylboronic acids. This work constitutes the first Suzuki–Miyaura coupling involving the imidazole ring of a histidine.

4. Experimental section

4.1. Synthesis of 4(5)-methyl-5(4)-phenylimidazole (4)

4.1.1. 1-Benzyl-4-bromo-5-methylimidazole (2a) and 1-benzyl-5-bromo-4-methylimidazole (2b). *N*-Bromosuccinimide (420 mg, 2.4 mmol) was added to a solution of a regioisomeric mixture of 1-benzyl-5-methylimidazole and 1-benzyl-4-methylimidazole (1:1.3)[19] (422 mg, 2.4 mmol) in dry acetonitrile (55 mL) at 0 °C. The reaction mixture was stirred for 30 min under N_2 at this temperature. Pyridine (4 μL) was added and the mixture was concentrated in vacuo. Triethylamine (40 μL) was added to the concentrated solution. Removal of the solvent gave a residue, which was purified by column chromatography. Elution

Table 2. SEM group removal of 5-arylhistidines **7–11**



Entry	Arylhistidine	Time (h)	Yield[a] (%)	Product	Ar
1	**7a**	2.5	99	**12**	
2	**7b**	1.5	97	**12**	
3	**8a**	1.5	70	**13**	
4	**8b**	1.5	91	**13**	
5	**9a**	3.5	90	**14**	
6	**9b**	1.5	91	**14**	
7	**10a**	2.5	90	**15**	
8	**10b**	3.5	92	**15**	
9	**11a**	2.0	99	**16**	
10	**11b**	2.0	99	**16**	

[a] Isolated yields after chromatography.

with hexane/EtOAc/NH_3 (83:16:1) afforded **2a** as a yellow solid (162 mg, 27%). R_f (EtOAc/NH_3, 99:1) 0.60; IR (neat) 2920, 1552, 1485, 1438, 1221, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.11 (s, 3H, CH_3), 5.09 (s, 2H, CH_2), 7.09–7.13 (m, 2H, *o*-CH_{arom}), 7.31–7.41 (m, 3H, *m*- and *p*-CH_{arom}), 7.44 (s, 1H, CH-2_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.96 (CH_3), 49.60 (CH_2), 114.55 (C-4_{imid}), 125.25 (C-5_{imid}), 126.68 (2×*o*-CH_{arom}), 128.23 (*p*-CH_{arom}), 129.04 (2×*m*-CH_{arom}), 135.30 (C_{arom}), 135.98 (CH-2_{imid}); MS (ESI) *m*/*z* (%) 250.9 (100) $[M+H]^+$, 253.0 (96).

Elution with hexane/EtOAc/NH_3 (79:20:1) afforded **2b** as a white solid (198 mg, 33%). R_f (EtOAc/NH_3, 99:1) 0.50; IR (neat) 2923, 1564, 1494, 1429, 1231, 723 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.26 (s, 3H, CH_3), 5.11 (s, 2H, CH_2), 7.15–7.20 (m, 2H, *o*-CH_{arom}), 7.35–7.40 (m, 3H, *m*- and *p*-CH_{arom}), 7.55 (s, 1H, CH-2_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.15 (CH_3), 49.82 (CH_2), 100.89 (C-5_{imid}), 127.16 (2×*o*-CH_{arom}), 128.15 (*p*-CH_{arom}), 128.92 (2×*m*-CH_{arom}), 135.65 (C_{arom}), 136.91 (CH-2_{imid}), 137.20 (C-4_{imid}); MS (ESI) *m*/*z* (%) 250.9 (100) $[M+H]^+$, 253.0 (96).

4.1.2. 1-Benzyl-5-methyl-4-phenylimidazole (3a) and 1-benzyl-4-methyl-5-phenylimidazole (3b). *Method A.* A mixture of **2a** and **2b** (1:1.2) (966 mg, 3.8 mmol) and $Pd(PPh_3)_4$ (225 mg, 5 mol %) was dissolved in degassed toluene (9.3 mL). A degassed solution of phenylboronic acid (534 mg, 4.2 mmol) in absolute ethanol (5.4 mL) and aqueous 2 M Na_2CO_3 (9.3 mL, 19 mmol) were added to the above mixture. The reaction was heated at 110 °C for 24 h. After this time, the reaction mixture was extracted with CH_2Cl_2 (25 mL), the organic layer was washed with brine (25 mL), and dried. The solvent was evaporated leaving an amber colored oil, which was purified by column chromatography. Elution with hexane/EtOAc (1:2) afforded a mixture of **3a** and **3b** (669 mg, 71%) as a yellow oil.

Method B. A 30-mL vial containing a magnetic stir bar was charged with a solution of **2a** and **2b** (1:1.2) (200 mg, 0.8 mmol) and $Pd(PPh_3)_4$ (46 mg, 5 mol %) in degassed toluene (2 mL). Then, a degassed solution of phenylboronic acid (110 mg, 0.9 mmol) in EtOH (1.25 mL) and aqueous 2 M Na_2CO_3 (2 mL, 4.0 mmol) were added. The vial was sealed and heated under N_2 in the microwave lab station. Firstly, a microwave ramp (300 W maximum) was applied for 7 min to reach 110 °C. The reaction mixture was irradiated at this temperature for 10 min. After this time, upon cooling, the reaction mixture was extracted with EtOAc (25 mL). The organic solution was washed with water (25 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography. Elution with hexane/EtOAc (3:1) afforded **3a** as a colorless oil (16 mg, 8%). R_f (EtOAc/NH_3, 98:2) 0.48; ^1H NMR (200 MHz, $CDCl_3$) δ 2.22 (s, 3H, CH_3), 5.04 (s, 2H, CH_2), 7.01–7.05 (m, 2H, *o*′-CH_{arom}), 7.13–7.37 (m, 5H, *o*-, *m*- and *p*-CH_{arom}), 7.51 (s, 1H, CH-2_{imid}), 7.56–7.62 (m, 3H, *m*′- and *p*′-CH_{arom}); MS (ESI) *m*/*z* (%) 249.2 (100) $[M+H]^+$.

Gradient elution with hexane/EtOAc from 2:1 to 0:1 afforded **3b** as a yellow oil (122 mg, 62%). R_f (EtOAc/NH_3, 98:2) 0.30; ^1H NMR (200 MHz, $CDCl_3$) δ 2.15 (s, 3H, CH_3), 4.93 (s, 2H, CH_2), 6.86–6.91 (m, 2H, *o*′-CH_{arom}), 7.09–7.31 (m, 5H, *o*-, *m*- and *p*-CH_{arom}), 7.33–7.48 (m, 3H, *m*′- and *p*′-CH_{arom}), 7.42 (s, 1H, CH-2_{imid}); MS (ESI) *m*/*z* (%) 249.2 (100) $[M+H]^+$.

4.1.3. 4(5)-Methyl-5(4)-phenylimidazole (4). To a 100 mL two-necked flask cooled to −78 °C were added freshly cut sodium metal (211 mg, 9.2 mmol) and liquid ammonia (50 mL). When the solution became blue in color (20 min), *t*-BuOH (440 μL, 4.6 mmol) in anhydrous THF (8 mL) was added followed by a mixture of **3a** and **3b** (669 mg, 2.69 mmol) in anhydrous THF (25 mL). The reaction mixture was stirred at −78 °C for 45 min; by then, all the blue color had disappeared. Ammonia was evaporated by replacing the cooling bath with a water bath (20–30 °C). The reaction mixture was then quenched with aqueous NH_4Cl (2 mL) and extracted with EtOAc (25 mL). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed giving a residue, which was purified by column chromatography. Gradient elution with hexane/EtOAc from 1:2 to 1:8 afforded **4** as a white solid (286 mg, 68%). R_f (EtOAc/NH_3, 98:2) 0.18; mp 186–188 °C; IR (neat) 1599, 1519, 1472, 952, 768, 699 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 2.47 (s, 3H, CH_3), 7.30 (t, J=7.4 Hz, 1H, *p*-CH_{arom}), 7.48 (t, J=7.4 Hz, 2H, *m*-CH_{arom}), 7.67 (s, 1H, CH-2_{imid}), 7.71 (d, J=7.4 Hz, 2H, *o*-CH_{arom}); ^{13}C NMR (50 MHz, DMSO-d_6) δ 11.95 (CH_3), 124.93 (C-5_{imid}), 125.49 (*p*-CH_{arom}), 125.77 (2×*o*-CH_{arom}), 128.30 (2×*m*-CH_{arom}), 132.34 (C_{arom}), 133.68 (CH-2_{imid}), 134.58 (C-4_{imid}); MS (ESI) *m*/*z* (%) 159.1 (100) $[M+H]^+$;

HRMS (ESI) *m/z* calcd for $C_{10}H_{11}N_2$ $[M+H]^+$ 159.091675, found 159.091571.

4.2. Synthesis of 5-arylhistidines

4.2.1. Methyl *N*(α)-acetyl-5-bromo-L-histidinate (5) and methyl *N*(α)-acetyl-2,5-dibromo-L-histidinate. Ac-His-OH·H_2O (5.5 g, 25.4 mmol) was added to a mixture of anhydrous methanol (51 mL) and thionyl chloride (3.5 mL, 48.2 mmol). The reaction mixture was stirred at room temperature under N_2 for 2 h. The solvent was then removed in vacuo, H_2O (40 mL) was added followed by the addition of $NaHCO_3$ until pH=4–5. The solvent was removed affording a residue, which was purified by column chromatography. Elution with EtOAc/MeOH/NH_3 (10:2:0.2) gave methyl *N*(α)-acetyl-L-histidinate as a white solid (4.8 g, 90%). R_f ($CHCl_3$/MeOH/HOAc, 5:3:1) 0.49; IR (neat) 3269, 3199, 1738, 1650, 1541, 1435, 1374, 1211, 1175 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.92 (s, 3H, CH_3CO), 2.91 (dd, *J*=8.0 and 14.6 Hz, 1H, CH_2-β), 3.01 (dd, *J*=5.8 and 14.6 Hz, 1H, CH_2-β), 3.68 (s, 3H, CO_2CH_3), 4.55 (ddd, *J*=5.8, 8.0, and 7.4 Hz, 1H, CH-α), 6.89 (s, 1H, CH-5_{imid}), 7.62 (s, 1H, CH-2_{imid}), 8.31 (d, *J*=7.4 Hz, 1H, CONH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 22.26 (CH_3CO), 26.83 (CH_2-β), 51.87 (CO_2CH_3), 52.03 (CH-α), 116.97 (CH-5_{imid}), 130.47 (C-4_{imid}), 134.06 (CH-2_{imid}), 169.60 (CONH), 171.52 (COO); MS (ESI) *m/z* (%) 212.2 (47) $[M+H]^+$.

N-Bromosuccinimide (4.4 g, 23.9 mmol) was added to a solution of methyl *N*(α)-acetyl-L-histidinate (4.6 g, 21.8 mmol) in dry acetonitrile (125 mL) at 0 °C. The reaction mixture was stirred for 15 min at this temperature under N_2. Then, pyridine (40 μL) was added and the mixture was concentrated in vacuo. Triethylamine (0.4 mL) was added to the concentrated solution. Removal of the solvent gave a residue, which was purified by column chromatography. Elution with EtOAc/MeOH (99:1) gave methyl *N*(α)-acetyl-2,5-dibromo-L-histidinate as a white solid (1.1 g, 13%). R_f (EtOAc/MeOH, 5:1) 0.70; mp 144–146 °C; IR (neat) 3064, 2969, 1701, 1644, 1535, 1431, 1371, 1177, 971 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.13 (s, 3H, CH_3CO), 3.06 (dd, *J*=6.6 and 15.4 Hz, 1H, CH_2-β), 3.19 (dd, *J*=6.4 and 15.4 Hz, 1H, CH_2-β), 3.81 (s, 3H, CO_2CH_3), 4.81–4.91 (m, 1H, CH-α), 6.56 (d, *J*=7.8 Hz, 1H, CONH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.11 (CH_3CO), 27.87 (CH_2-β), 51.61 (CO_2CH_3), 53.01 (CH-α), 114.39 (C-5_{imid}), 115.29 (C-2_{imid}), 126.81 (C-4_{imid}), 171.29 (CONH), 171.34 (COO); MS (ESI) *m/z* (%) 367.9 (59), 369.9 (100), 372.0 (44) $[M+H]^+$.

Elution with EtOAc/MeOH/NH_3 (90:9:1) afforded **5** as a white solid (3.8 g, 60%). R_f (EtOAc/MeOH, 5:1) 0.18; mp 165–167 °C; IR (neat) 3321, 3277, 1730, 1661, 1544, 1434, 1371, 1177, 961 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.93 (s, 3H, CH_3CO), 2.95 (dd, *J*=7.4 and 14.8 Hz, 1H, CH_2-β), 3.06 (dd, *J*=7.4 and 14.8 Hz, 1H, CH_2-β), 3.67 (s, 3H, CO_2CH_3), 4.52 (q, *J*=7.4 Hz, 1H, CH-α), 7.66 (s, 1H, CH-2_{imid}), 8.39 (d, *J*=7.4 Hz, 1H, CONH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 22.30 (CH_3CO), 29.04 (CH_2-β), 51.70 (CO_2CH_3), 52.45 (CH-α), 116.52 (C-5_{imid}), 133.21 (C-4_{imid}), 134.34 (CH-2_{imid}), 169.28 (CONH), 172.24 (COO); MS (ESI) *m/z* (%) 290.0 (100), 291.9 (96) $[M+H]^+$. Anal. Calcd for $C_9H_{12}BrN_3O_3$: C, 37.26; H, 4.17; N, 14.48. Found: C, 36.95; H, 4.53; N, 14.24.

4.2.2. Methyl *N*(α)-acetyl-5-bromo-*N*(π)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (6a) and methyl *N*(α)-acetyl-5-bromo-*N*(τ)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (6b). DBU (0.2 mL, 1.4 mmol) was added to a solution of **5** (272 mg, 0.9 mmol) in dry DMF (1.8 mL) at 0 °C. The reaction mixture was stirred at this temperature under N_2 for 1.5 h. After this time, 2-(trimethylsilyl)ethoxymethyl chloride was added (0.2 mL, 0.9 mmol) and the reaction mixture was stirred at 0 °C under N_2 for 1.5 h. Next the crude product was poured into a mixture of water–ice (150 mL) and the product was extracted with toluene/EtOAc (1:1, 40 mL). The organic layer was washed with brine (40 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent afforded an oil, which was purified by column chromatography. Elution with hexane/EtOAc (1:2) gave **6a** as a colorless oil (96 mg, 24%). R_f (EtOAc/MeOH, 5:1) 0.52; IR (neat) 2952, 1743, 1663, 1544, 1436, 1371, 1235, 1207, 1086, 834 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.03 (s, 9H, $(CH_3)_3Si$), 0.93–1.02 (m, 2H, CH_2Si), 2.00 (s, 3H, CH_3CO), 3.09 (dd, *J*=7.6 and 15.2 Hz, 1H, CH_2-β), 3.18 (dd, *J*=6.8 and 15.2 Hz, 1H, CH_2-β), 3.41–3.67 (m, 2H, CH_2O), 3.78 (s, 3H, CO_2CH_3), 4.82–4.93 (m, 1H, CH-α), 5.30 (d, *J*=11.0 Hz, 1H, NCH_2O), 5.43 (d, *J*=11.0 Hz, 1H, NCH_2O), 6.34 (d, *J*=7.8 Hz, 1H, CONH), 7.49 (s, 1H, CH-2_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ −1.51 ($(CH_3)_3Si$), 17.62 (CH_2Si), 22.99 (CH_3CO), 26.69 (CH_2-β), 51.35 (CO_2CH_3), 52.82 (CH-α), 66.49 (CH_2O), 74.91 (NCH_2O), 117.72 (C-5_{imid}), 124.26 (C-4_{imid}), 137.26 (CH-2_{imid}), 169.68 (CONH), 171.56 (COO); MS (ESI) *m/z* (%) 419.9 (91), 421.9 (100) $[M+H]^+$. Anal. Calcd for $C_{15}H_{26}BrN_3O_4Si$: C, 42.86; H, 6.23; N, 10.00. Found: C, 42.76; H, 6.60; N, 10.34.

Elution with EtOAc/MeOH (99:1) afforded **6b** as a colorless oil (192 mg, 49%). R_f (EtOAc/MeOH, 5:1) 0.41; IR (neat) 2952, 1744, 1665, 1529, 1436, 1373, 1248, 1211, 1103, 835 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.01 (s, 9H, $(CH_3)_3Si$), 0.93 (t, *J*=8.0 Hz, 2H, CH_2Si), 2.05 (s, 3H, CH_3CO), 3.00 (dd, *J*=4.8 and 14.8 Hz, 1H, CH_2-β), 3.16 (dd, *J*=4.8 and 14.8 Hz, 1H, CH_2-β), 3.54 (t, *J*=8.0 Hz, 2H, CH_2O), 3.72 (s, 3H, CO_2CH_3), 4.88 (dt, *J*=4.8 and 8.0 Hz, 1H, CH-α), 5.26 (s, 2H, NCH_2O), 7.02 (d, *J*=8.0 Hz, 1H, CONH), 7.65 (s, 1H, CH-2_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ −1.38 ($(CH_3)_3Si$), 17.61 (CH_2Si), 23.14 (CH_3CO), 28.66 (CH_2-β), 51.51 (CO_2CH_3), 52.25 (CH-α), 66.52 (CH_2O), 74.78 (NCH_2O), 102.11 (C-5_{imid}), 136.51 (C-4_{imid}), 138.08 (CH-2_{imid}), 169.84 (CONH), 171.67 (COO); MS (ESI) *m/z* (%) 420.1 (100), 422.1 (87) $[M+H]^+$; HRMS (ESI) *m/z* calcd for $C_{15}H_{26}BrN_3NaO_4Si$ $[M]^+$ 442.0774, 444.0753, found 442.0777, 444.0757.

4.2.3. General method for the arylation of histidines 6a and 6b under microwave irradiation. A 30-mL vial containing a magnetic stir bar was charged with a solution of **6a** or **6b** (1 mmol), $Pd_2(dba)_3$, and P(*o*-tolyl)$_3$ in degassed toluene (15 mL). Then, a degassed solution of the corresponding arylboronic acid (2.1 mmol) in MeOH (10 mL) and aqueous 2 M KF (2 mmol) were added. The vial was sealed and heated under N_2 in the microwave lab station. Firstly, a microwave ramp (300 W maximum) was applied

for 7 min to reach 110 °C. The reaction mixture was irradiated at this temperature for periods of 10 or 15 min. After the total reaction time, upon cooling, the solvent was evaporated and the residue dissolved in EtOAc (50 mL). The organic solution was washed with water (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. Products were isolated by column chromatography.

4.2.3.1. Methyl *N*(α)-acetyl-5-phenyl-*N*(π)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (7a). From **6a** (100 mg, 0.24 mmol) following the general procedure using $Pd_2(dba)_3$ (10 mol %), P(*o*-tolyl)$_3$ (0.12 mmol), and phenylboronic acid, after 15 min irradiation, elution with hexane/EtOAc (1:1) afforded **7a** (82 mg, 82%) as a colorless oil. R_f (EtOAc/MeOH, 5:1) 0.48; IR (neat) 2952, 1742, 1662, 1504, 1438, 1367, 1248, 1200, 1081, 858, 835 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ −0.06 (s, 9H, $(CH_3)_3Si$), 0.85–0.94 (m, 2H, CH_2Si), 1.66 (s, 3H, CH_3CO), 3.33 (d, J=7.0 Hz, 2H, CH_2-β), 3.44 (s, 3H, CO_2CH_3), 3.46–3.55 (m, 2H, CH_2O), 4.70 (dt, J=7.0 and 7.8 Hz, 1H, CH-α), 5.27 (s, 2H, NCH_2O), 5.96 (d, J=7.8 Hz, 1H, CONH), 7.21 (tt, J=2.4 and 7.2 Hz, 1H, *p*-CH_{arom}), 7.33 (td, J=1.4 and 7.2 Hz, 2H, *m*-CH_{arom}), 7.52 (s, 1H, CH-2$_{imid}$), 7.55 (dt, J=2.4 and 7.2 Hz, 2H, *o*-CH_{arom}); ^{13}C NMR (50 MHz, $CDCl_3$) δ −1.48 ($(CH_3)_3Si$), 17.65 (CH_2Si), 22.70 (CH_3CO), 26.38 (CH_2-β), 51.83 (CO_2CH_3), 52.42 (CH-α), 66.24 (CH_2O), 74.24 (NCH_2O), 122.05 (C-5$_{imid}$), 127.07 (*p*-CH_{arom}), 127.38 (2×*o*-CH_{arom}), 128.64 (2×*m*-CH_{arom}), 134.81 (C_{arom}), 137.83 (CH-2$_{imid}$), 141.29 (C-4$_{imid}$), 169.61 (CONH), 171.70 (COO); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{32}N_3O_4Si$ $[M]^+$ 418.2157, found 418.2144; calcd for $C_{21}H_{31}N_3NaO_4Si$ $[M]^+$ 440.1976, found 440.1958.

4.2.3.2. Methyl *N*(α)-acetyl-5-phenyl-*N*(τ)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (7b). From **6b** (75 mg, 0.18 mmol) following the general procedure using $Pd_2(dba)_3$ (10 mol %), P(*o*-tolyl)$_3$ (0.09 mmol), and phenylboronic acid, after 10 min irradiation, gradient elution with hexane/EtOAc from 3:7 to 0:1 afforded **7b** (46 mg, 62%) as a yellow oil. R_f (EtOAc/MeOH, 10:1) 0.45; IR (neat) 2952, 1742, 1667, 1526, 1493, 1371, 1247, 1205, 1174, 1085, 858, 835 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ −0.01 (s, 9H, $(CH_3)_3Si$), 0.83–0.91 (m, 2H, CH_2Si), 2.04 (s, 3H, CH_3CO), 3.02 (dd, J=5.0 and 14.8 Hz, 1H, CH_2-β), 3.18 (dd, J=5.0 and 14.8 Hz, 1H, CH_2-β), 3.39–3.48 (m, 2H, CH_2O), 3.55 (s, 3H, CO_2CH_3), 4.78 (dt, J=5.0 and 7.6 Hz, 1H, CH-α), 5.14 (s, 2H, NCH_2O), 7.34–7.39 (m, 2H, *o*-CH_{arom}), 7.44–7.54 (m, 3H, *m*- and *p*-CH_{arom}), 7.65 (s, 1H, CH-2$_{imid}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ −1.49 ($(CH_3)_3Si$), 17.69 (CH_2Si), 23.16 (CH_3CO), 28.23 (CH_2-β), 51.95 (CO_2CH_3), 52.10 (CH-α), 66.31 (CH_2O), 74.02 (NCH_2O), 77.21 (C-5$_{imid}$), 128.53 (*p*-CH_{arom}), 128.74 (2×*o*-CH_{arom}), 130.26 (2×*m*-CH_{arom}), 135.06 (C_{arom}), 135.18 (C-4$_{imid}$), 137.26 (CH-2$_{imid}$), 170.00 (CONH), 171.90 (COO); MS (ESI) *m*/*z* (%) 418.0 (100) $[M+H]^+$; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{32}N_3O_4Si$ $[M]^+$ 418.215659, found 418.215322.

4.2.3.3. Methyl *N*(α)-acetyl-5-(2-methoxy-5-methylphenyl)-*N*(π)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (8a). From **6a** (75 mg, 0.18 mmol) following the general procedure using $Pd_2(dba)_3$ (10 mol %), P(*o*-tolyl)$_3$ (0.09 mmol), and 2-methoxy-5-methylphenylboronic acid, after 1 h irradiation, elution with hexane/EtOAc (3:7) afforded **8a** (45 mg, 54%) as a colorless oil. R_f (EtOAc/MeOH, 10:1) 0.38; IR (neat) 2952, 1744, 1666, 1509, 1243, 1208, 1179, 1085, 1030, 858, 835 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ −0.03 (s, 9H, $(CH_3)_3Si$), 0.95–1.03 (m, 2H, CH_2Si), 1.74 (s, 3H, CH_3CO), 2.33 (s, 3H, CH_3), 3.19 (dd, J=8.8 and 15.3 Hz, 1H, CH_2-β), 3.32 (dd, J=5.6 and 15.3 Hz, 1H, CH_2-β), 3.55–3.63 (m, 2H, CH_2O), 3.60 (s, 3H, CO_2CH_3), 3.83 (s, 3H, OCH_3), 4.66–4.74 (m, 1H, CH-α), 5.32 (s, 2H, NCH_2O), 6.07 (d, J=7.4 Hz, 1H, CONH), 6.89 (d, J=8.3 Hz, 1H, CH-3$_{arom}$), 7.15 (dd, J=2.1 and 8.3 Hz, 1H, CH-4$_{arom}$), 7.32 (d, J=2.1 Hz, 1H, CH-6$_{arom}$), 7.63 (s, 1H, CH-2$_{imid}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ −1.50 ($(CH_3)_3Si$), 17.60 (CH_2Si), 20.26 (CH_3), 22.58 (CH_3CO), 25.98 (CH_2-β), 51.56 (CO_2CH_3), 52.20 (CH-α), 55.61 (OCH_3), 66.20 (CH_2O), 74.34 (NCH_2O), 111.39 (CH-3$_{arom}$), 123.46 (C-5$_{imid}$), 123.63 (C-1$_{arom}$), 129.44 (CH-6$_{arom}$), 130.24 (C-5$_{arom}$), 132.56 (CH-4$_{arom}$), 137.85 (CH-2$_{imid}$), 138.40 (C-4$_{imid}$), 153.86 (C-2$_{arom}$), 169.59 (CONH), 171.92 (COO); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{36}N_3O_5Si$ $[M]^+$ 462.241874, found 462.239847.

4.2.3.4. Methyl *N*(α)-acetyl-5-(2-methoxy-5-methylphenyl)-*N*(τ)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (8b). From **6b** (75 mg, 0.18 mmol) following the general procedure using $Pd_2(dba)_3$ (10 mol %), P(*o*-tolyl)$_3$ (0.09 mmol), and 2-methoxy-5-methylphenylboronic acid, after 1 h irradiation, elution with hexane/EtOAc (3:7) afforded **8b** (30 mg, 36%) as a yellow oil. R_f (EtOAc/MeOH, 10:1) 0.25; IR (neat) 2951, 1745, 1671, 1500, 1246, 1208, 1169, 1088, 1025, 858, 835 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ −0.05 (s, 9H, $(CH_3)_3Si$), 0.74–0.82 (m, 2H, CH_2Si), 2.02 (s, 1.5H, CH_3CO), 2.04 (s, 1.5H, CH_3CO), 2.35 (s, 3H, CH_3), 2.86–3.02 (m, 2H, CH_2-β), 3.24–3.32 (m, 2H, CH_2O), 3.51 (s, 1.5H, CO_2CH_3), 3.65 (s, 1.5H, CO_2CH_3), 3.78 (s, 3H, OCH_3), 4.69–4.77 (m, 1H, CH-α), 4.96–5.27 (m, 2H, NCH_2O), 6.90 (d, J=8.6 Hz, 1H, CH-3$_{arom}$), 6.99 (d, J=2.1 Hz, 1H, CH-6$_{arom}$), 7.24 (dd, J=2.1 and 8.6 Hz, 1H, CH-4$_{arom}$), 7.32 (d, J=7.0 Hz, 0.5H, CONH), 7.41 (d, J=7.0 Hz, 0.5H, CONH), 7.66 (s, 1H, CH-2$_{imid}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ −1.57 ($(CH_3)_3Si$), 17.65 (CH_2Si), 20.35 (CH_3), 23.09 (CH_3CO), 28.37 (CH_2-β), (51.77, 52.31) (CO_2CH_3), 51.98 (CH-α), 55.48 (OCH_3), 66.17 (CH_2O), (74.38, 74.67) (NCH_2O), 111.02 (CH-3$_{arom}$), 117.23 (C-1$_{arom}$), 126.53 (C-5$_{arom}$), (130.02, 130.25) (C-5$_{imid}$), 130.99 (CH-6$_{arom}$), 133.16 (CH-4$_{arom}$), (135.01, 135.18) (C-4$_{imid}$), 137.12 (CH-2$_{imid}$), 155.33 (C-2$_{arom}$), 169.92 (CONH), (171.91, 172.10) (COO); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{36}N_3O_5Si$ $[M]^+$ 462.2419, found 462.2406; calcd for $C_{23}H_{35}N_3NaO_5Si$ $[M]^+$ 484.2238, found 484.2211.

4.2.3.5. Methyl *N*(α)-acetyl-5-(2-methoxyphenyl)-*N*(π)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (9a). From **6a** (75 mg, 0.18 mmol) following the general procedure using $Pd_2(dba)_3$ (20 mol %), P(*o*-tolyl)$_3$ (0.18 mmol), and 2-methoxyphenylboronic acid, after 1 h irradiation, elution with hexane/EtOAc (3:7) afforded **9a** (54 mg, 68%) as a colorless oil. R_f (EtOAc/MeOH, 10:1) 0.30; IR (neat) 2951, 1740, 1663, 1503, 1435, 1370, 1243, 1202, 1086, 1025, 858, 836 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.04 (s, 9H, $(CH_3)_3Si$), 0.95–1.03 (m, 2H, CH_2Si), 1.74 (s, 3H,

CH_3CO), 3.24 (dd, J=7.0 and 15.6 Hz, 1H, CH_2-β), 3.36 (dd, J=5.8 and 15.6 Hz, 1H, CH_2-β), 3.55–3.64 (m, 2H, CH_2O), 3.57 (s, 3H, CO_2CH_3), 3.86 (s, 3H, OCH_3), 4.67–4.77 (m, 1H, CH-α), 5.33 (s, 2H, NCH_2O), 6.06 (d, J=7.2 Hz, 1H, CONH), 7.00 (dd, J=0.9 and 7.6 Hz, 1H, CH-3_{arom}), 7.08 (td, J=0.9 and 7.6 Hz, 1H, CH-5_{arom}), 7.37 (td, J=1.7 and 7.6 Hz, 1H, CH-4_{arom}), 7.50 (dd, J=1.7 and 7.6 Hz, 1H, CH-6_{arom}), 7.65 (s, 1H, CH-2_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ −1.49 ($(CH_3)_3Si$), 17.61 (CH_2Si), 22.66 (CH_3CO), 26.03 (CH_2-β), 51.54 (CO_2CH_3), 52.25 (CH-α), 55.47 (OCH_3), 66.24 (CH_2O), 74.35 (NCH_2O), 111.30 (CH-3_{arom}), 121.05 (CH-5_{arom}), 123.68 (C-5_{imid}), 123.72 (C-1_{arom}), 129.13 (CH-6_{arom}), 132.03 (CH-4_{arom}), 137.91 (CH-2_{imid}), 138.23 (C-4_{imid}), 156.01 (C-2_{arom}), 169.64 (CONH), 171.88 (COO); HRMS (ESI) m/z calcd for $C_{22}H_{34}N_3O_5Si$ $[M]^+$ 448.2262, found 448.2257.

4.2.3.6. Methyl *N*(α)-acetyl-5-(2-methoxyphenyl)-*N*(τ)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (9b). From **6b** (75 mg, 0.18 mmol) following the general procedure using $Pd_2(dba)_3$ (40 mol %), P(*o*-tolyl)$_3$ (0.36 mmol), and 2-methoxyphenylboronic acid, after 10 min irradiation, elution with hexane/EtOAc (4:6) afforded **9b** (41 mg, 51%) as a yellow oil. R_f (EtOAc/MeOH, 5:1) 0.33; IR (neat) 2952, 1745, 1668, 1526, 1493, 1435, 1247, 1207, 1173, 1088, 1023, 858, 836 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ −0.05 (s, 9H, $(CH_3)_3Si$), 0.73–0.81 (m, 2H, CH_2Si), 2.01 (s, 3H, CH_3CO), 2.89–3.15 (m, 2H, CH_2-β), 3.24–3.33 (m, 2H, CH_2O), 3.50 (s, 1.5H, CO_2CH_3), 3.63 (s, 1.5H, CO_2CH_3), 3.82 (s, 3H, OCH_3), 4.68–4.77 (m, 1H, CH-α), 4.97–5.33 (m, 2H, NCH_2O), 7.00–7.10 (m, 2H, CH-3_{arom} and CH-5_{arom}), 7.18 (br, 1H, CONH), 7.41–7.50 (m, 2H, CH-4_{arom} and CH-6_{arom}), 7.67 (s, 1H, CH-2_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ −1.57 ($(CH_3)_3Si$), 17.60 (CH_2Si), 23.07 (CH_3CO), 28.31 (CH_2-β), (51.52, 52.27) (CO_2CH_3), 51.95 (CH-α), 55.34 (OCH_3), 66.13 (CH_2O), (74.35, 74.65) (NCH_2O), 111.03 (CH-3_{arom}), 117.50 (C-1_{arom}), (120.79, 121.00) (CH-5_{arom}), (126.34, 126.57) (C-5_{imid}), 130.63 (CH-6_{arom}), 132.68 (CH-4_{arom}), (135.10, 135.32) (C-4_{imid}), 137.13 (CH-2_{imid}), (157.18, 157.39) (C-2_{arom}), 169.95 (CONH), (171.89, 172.05) (COO); HRMS (ESI) m/z calcd for $C_{22}H_{34}N_3O_5Si$ $[M]^+$ 448.226224, found 448.224059.

4.2.3.7. Methyl *N*(α)-acetyl-5-(3-pyridyl)-*N*(π)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (10a). From **6a** (116 mg, 0.28 mmol) following the general procedure using $Pd_2(dba)_3$ (40 mol %), P(*o*-tolyl)$_3$ (0.56 mmol), and 3-pyridylboronic acid, after 10 min irradiation, gradient elution with EtOAc/MeOH from 95:5 to 92:8 afforded **10a** (46 mg, 40%) as a colorless oil. R_f (EtOAc/MeOH, 5:1) 0.18; IR (neat) 2952, 1743, 1665, 1368, 1249, 1083, 858, 835 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.03 (s, 9H, $(CH_3)_3Si$), 0.95–1.03 (m, 2H, CH_2Si), 1.82 (s, 3H, CH_3CO), 3.38–3.42 (m, 2H, CH_2-β), 3.53 (s, 3H, CO_2CH_3), 3.56–3.65 (m, 2H, CH_2O), 4.79–4.90 (m, 1H, CH-α), 5.32 (d, J=11.0 Hz, 1H, NCH_2O), 5.41 (d, J=11.0 Hz, 1H, NCH_2O), 6.43 (d, J=7.8 Hz, 1H, CONH), 7.34 (bb, 1H, CH-5_{Py}), 7.66 (s, 1H, CH-2_{imid}), 8.01 (d, J=8.0 Hz, 1H, CH-4_{Py}), 8.53 (bb, 1H, CH-6_{Py}), 8.91 (bb, 1H, CH-2_{Py}); ^{13}C NMR (50 MHz, $CDCl_3$) δ −1.50 ($(CH_3)_3Si$), 17.65 (CH_2Si), 22.72 (CH_3CO), 26.75 (CH_2-β), 51.59 (CO_2CH_3), 52.48 (CH-α), 66.39 (CH_2O), 74.37 (NCH_2O), 123.36 (C-5_{imid}, CH-5_{Py}), 130.73 (C-3_{Py}), 134.78 (CH-4_{Py}), 137.96 (C-4_{imid}), 138.39 (CH-2_{imid}), 147.80 (CH-6_{Py}), 148.00 (CH-2_{Py}), 169.68 (CONH), 171.47 (COO); HRMS (ESI) m/z calcd for $C_{20}H_{31}N_4O_4Si$ $[M]^+$ 419.2109, found 419.2092; calcd for $C_{20}H_{30}N_4NaO_4Si$ $[M]^+$ 441.1929, found 441.1902.

4.2.3.8. Methyl *N*(α)-acetyl-5-(3-pyridyl)-*N*(τ)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (10b). From **6b** (75 mg, 0.18 mmol) following the general procedure using $Pd_2(dba)_3$ (40 mol %), P(*o*-tolyl)$_3$ (0.36 mmol), and 3-pyridylboronic acid, after 10 min irradiation, elution with EtOAc/MeOH/NH_3 (96:3:1) afforded **10b** (25 mg, 33%) as a yellow oil. R_f (EtOAc/MeOH, 5:1) 0.20; IR (neat) 2952, 1744, 1667, 1494, 1248, 1207, 1174, 1086, 858, 836 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.01 (s, 9H, $(CH_3)_3Si$), 0.86–0.94 (m, 2H, CH_2Si), 2.05 (s, 3H, CH_3CO), 3.01 (dd, J=5.0 and 15.0 Hz, 1H, CH_2-β), 3.17 (dd, J=5.0 and 15.0 Hz, 1H, CH_2-β), 3.45–3.53 (m, 2H, CH_2O), 3.58 (s, 3H, CO_2CH_3), 4.82 (dt, J=5.0 and 7.8 Hz, 1H, CH-α), 5.13 (s, 2H, NCH_2O), 7.44 (dd, J=5.0 and 7.8 Hz, 1H, CH-5_{Py}), 7.46 (d, J=7.8 Hz, 1H, CONH), 7.67 (s, 1H, CH-2_{imid}), 7.77 (dt, J=2.0 and 7.8 Hz, 1H, CH-4_{Py}), 8.63 (d, J=2.0 Hz, 1H, CH-2_{Py}), 8.69 (dd, J=2.0 and 5.0 Hz, 1H, CH-6_{Py}); ^{13}C NMR (50 MHz, $CDCl_3$) δ −0.85 ($(CH_3)_3Si$), 18.34 (CH_2Si), 23.80 (CH_3CO), 28.89 (CH_2-β), 52.56 (CO_2CH_3), 52.72 (CH-α), 67.07 (CH_2O), 74.82 (NCH_2O), 124.10 (CH-5_{Py}), 125.74 (C-5_{imid}), 127.46 (C-3_{Py}), 137.40 (C-4_{imid}), 138.24 (CH-4_{Py}), 138.62 (CH-2_{imid}), 150.28 (CH-6_{Py}), 151.36 (CH-2_{Py}), 170.62 (CONH), 172.43 (COO); HRMS (ESI) m/z calcd for $C_{20}H_{31}N_4O_4Si$ $[M]^+$ 419.2109, found 419.2096; calcd for $C_{20}H_{30}N_4NaO_4Si$ $[M]^+$ 441.1929, found 441.1915.

4.2.3.9. Methyl *N*(α)-acetyl-5-(3-thienyl)-*N*(π)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (11a). From **6a** (75 mg, 0.18 mmol) following the general procedure using $Pd_2(dba)_3$ (20 mol %), P(*o*-tolyl)$_3$ (0.18 mmol), and 3-thienylboronic acid, after 15 min irradiation, elution with hexane/EtOAc (4:6) afforded **11a** (64 mg, 85%) as a yellow oil. R_f (EtOAc/MeOH, 10:1) 0.33; IR (neat) 2952, 1742, 1660, 1248, 1199, 1083, 857, 835 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.02 (s, 9H, $(CH_3)_3Si$), 0.93–1.01 (m, 2H, CH_2Si), 1.82 (s, 3H, CH_3CO), 3.37 (d, J=7.4 Hz, 2H, CH_2-β), 3.54–3.62 (m, 2H, CH_2O), 3.58 (s, 3H, CO_2CH_3), 4.84 (q, J=7.4 Hz, 1H, CH-α), 5.35 (s, 2H, NCH_2O), 6.41 (d, J=7.4 Hz, 1H, CONH), 7.37 (dd, J=2.8 and 5.1 Hz, 1H, CH-5_{thien}), 7.45 (dd, J=1.4 and 5.1 Hz, 1H, CH-4_{thien}), 7.54 (dd, J=1.4 and 2.8 Hz, 1H, CH-2_{thien}), 7.68 (s, 1H, CH-2_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ −1.55 ($(CH_3)_3Si$), 17.61 (CH_2Si), 22.64 (CH_3CO), 26.52 (CH_2-β), 51.66 (CO_2CH_3), 52.45 (CH_2-α), 66.33 (CH_2O), 74.29 (NCH_2O), 120.96 (CH-2_{thien}), 121.83 (C-5_{imid}), 125.90 (CH-5_{thien}), 126.53 (CH-4_{thien}), 134.87 (C-3_{thien}), 136.61 (C-4_{imid}), 137.40 (CH-2_{imid}), 169.78 (CONH), 171.73 (COO); HRMS (ESI) m/z calcd for $C_{19}H_{30}N_3O_4SSi$ $[M]^+$ 424.1721, found 424.1709.

4.2.3.10. Methyl *N*(α)-acetyl-5-(3-thienyl)-*N*(τ)-[2-(trimethylsilyl)ethoxymethyl]-L-histidinate (11b). From **6b** (75 mg, 0.18 mmol) following the general procedure using $Pd_2(dba)_3$ (20 mol %), P(*o*-tolyl)$_3$ (0.18 mmol), and 3-thienylboronic acid, after 30 min irradiation, elution with hexane/EtOAc (1:2) afforded **11b** (41 mg, 54%) as a yellow

oil. R_f (EtOAc/MeOH, 5:1) 0.35; IR (neat) 2952, 1744, 1669, 1493, 1248, 1083, 858, 836 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ −0.01 (s, 9H, $(CH_3)_3Si$), 0.85–0.93 (m, 2H, CH_2Si), 2.00 (s, 3H, CH_3CO), 3.00 (dd, J=5.0 and 14.8 Hz, 1H, CH_2-β), 3.21 (dd, J=5.0 and 14.8 Hz, 1H, CH_2-β), 3.44–3.52 (m, 2H, CH_2O), 3.57 (s, 3H, CO_2CH_3), 4.79 (dt, J=5.0 and 10.0 Hz, 1H, CH-α), 5.14 (s, 2H, NCH_2O), 7.17–7.20 (m, 1H, CH-5_{thien}), 7.43–7.49 (m, 3H, CH-4_{thien}, CH-2_{thien}, CONH), 7.60 (s, 1H, CH-2_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ −1.56 ($(CH_3)_3Si$), 17.64 (CH_2Si), 23.02 (CH_3CO), 28.45 (CH_2-β), 51.93 (CO_2CH_3), 52.02 (CH-α), 66.14 (CH_2O), 73.95 (NCH_2O), 125.14 (CH-2_{thien}), 125.45 (C-5_{imid}), 126.19 (CH-5_{thien}), 128.44 (CH-4_{thien}), 128.54 (C-3_{thien}), 135.35 (C-4_{imid}), 137.20 (CH-2_{imid}), 169.93 (CONH), 171.84 (COO); HRMS (ESI) m/z calcd for $C_{19}H_{30}N_3O_4SSi$ $[M]^+$ 424.1721, found 424.1737; calcd for $C_{19}H_{29}N_3NaO_4SSi$ $[M]^+$ 446.1540, found 424.1548.

4.2.4. General method for the removal of the SEM group. The corresponding arylhistidines **7–11** (1 mmol) were dissolved in TFA/CH_2Cl_2 (2:1, 24 mL) and stirred at room temperature. After the total reaction time (Table 2), the solvent was evaporated. Products were isolated by column chromatography.

4.2.4.1. Methyl *N*(α)-acetyl-5-phenyl-L-histidinate (12). From **7a** (81 mg, 0.19 mmol) following the general procedure after 2.5 h reaction, elution with EtOAc/MeOH/NH_3 (98:1:1) afforded **12** (55 mg, 99%) as a colorless oil. From **7b** (108 mg, 0.26 mmol) following the general procedure after 1.5 h reaction, elution with EtOAc/MeOH/NH_3 (98:1:1) afforded **12** (72 mg, 97%) as a colorless oil. R_f (EtOAc/MeOH/NH_3, 98:1:1) 0.33; $[\alpha]_D^{20}$ 9.74 (c 0.27, MeOH); IR (neat) 1741, 1659, 1436, 1374, 1198, 1177, 1130 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.95 (s, 3H, CH_3CO), 3.21 (dd, J=5.2 and 15.4 Hz, 1H, CH_2-β), 3.35 (dd, J=5.2 and 15.4 Hz, 1H, CH_2-β), 3.50 (s, 3H, CO_2CH_3), 4.81 (dt, J=5.2 and 7.8 Hz, 1H, CH-α), 7.26–7.43 (m, 5H, CH_{arom}), 7.53 (s, 1H, CH-2_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.06 (CH_3CO), 27.56 (CH_2-β), 51.14 (CO_2CH_3), 51.20 (CH-α), 126.14 (2×o-CH_{arom}), 126.45 (p-CH_{arom}), 127.88 (2×m-CH_{arom}), 128.68, 129.72, 130.35 (C-4_{imid}, C-5_{imid}, C-1_{arom}), 133.55 (CH-2_{imid}), 169.43 (CONH), 170.99 (COO); HRMS (ESI) m/z calcd for $C_{15}H_{18}N_3O_3$ $[M]^+$ 288.1343, found 288.1339; calcd for $C_{15}H_{17}N_3NaO_3$ $[M]^+$ 310.11.62, found 310.1171.

4.2.4.2. Methyl *N*(α)-acetyl-5-(2-methoxy-5-methylphenyl)-L-histidinate (13). From **8a** (121 mg, 0.26 mmol) following the general procedure after 1.5 h reaction, elution with EtOAc afforded **13** (61 mg, 70%) as a pale yellow solid. From **8b** (49 mg, 0.11 mmol) following the general procedure after 1.5 h reaction, elution with EtOAc afforded **13** (32 mg, 91%) as a pale yellow solid. R_f (EtOAc/MeOH, 10:3) 0.36; mp 50–51 °C; $[\alpha]_D^{19}$ 10.47 (c 0.28, MeOH); IR (neat) 1742, 1658, 1502, 1437, 1241, 1026, 807 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.96 (s, 3H, CH_3CO), 2.34 (s, 3H, CH_3), 3.16 (dd, J=4.7 and 14.8 Hz, 1H, CH_2-β), 3.33 (dd, J=6.2 and 14.8 Hz, 1H, CH_2-β), 3.57 (s, 3H, CO_2CH_3), 3.84 (s, 3H, OCH_3), 4.82 (ddd, J=4.7, 6.2, and 7.4 Hz, 1H, CH-α), 6.89 (d, J=8.4 Hz, 1H, CH-3_{arom}), 7.13 (dd, J=2.0 and 8.4 Hz, 1H, CH-4_{arom}), 7.21 (d, J=2.0 Hz, 1H, CH-6_{arom}), 7.45 (d, J=7.4 Hz, 1H, NHCO), 7.59 (s, 1H, CH-2_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.38 (CH_3), 22.92 (CH_3CO), 28.86 (CH_2-β), 51.99 (CO_2CH_3), 52.18 (CH-α), 55.63 (OCH_3), 111.33 (CH-3_{arom}), 118.69 (C-1_{arom}), 125.61 (C-5_{imid}), 129.45 (CH-6_{arom}), 130.29 (CH-4_{arom}), 130.39 (C-4_{imid}), 132.30 (C-5_{arom}), 133.71 (CH-2_{imid}), 153.80 (C-2_{arom}), 170.29 (CONH), 172.08 (COO); HRMS (ESI) m/z calcd for $C_{17}H_{22}N_3O_4$ $[M]^+$ 332.1605, found 332.1591; calcd for $C_{17}H_{21}N_3NaO_4$ $[M]^+$ 354.1424, found 354.1408.

4.2.4.3. Methyl *N*(α)-acetyl-5-(2-methoxyphenyl)-L-histidinate (14). From **9a** (85 mg, 0.19 mmol) following the general procedure after 3.5 h reaction, elution with EtOAc/MeOH (99:1) afforded **14** (54 mg, 90%) as a pale yellow solid. From **9b** (85 mg, 0.19 mmol) following the general procedure after 1.5 h reaction, elution with EtOAc/MeOH (99:1) afforded **14** (55 mg, 91%) as a pale yellow solid. R_f (EtOAc/MeOH, 10:3) 0.36; mp 50–51 °C; $[\alpha]_D^{19}$ 9.55 (c 0.22, MeOH); IR (neat) 1740, 1661, 1435, 1375, 1246, 1200, 1178, 1127, 1022, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.92 (s, 3H, CH_3CO), 3.21 (d, J=6.0 Hz, 2H, CH_2-β), 3.56 (s, 3H, CO_2CH_3), 3.84 (s, 3H, OCH_3), 4.81 (dt, J=6.0 and 7.8 Hz, 1H, CH-α), 6.98–7.07 (m, 2H, CH-3_{arom} and CH-5_{arom}), 7.33–7.42 (m, 2H, CH-4_{arom} and CH-6_{arom}), 7.54 (d, J=7.8 Hz, 1H, CONH), 7.81 (s, 1H, CH-2_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.72 (CH_3CO), 28.00 (CH_2-β), 51.99 (CO_2CH_3), 52.22 (CH_2-α), 55.45 (OCH_3), 111.35 (CH-3_{arom}), 117.84 (C-1_{arom}), 121.06 (CH-5_{arom}), 126.70 (C-5_{imid}), 129.71 (C-4_{imid}), 130.10 (CH-6_{arom}), 130.30 (CH-4_{arom}), 133.24 (CH-2_{imid}), 156.24 (C-2_{arom}), 170.71 (CONH), 171.68 (COO); HRMS (ESI) m/z calcd for $C_{16}H_{20}N_3O_4$ $[M]^+$ 318.1448, found 318.1435; calcd for $C_{16}H_{19}N_3NaO_4$ $[M]^+$ 340.1268, found 340.1250.

4.2.4.4. Methyl *N*(α)-acetyl-5-(3-pyridyl)-L-histidinate (15). From **10a** (71 mg, 0.17 mmol) following the general procedure after 2.5 h reaction, elution with EtOAc/MeOH/NH_3 (96:3:1) afforded **15** (44 mg, 90%) as a colorless oil. From **10b** (43 mg, 0.10 mmol) following the general procedure after 3.5 h reaction, elution with EtOAc/MeOH/NH_3 (96:3:1) afforded **15** (27 mg, 92%) as a colorless oil. R_f (EtOAc/MeOH, 10:3) 0.1; $[\alpha]_D^{20}$ 6.99 (c 0.27, MeOH); IR (neat) 1740, 1658, 1199, 1177, 1130, 712 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.99 (s, 3H, CH_3CO), 3.28 (dd, J=6.6 and 15.4 Hz, 1H, CH_2-β), 3.41 (dd, J=5.4 and 15.4 Hz, 1H, CH_2-β), 3.63 (s, 3H, CO_2CH_3), 4.86 (ddd, J=5.4, 6.6, and 7.4 Hz, 1H, CH-α), 7.38 (d, J=7.4 Hz, 1H, CONH), 7.40 (dd, J=4.8 and 8.0 Hz, 1H, CH-5_{Py}), 7.85 (s, 1H, CH-2_{imid}), 7.94 (dt, J=1.8 and 8.0 Hz, 1H, CH-4_{Py}), 8.54 (dd, J=1.8 and 4.8 Hz, 1H, CH-6_{Py}), 8.80 (d, J=1.8 Hz, 1H, CH-2_{Py}); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.89 (CH_3CO), 28.41 (CH_2-β), 52.08 (CO_2CH_3), 52.54 (CH-α), 123.86 (CH-5_{Py}), 127.82, 128.46, 129.91 (C-3_{Py}, C-4_{imid}, C-5_{imid}), 134.91 (CH-4_{Py}), 135.31 (CH-2_{imid}), 147.61 (CH-6_{Py}), 147.83 (CH-2_{Py}), 170.86 (CONH), 171.61 (COO); HRMS (ESI) m/z calcd for $C_{14}H_{17}N_4O_3$ $[M]^+$ 289.1295, found 289.1293; calcd for $C_{14}H_{16}N_4NaO_3$ $[M]^+$ 311.1115, found 311.1114.

4.2.4.5. Methyl *N*(α)-acetyl-5-(3-thienyl)-L-histidinate (16). From **11a** (121 mg, 0.29 mmol) following the general

procedure after 2.0 h reaction, gradient elution from EtOAc/MeOH (99:1) to EtOAc/MeOH/NH_3 (98:1:1) afforded **16** (83 mg, 99%) as a yellow solid. From **11b** (84 mg, 0.20 mmol) following the general procedure after 2.0 h reaction, gradient elution from EtOAc/MeOH (99:1) to EtOAc/MeOH/NH_3 (98:1:1) afforded **16** (57 mg, 99%) as a yellow solid. R_f (EtOAc/MeOH, 10:3) 0.33; mp 49–50 °C; $[\alpha]_D^{19}$ 7.55 (*c* 0.26, MeOH); IR (neat) 1739, 1660, 1198, 1177, 1129 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.95 (s, 3H, CH_3CO), 3.25 (dd, *J*=8.0 and 15.2 Hz, 1H, CH_2-β), 3.38 (dd, *J*=5.2 and 15.2 Hz, 1H, CH_2-β), 3.64 (s, 3H, CO_2CH_3), 4.78–4.88 (m, 1H, CH-α), 7.31 (d, *J*=4.4 Hz, 1H, CH-4_{thien}), 7.40 (dd, *J*=2.8 and 4.4 Hz, 1H, CH-5_{thien}), 7.50 (d, *J*=2.8 Hz, 1H, CH-2_{thien}), 7.60 (d, *J*=8.0 Hz, 1H, CONH), 7.87 (s, 1H, CH-2_{imid}); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.71 (CH_3CO), 27.98 (CH_2-β), 52.14 (CO_2CH_3), 52.59 (CH-α), 122.42 (CH-2_{thien}), 126.11 (CH-5_{thien}), 126.56 (C-5_{imid}), 126.99 (CH-4_{thien}), 127.35 (C-3_{thien}), 129.94 (C-4_{imid}), 133.38 (CH-2_{imid}), 171.16 (CONH), 171.44 (COO); HRMS (ESI) *m*/*z* calcd for $C_{13}H_{16}N_3O_3S$ $[M]^+$ 294.0907, found 294.0893; calcd for $C_{13}H_{15}N_3NaO_3S$ $[M]^+$ 316.0726, found 316.0714.

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