Synthesis of 4(5)-Acyl-2-aminoimidazoles and Vinylogues

Christoph Pöverlein,[a] Nicolas Jacobi,[b] Peter Mayer,[a] Thomas Lindel*[b]

[a] Department of Chemistry and Biochemistry, Faculty of Chemistry and Pharmacy, Ludwig Maximilian University, Butenandtstr. 5-13, 81377 Munich, Germany

[b] Institute of Organic Chemistry, Faculty of Life Sciences, TU Braunschweig, Hagenring 30, 38106 Brunswick, Germany
Fax +49(531)3917744; E-mail: th.lindel@tu-bs.de

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Abstract: A convenient protocol for the preparation of 4(5)-acyl-2-aminoimidazoles and vinylogues is disclosed employing a crystalline imidazole-derived iminophosphorane as the coupling partner in Heck and Sonogashira reactions. For the first time, derivatives of urocanic acid bearing a free amino group in the 2′-position are described.

Key words: aminoimidazole, iminophosphorane, cross coupling, pyrrole-imidazole-alkaloids, alkyne hydration

2-Aminoimidazoles are of interest in the life sciences, because their guanidine partial structure is embedded in the aromatic system of an imidazole. Compared to the arginine side chain, the basicity of the guanidine unit of 2-aminoimidazole is diminished by 4–5 pK_a units, while similar interactions with biochemical targets can be expected. Marine sponges make use of this technology.[1] Recently, we have synthesized the new amino acid 2′-aminohomohistidine (2′-Ahh) as a less basic analogue of arginine.[2]

Surprisingly, 2-aminoimidazoles have not played an important role in medicinal chemistry, possibly due to limittations regarding their synthesis. In particular, knowledge regarding the chemical functionalization of free 2-aminoimidazole is still limited. With regard to the 4(5)-position, Horne reported hydroxyalkylations in up to 40% yields.[3] In this study, we address the synthesis of 4(5)-acyl-2-aminoimidazoles (n = 0, Figure 1) and of derivatives of the physiologically important urocanic acid[4] (n = 1) with an additional amino group in the imidazole 2-position.

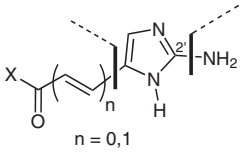
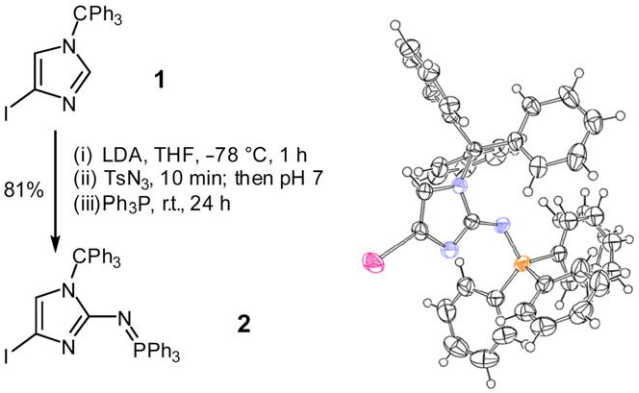


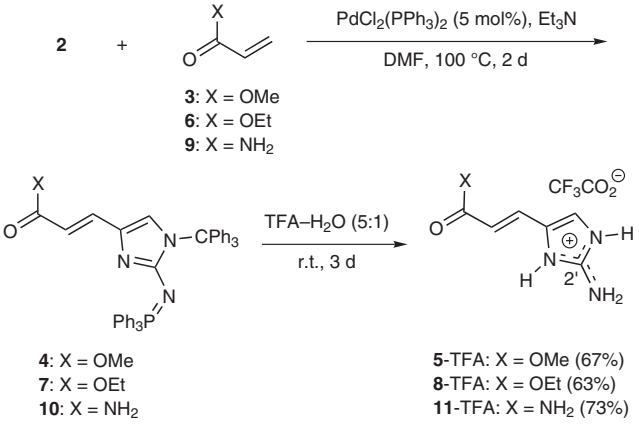
Figure 1 Target structures and retrosynthetic cuts

Searching for a suitable synthetic equivalent of 2-aminoimidazole, we found that the crystalline[5] iminophosphorane **2** can be obtained from 4-iodo-1-trityl-1*H*-imidazole (**1**) in one step via Staudinger reduction of the intermediate azide (Scheme 1). We wondered whether **2** could serve as an easy-to-handle building block for the synthesis of (4)5-substituted 2-aminoimidazoles.



Scheme 1 Crystalline iminophosphorane **2**

Indeed, iminophosphorane **2** underwent Heck reactions with acrylic acid derivatives **3**, **6**, and **9** giving convenient access to derivatives of the hitherto unknown 2′-aminourocanic acid (Scheme 2). Deprotection of the crude coupling products **4**, **7**, and **10** proceeded smoothly on treatment with trifluoroacetic acid providing **5**-TFA, **8**-TFA, and **11**-TFA, which were purified by reverse-phase chromatography and constitute the first examples of urocanic acid derivatives bearing a free amino group in the 2′-position.



Scheme 2 Synthesis of 2′-aminourocanic acid derivatives (yields over 2 steps)

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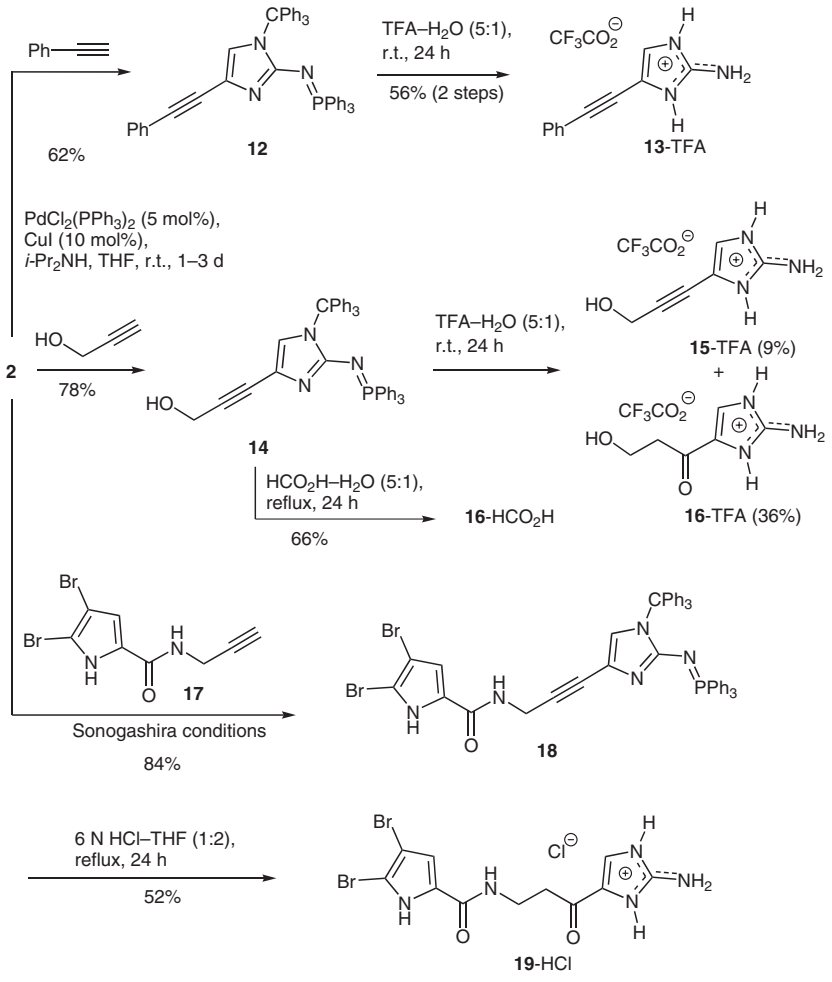
We anticipated that alkynylation of **2** might provide indirect access to 4(5)-acyl-2-aminoimidazoles, because metal-free hydration of triple bonds is facilitated if they are conjugated to electron-rich aromatic systems.[6] This would be helpful, because alternative acylation with acid chlorides is limited to weakly functionalized acyl components.

Sonogashira reactions of **2** with model compounds phenylacetylene and propargylic alcohol proceeded smoothly affording coupling products **12** and **14** in 62% and 78% yield, respectively (Scheme 3). Deprotection under acidic conditions (TFA–H_2O, 5:1) led to immediate removal of the trityl group. Hydrolysis of the N=P bond was complete after 24 hours; in the absence of water, only the trityl group was cleaved. 4-(Phenylethynyl)-1*H*-imidazol-2-ylamine trifluoroacetic acid salt (**13**-TFA) was isolated as the sole, stable product. Even under harsher conditions [H_2O–EtOH (4:1), reflux, 24 h] no acyl compound was formed.

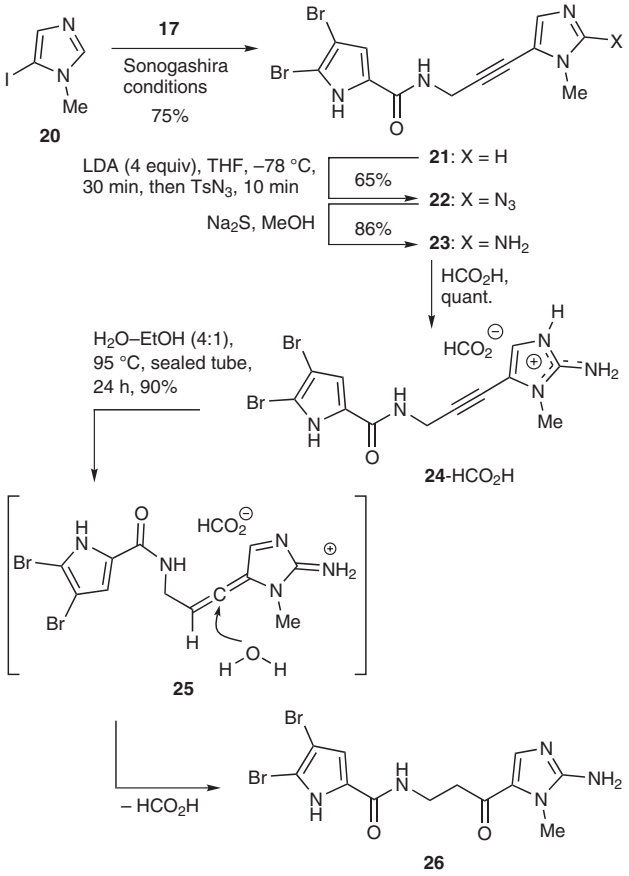
However, the major product obtained on hydrolysis of propargylic alcohol **14** was acyl compound **16**-TFA (36%), accompanied by smaller amounts of alkyne **15**-TFA (9%). An alternative procedure [HCO_2H–H_2O (5:1), reflux, 24 h] provided **16**-HCO_2H in higher yield (66%). Formal addition of water to the triple bond was also observed on hydrolysis of the putative dehydrooroidin precursor **18**,[5] prepared via Sonogashira reaction of **2** with propargylic amine **17**. In fact, formation of the acyl compound could not be avoided. Exclusive formation of the acyl compound **19**-HCl, tautomer of hydroxyoroidin, was achieved on hydrolysis of **18** with 6 N hydrochloric acid–tetrahydrofuran (1:2).

Hydration occurs also in the absence of the iminophosphorane group and in the presence of an imidazole *N*-methyl group, as can be concluded from the behavior of the formate of bromodehydrokeramadine (**24**-HCO_2H, prepared via azidation of 2-free imidazole **21** and reduction of **22** with Na_2S)[7] (Scheme 4). On treatment of **24** with water–ethanol at 95 °C, compound **26**, a tautomer of 'hydroxybromokeramadine', was obtained and converted into the free base by removing formic acid at 40 °C/1 mbar; intermediacy of allene **25** is likely. It should be noted that under the same conditions the nonmethylated natural product oroidin, containing an alkene instead of an alkyne moiety, undergoes intramolecular nucleophilic attack of the pyrrole nitrogen affording cyclooroidin.[8]

Compounds **19** and **26** proved to be surprisingly stable and survived heating in water, ethanol, or *N*,*N*-dimethyl-



Scheme 3 Synthesis of 4(5)-acyl-2-aminoimidazoles via hydration of the corresponding alkynes



Scheme 4 Hydration of bromodehydrokeramadine (**23**)

formamide up to 100 °C without degradation. We are currently exploring the conversion of **19** into the azepinone stevensine, which would formally proceed via nucleophilic attack of the pyrrole carbon at the new carbonyl group, followed by dehydration.

Our new synthesis of 4(5)-acyl-2-aminoimidazoles via iminophosphorane **2** appears to be superior to the two other approaches already described. Intramolecular ring opening of *N*-(1,2,4-oxadiazol-3-yl)-β-enamino ketones[9] yields 4-acyl-2-aminoimidazoles only as minor products if they are 5-unsubstituted.[10] Conversion of 4-acyl-2-aminooxazoles into 4-acyl-2-aminoimidazoles occurs on treatment with ammonia or primary or secondary amines in 30–60% yields and with the formation of side products.[11] Regarding the synthesis of oroidin or keramadine derivatives, the amino group should be introduced after the Sonogashira coupling[12,13] of 2-free imidazoles **1** or **20** with alkyne **17**.

Melting points were determined with a Büchi Melting Point B540 apparatus and are uncorrected. NMR spectra were taken with a Varian NMR System 300 MHz, a Varian NMR System 400 MHz Inova 400 and a Varian NMR System 600 MHz [300, 400, and 600 MHz for ^{1}H, 75.7, 100.5, and 150.8 MHz for ^{13}C (referenced to solvent signals or TMS)]. All measurements were carried out at 300 K. MS spectra were obtained with a Finnigan MAT95Q and a Thermo Finnigan LTQ FT spectrometer. IR spectra were recorded with a Perkin-Elmer PE 1600 FT-IR spectrophotometer. UV/Vis spectra were measured with a Perkin-Elmer Lambda-16 UV spectrometer. Chemicals were purchased from commercial suppliers and used without further purification. Silica gel 60 (40–63 μm, Merck) and LiChroprep RP-18 (Merck, 40–63 μm, 94 g, 3-cm column, regeneration: MeOH) were used for column chromatography.

N-(4-Iodo-1-trityl-1*H*-imidazol-2-yl)triphenylphosphoranylideneamine (2)

A 2.5 M soln of BuLi in hexane (30.0 mL, 75.0 mmol, 1.5 equiv) was added to a soln of *i*-Pr_2NH (11.3 mL, 80.0 mmol, 1.6 equiv) in anhyd THF (50 mL) at 0 °C and the soln was stirred for 15 min. At –78 °C, the LDA soln was added to a soln of 4-iodo-1-trityl-1*H*-imidazole (**1**, 21.80 g, 50.0 mmol, 1.0 equiv)[14] in anhyd THF (300 mL). The mixture was stirred for 1 h and TsN_3 (14.80 g, 75.0 mmol, 1.5 equiv)[15] was added dropwise. After 10 min, the reaction was quenched by the addition of aq buffer (pH 7, 50 mL). Solid Ph_3P (19.67 g, 75.0 mmol, 1.5 equiv) was added over 30 min and the mixture was stirred for 24 h. A portion of **2** (usually 20–25%) was isolable in analytically pure form by filtration. To the filtrate was added H_2O (500 mL) and THF was removed in vacuo. The resulting suspension was filtered and the solid product was washed with H_2O (200 mL) and aq 2 M HCl (100 mL) and dried in vacuo. To purify the solid, Et_2O (300 mL) was added and the suspension was stirred for 2 h. The precipitate was filtered, washed (Et_2O), and dried. Product **2** (28.83 g, 81%) was obtained as a yellow powder; mp 208–209 °C; R_f = 0.30 ($CHCl_3$–EtOAc, 10:1).

IR (ATR): 3155, 3056, 3022, 1577, 1515, 1486, 1446, 1436, 1399, 1363, 1240, 1186, 1149, 1111, 1042, 1027, 999, 928, 904, 749, 730, 720, 691, 668, 639 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.52 (d, *J* = 2.4 Hz, 1 H, NCHCI), 7.14–7.34 (m, 27 H, H_{phenyl}), 7.37–7.45 (m, 3 H, H_{phenyl}).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 74.2, 76.7, 121.5 (d, *J* = 1.7 Hz), 126.4, 127.2, 127.9 (d, *J* = 12.6 Hz), 129.6 (d. *J* = 101.4 Hz), 130.3, 131.3 (d, *J* = 2.9 Hz), 133.0 (d, *J* = 10.4 Hz), 143.3, 153.4.

MS (ESI+): *m*/*z* (%) = 243 (100), 343 (52), 586 (77), 587 (63), 712 (16) $[M + H]^+$.

HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{40}H_{32}IN_3P$: 712.1379; found: 712.1357.

UV/Vis ($CHCl_3$): λ_{max} (log ε) = 266 (2.90), 295 nm (2.69).

Anal. Calcd for $C_{40}H_{31}IN_3P$: C, 67.52; H, 4.39; N, 5.91. Found: C, 67.48; H, 4.37; N, 5.84.

Methyl 3-(2-Amino-1*H*-imidazol-4-yl)acrylate Trifluoroacetic Acid Salt (5-TFA); Typical Procedure

Iminophosphorane **2** (712 mg, 1.00 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (35.0 mg, 0.05 mmol, 5 mol%), methyl acrylate (**3**, 0.45 mL, 5.00 mmol, 5.00 equiv), and Et_3N (0.3 mL, 2.0 mmol, 2.0 equiv) were dissolved in DMF (40 mL). The mixture was heated in a sealed tube at 120 °C for 48 h. Consumption was monitored by TLC. All volatiles were removed. For characterization, a sample was purified by column chromatography (silica gel, $CHCl_3$–EtOAc, 5:1) yielding **4** as an orange solid; mp 231–232 °C; R_f = 0.42 ($CHCl_3$–EtOAc, 4:1).

IR (ATR): 3150, 3058, 3024, 2948, 1702, 1703, 1621, 1576, 1545, 1514, 1491, 1435, 1374, 1354, 1292, 1266, 1246, 1233, 1216, 1189, 1149, 1125, 1107, 1020, 998, 974, 931, 906, 896, 880, 857, 747, 717, 690, 661, 643 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.67 (s, 3 H, CH_3), 6.09 (d, *J* = 15.1 Hz, 1 H, COCH), 6.76 (d, *J* = 2.6 Hz, 1 H, NCCHN), 7.17–7.34 (m, 28 H, H_{phenyl}, C*H*CHCO), 7.37–7.43 (m, 3 H, H_{phenyl}).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 50.1, 74.4, 111.1, 122.2, 126.5, 127.2, 127.9 (d, *J* = 12.4 Hz), 129.3 (d, *J* = 102.0 Hz), 130.2, 131.4

(d, J = 2.5 Hz), 132.7, 133.0 (d, J = 10.2 Hz), 137.9, 143.2, 154.1 (d, J = 3.3 Hz), 168.8.

MS (ESI+): m/z (%) = 670 (100) $[M + H]^+$.

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{44}H_{37}N_3O_2P$: 670.2623; found: 670.2628.

UV/Vis ($CHCl_3$): λ_{max} (log ε) = 261 (3.11), 361 nm (3.21).

The main portion of crude **4** was treated with TFA–H_2O (5:1, 6 mL) for 2 d (monitored by TLC). The mixture was concentrated in vacuo and MeOH (20 mL) and H_2O (20 mL) were added. The suspension was filtered and purified by chromatography (RP-18, MeOH–H_2O +0.5% TFA, 1:6) yielding **5**-TFA (189 mg, 67%) as a yellow solid; mp 161–162 °C (dec.); R_f = 0.48 ($CHCl_3$–MeOH–NH_4OH, 40:10:1).

IR (ATR): 3428, 3339, 3058, 3014, 2948, 2510, 2296, 1678, 1617, 1573, 1539, 1459, 1431, 1312, 1238, 1194, 1156, 1027, 951, 933, 844, 820, 800, 773, 740, 726, 632 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 3.73 (s, 3 H, CH_3), 6.02 (d, J = 15.7 Hz, 1 H, COCH), 6.91 (s, 1 H, NCCHN), 7.39 (d, J = 15.7 Hz, 1 H, COCHC*H*).

^{13}C NMR (100.5 MHz, CD_3OD): δ = 51.9, 111.2, 126.9, 129.7, 135.3, 154.2, 170.2.

MS (ESI+): m/z (%) = 168 (100) $[M + H]^+$.

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_7H_{10}N_3O_2$: 168.0773; found: 168.0766.

UV/Vis (MeOH): λ_{max} (log ε) = 331 nm (3.24).

Ethyl 3-(2-Amino-1*H*-imidazol-4-yl)acrylate Trifluoroacetic Acid Salt (8-TFA)

Following the typical procedure using iminophosphorane **2** (712 mg, 1.00 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol, 5 mol%), ethyl acrylate (**6**, 0.54 mL, 5.00 mmol, 5.00 equiv), Et_3N (0.3 mL, 2.0 mmol, 2.0 equiv), and DMF (40 mL); time: 52 h. For characterization, a sample was purified by column chromatography (silica gel, $CHCl_3$–EtOAc, 5:1) yielding **7** as a yellow solid; mp 237 °C; R_f = 0.40 ($CHCl_3$–EtOAc, 4:1).

IR (ATR): 3056, 2977, 1688, 1617, 1576, 1541, 1512, 1490, 1437, 1378, 1365, 1246, 1234, 1152, 1124, 1108, 1039, 1025, 999, 970, 933, 883, 816, 746, 719, 690, 667, 624 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.1 Hz, 3 H, CH_3), 4.15 (q, J = 7.1 Hz, 2 H, CH_2), 6.07 (d, J = 15.1 Hz, 1 H, COCH), 6.76 (d, J = 2.6 Hz, 1 H, NCCHN), 7.18–7.22 (m, 9 H, H_{phenyl}), 7.23–7.29 (m, 13 H, H_{phenyl}, COCHC*H*), 7.30–7.33 (m, 6 H, H_{phenyl}), 7.40–7.44 (m, 3 H, H_{phenyl}).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 14.5, 59.5, 74.3, 111.6, 122.2, 126.5, 127.2, 127.9 (d, J = 12.4 Hz), 129.3 (d, J = 102.0 Hz), 130.2, 131.4 (d, J = 2.4 Hz), 132.8, 133.0 (d, J = 10.2 Hz), 137.7, 143.3, 154.1 (d, J = 4.3 Hz), 168.4.

MS (ESI+): m/z (%) = 684 (100) $[M + H]^+$.

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{45}H_{39}N_3O_2P$: 684.2780; found: 648.2781.

UV/Vis ($CHCl_3$): λ_{max} (log ε) = 261 (3.17), 360 nm (3.24).

The main portion of crude **7** was treated with TFA–H_2O (5:1, 6 mL) for 2 d (monitored by TLC) following the typical procedure; chromatography (RP-18, MeOH–H_2O + 0.5% TFA, 1:6) gave **8**-TFA (185 mg, 63%) as yellow solid; mp 122–124 °C; R_f = 0.14 (RP-18, MeOH–H_2O, 1:5).

IR (ATR): 3387, 3352, 3326, 3210, 3119, 1786, 1694, 1651, 1621, 1398, 1370, 1330, 1303, 1221, 1189, 1145, 1105, 1037, 1014, 991, 872, 809, 786, 705 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 1.30 (t, J = 7.1 Hz, 3 H, CH_3), 4.23 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 6.27 (dd, J = 16.1, 0.6 Hz, 1 H, COCH), 7.19 (br s, 1 H, NCHCN), 7.40 (dd, J = 16.1, 0.4 Hz, 1 H, COCHC*H*).

^{13}C NMR (100.5 MHz, CD_3OD): δ = 14.6, 61.9, 118.2, 118.6, 125.5, 130.5, 150.4, 167.9.

MS (ESI+): m/z (%) = 182 (100) $[M + H]^+$.

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_8H_{12}N_3O_2$: 182.0930; found: 182.0921.

3-(2-Amino-1*H*-imidazol-4-yl)acrylamide Trifluoroacetic Acid Salt (11-TFA)

Following the typical procedure using iminophosphorane **2** (712 mg, 1.00 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol, 5 mol%), acrylamide (355 mg, 5.00 mmol, 5.00 equiv), Et_3N (0.3 mL, 2.0 mmol, 2.0 equiv), and DMF (40 mL); time 48 h. For characterization, a sample was purified by column chromatography (silica gel, EtOAc–EtOH–NH_3, 10:1:0.1) yielding **10** as yellow solid; mp 162 °C (dec.); R_f = 0.41 (EtOAc–EtOH–NH_3, 10:1:0.1).

IR (ATR): 3451, 3054, 1671, 1597, 1551, 1521, 1491, 1436, 1386, 1366, 1267, 1232, 1184, 1152, 1108, 1044, 1026, 999, 976, 936, 906, 882, 856, 812, 746, 717, 691, 666, 648, 614 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 5.25 (br s, 2 H, NH_2), 6.10 (d, J = 15.0 Hz, 1 H, COCH), 6.72 (d, J = 2.4 Hz, 1 H, NCCHN), 7.11 (d, J = 15 Hz, 1 H, COCHC*H*), 7.18–7.19 (m, 9 H, H_{phenyl}), 7.23–7.29 (m, 12 H, H_{phenyl}), 7.30–7.32 (m, 6 H, H_{phenyl}), 7.40–7.43 (m, 3 H, H_{phenyl}).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 74.3, 113.7, 121.6, 126.5, 127.2, 128.0 (d, J = 12.3 Hz), 129.5 (d, J = 104.5 Hz), 130.2, 131.4, 132.6, 132.9 (d, J = 10.2 Hz), 134.9, 143.3, 153.8, 169.5.

MS (ESI+): m/z (%) = 655 (100) $[M + H]^+$.

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{43}H_{36}N_4OP$: 655.2627; found: 655.2623.

UV/Vis ($CHCl_3$): λ_{max} (log ε) = 267 (3.06), 352 nm (3.09).

The main portion of crude **10** was treated with TFA–H_2O (5:1, 6 mL) for 2 d (monitored by TLC) following the typical procedure; chromatography (RP-18, MeOH–H_2O + 0.5% TFA, 1:6) gave **11**-TFA (194 mg, 73%) as a yellow solid; mp 143 °C; R_f = 0.18 (RP-18, MeOH–H_2O, 1:5).

IR (ATR): 3392, 3311, 3199, 3053, 2795, 1777, 1676, 1638, 1582, 1401, 1186, 1133, 1022, 981, 965, 844, 788, 723, 705 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 6.37 (d, ^3J = 15.9 Hz, 1 H, COCH), 7.12 (s, 1 H, NCHCN), 7.26 (d, ^3J = 15.9 Hz, 1 H, COCHC*H*).

^{13}C NMR (100.5 MHz, CD_3OD): δ = 117.3, 120.9, 125.8, 127.4, 150.3, 169.9.

MS (ESI+): m/z (%) = 153 (100) $[M + H]^+$.

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_6H_9N_4O$: 153.0776; found: 153.0770.

Sonogashira Reactions

All reactions were carried out under argon. THF (p.a. quality) was carefully degassed in a supersonic bath for at least 15 min before use. The solns of iminophosphorane **2** and of the alkyne component were degassed for additional 15 min.

4-(Phenylethynyl)-2-(triphenylphosphoranylideneamino)-1-trityl-1*H*-imidazole (12) and 4-(Phenylethynyl)-1*H*-imidazol-2-ylamine Trifluoroacetic Acid Salt (13-TFA)

Iminophosphorane **2** (712 mg, 1.00 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (35.0 mg, 0.05 mmol, 5 mol%), CuI (20.0 mg, 0.10 mmol, 10 mol%), and i-Pr_2NH (0.3 mL, 2.0 mmol, 2.0 equiv) were

dissolved in THF (40 mL). Phenylacetylene (0.4 mL, 3.5 mmol, 3.5 equiv) in THF (10 mL) was added. After 48 h at r.t. the mixture was filtered, EtOAc (100 mL) was added and the organic layer was washed with aq NH_4Cl (50 mL) and brine (2 × 50 mL). For characterization of the coupling product **12**, the organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography (silica gel, $CHCl_3$ to $CHCl_3$–EtOAc, 4:1) to give **12** (426 mg, 62%) as a pale yellow solid; mp 240 °C; R_f = 0.26 ($CHCl_3$–EtOAc, 10:1).

IR (ATR): 3057, 2216, 1590, 1577, 1551, 1516, 1484, 1437, 1433, 1355, 1325, 1237, 1188, 1150, 1124, 1106, 1084, 1068, 1039, 1025, 999, 940, 916, 895, 880, 813, 769, 754, 748, 735, 718, 703, 687, 669, 647 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 6.83 (d, *J* = 2.6 Hz, 1 H, NCHCN), 7.09–7.20 (m, 25 H, H_{phenyl}), 7.24–7.26 (m, 5 H, H_{phenyl}), 7.32–7.36 (m, 5 H, H_{phenyl}).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 74.3, 86.4, 87.8, 117.4, 122.7, 124.2, 126.4, 127.1, 127.2, 127.9, 128.0 (d, *J* = 12.8 Hz), 129.8 (d, *J* = 102.7 Hz), 130.3, 131.3, 131.3 (d, *J* = 2.5 Hz), 132.8 (d, *J* = 10.3 Hz), 143.3, 152.4 (d, *J* = 5.0 Hz).

MS (ESI+): *m/z* (%) = 686 (100) $[M + H]^+$.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{48}H_{37}N_3P$: 686.2725; found: 686.2697.

For in situ deprotection of **12**, the organic layer was concentrated in vacuo and the residue was treated with TFA–H_2O (5:1, 6 mL) for 24 h (monitored by TLC). The mixture was concentrated in vacuo and MeOH (50 mL) and H_2O (20 mL) were added. The suspension was filtered and purified by chromatography (RP-18, MeOH–H_2O + 0.5% TFA, 1:2) yielding **13**-TFA (165 mg, 56%) as a yellow solid; R_f = 0.42 (RP-18, MeOH–H_2O + 0.5% AcOH, 4:3).

IR (ATR): 3337, 3193, 1778, 1686, 1489, 1445, 1197, 1138, 1023, 787, 775, 753, 724, 702, 688 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 7.09 (s, 1 H, NCHCN), 7.35–7.41 (m, 3 H, H_{phenyl}), 7.47–7.51 (m, 2 H, H_{phenyl}).

^{13}C NMR (100.5 MHz, CD_3OD): δ = 76.5, 94.9, 111.0, 118.6, 122.9, 129.8, 130.5, 132.5, 148.8.

MS (ESI+): *m/z* (%) = 184 (100) $[M + H]^+$.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{11}H_{10}N_3$: 184.0875; found: 184.0866.

UV/Vis (MeOH): λ_{max} (log ε) = 238 (4.02), 285 (4.10), 300 nm (4.10).

3-[2-(Triphenylphosphoranylideneamino)-1-trityl-1*H*-imidazol-4-yl]prop-2-yn-1-ol (14)

Iminophosphorane **2** (3.56 g, 5.00 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (175 mg, 0.25 mmol, 5 mol%), CuI (95 mg, 0.50 mmol, 10 mol%), and *i*-Pr_2NH (1.5 mL, 10 mmol, 2.0 equiv) were dissolved in THF (200 mL). Propargyl alcohol (1.2 mL, 20 mmol, 4.0 equiv) in THF (20 mL) was added. After 48 h at r.t. the mixture was filtered and concentrated in vacuo (important: no aqueous workup!). To the residue $CHCl_3$ (50 mL) and EtOAc (50 mL) were added. The mixture was stirred at 40–45 °C for 30 min, then cooled to 4 °C and the brown precipitate was filtered. The solid was dissolved in THF (100 mL) and purified by filtration through a small pad of silica gel (height, ca. 5 cm, diameter 4 cm) to give **14** (2.49 g, 78%) as a pale yellow solid; mp 208 °C (dec.); R_f = 0.56 (EtOAc).

IR (ATR): 3165, 3059, 2994, 2837, 2226, 1736, 1577, 1558, 1513, 1491, 1436, 1390, 1366, 1311, 1236, 1184, 1163, 1142, 1112, 1056, 1041, 1023, 995, 934, 917, 883, 752, 735, 722, 691 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.08 (d, *J* = 5.8 Hz, 2 H, C*H*$_2$OH), 5.00 (t, *J* = 5.8 Hz, 1 H, OH), 6.51 (d, *J* = 2.5 Hz, 1 H, NCCHN), 7.13–7.26 (m, 21 H, H_{phenyl}), 7.30–7.26 (m, 6 H, H_{phenyl}), 7.46–7.51 (m, 3 H, H_{phenyl}).

^{13}C NMR (100.5 MHz, DMSO-d_6): δ = 49.4, 73.7, 80.5, 87.8, 117.0, 120.9, 126.6, 127.2, 128.1 (d, *J* = 12.2 Hz), 129.0 (d, *J* = 101.4 Hz), 129.5, 131.7 (d, *J* = 2.8 Hz), 132.2 (d, *J* = 10.2 Hz), 142.7, 152.1 (d, *J* = 4.3 Hz).

MS (ESI+): *m/z* (%) = 640 (100) $[M + H]^+$.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{43}H_{35}N_3OP$: 640.2518; found: 640.2492.

UV/Vis (DMSO): λ_{max} (log ε) = 267 nm (3.71).

4,5-Dibromo-*N*-prop-2-ynyl-1*H*-pyrrole-2-carboxamide (17)

To a soln of 2,2,2-trichloro-1-(4,5-dibromo-1*H*-pyrrol-2-yl)ethanone (40.73 g, 0.110 mol, 1.0 equiv)[16] in CH_2Cl_2 (30 mL) were added Na_2CO_3 (13.60 g, 0.128 mol, 1.2 equiv) and a soln of propargylamine hydrochloride (11.72 g, 0.128 mol, 1.2 equiv) in MeCN (200 mL). The mixture was stirred at 40 °C until the ketone had been consumed (12 h). H_2O (300 mL), aq 2 M HCl (50 mL), and Et_2O (1 L) were added and the phases were separated. The organic layer was washed with aq 2 M HCl (100 mL) and brine (2 × 100 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the resulting solid was dissolved in $CHCl_3$ (50 mL) at 50 °C. After cooling to 4 °C for 1 h, filtration of the precipitate yielded **17** (26.95 g, 80%) as a pale yellow solid; mp 184–185 °C (dec.); R_f = 0.88 (hexane–EtOAc, 1:3).

IR (ATR): 3417, 3288, 3148, 3110, 2982, 2938, 2857, 2651, 1632, 1556, 1514, 1432, 1400, 1393, 1347, 1316, 1240, 1216, 979, 914, 814, 762, 678, 638 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.13 (t, *J* = 2.5 Hz, 1 H, C≡CH), 4.00 (dd, *J* = 5.6, 2.5 Hz, 2 H, CH_2), 6.94 (d, *J* = 2.7 Hz, BrCCH), 8.56 (t, *J* = 5.5 Hz, 1 H, NHC=O), 12.73 (br s, 1 H, NHCBr).

^{13}C NMR (100.5 MHz, DMSO-d_6): δ = 27.8, 73.0, 81.0, 97.8, 104.9, 112.9, 127.5, 158.4.

MS (ESI–): *m/z* (%) = 303/305/307 (37/100/37) $[M - H]^-$.

HRMS (ESI–): *m/z* $[M - H]^-$ calcd for $C_8H_5{}^{79}Br^{81}BrN_2O$: 304.8748; found: 304.8758.

UV/Vis ($CHCl_3$): λ_{max} (log ε) = 278 nm (3.75).

4,5-Dibromo-*N*-{3-[2-(triphenylphosphoranylideneamino)-1-trityl-1*H*-imidazol-4-yl]prop-2-ynyl}-1*H*-pyrrole-2-carboxamide (18)

Iminophosphorane **2** (3.56 g, 5.00 mmol, 1.00 equiv), $PdCl_2(PPh_3)_2$ (175 mg, 0.25 mmol, 5 mol%), CuI (95 mg, 0.50 mmol, 10 mol%), and *i*-Pr_2NH (1.5 mL, 10 mmol, 2.0 equiv) were dissolved in THF (200 mL). Alkyne **17** (2.14 g, 7.00 mmol, 1.4 equiv) in THF (50 mL) was added. After 48 h at r.t. the mixture was filtered, EtOAc (250 mL) was added, and the organic layer was washed with aq NH_4Cl (250 mL), and brine (2 × 150 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography (silica gel, $CHCl_3$ to $CHCl_3$–EtOAc, 1:1) to give **18** (3.72 g, 84%) as a pale yellow solid; mp 187–188 °C; R_f = 0.29 ($CHCl_3$–EtOAc, 1:1).

IR (ATR): 3117, 3053, 3028, 1639, 1576, 1565, 1517, 1491, 1444, 1392, 1362, 1322, 1246, 1156, 1140, 1108, 1044, 1025, 999, 976, 942, 843, 745, 718, 691, 650, 619 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 4.08 (d, *J* = 5.3 Hz, 2 H, CH_2), 6.51 (d, *J* = 2.4 Hz, 1 H, NCCHN), 6.87 (s, 1 H, BrCCH), 7.16–7.25 (m, 21 H, H_{phenyl}), 7.29–7.36 (m, 6 H, H_{phenyl}), 7.45–7.51 (m, 3 H, H_{phenyl}), 8.26 (t, *J* = 5.0 Hz, 1 H, NHCO), 12.46 (s, 1 H, BrCNH).

^{13}C NMR (100.5 MHz, DMSO-d_6): δ = 28.5, 73.5, 78.7, 84.1, 97.5, 104.2, 112.7, 116.6, 120.9, 126.3, 126.8, 127.5, 127.7 (d, *J* = 12.2 Hz), 128.9 (d, *J* = 101.6 Hz), 129.2, 131.3, 131.9 (d, *J* = 10.2 Hz), 142.6, 151.8, 158.0.

MS (ESI+): *m/z* (%) = 888/890/892 (36/100/55) $[M + H]^+$.

HRMS-ESI+: *m/z* $[M + H]^+$ calcd for $C_{48}H_{37}{}^{79}Br_2N_5OP$: 888.1102; found: 888.1086.

UV/Vis ($CHCl_3$): λ_{max} (log ε) = 274 nm (3.36).

1-(2-Amino-1*H*-imidazol-4-yl)-3-hydroxypropan-1-one Acid Salts 16

Method 1: Alcohol **14** (538 mg, 0.84 mmol) was treated with TFA–H_2O (5:1, 6 mL) for 24 h (monitored by TLC). The mixture was concentrated in vacuo and MeOH (50 mL), H_2O (250 mL), and Et_2O (300 mL) were added. The phases were separated and the aqueous layer was washed with Et_2O (2 × 150 mL). The aqueous layer was concentrated in vacuo and the residue was purified by chromatography (RP-18, MeOH–H_2O + 0.5% TFA, 1:8) to give **15**-TFA (20 mg, 9%) and acyl compound **16**-TFA (82 mg, 36%) as yellow solids.

Method 2: Alcohol **14** (320 mg, 0.50 mmol) was heated with HCO_2H–H_2O (5:1, 10 mL) under reflux for 24 h (monitored by TLC). The mixture was concentrated in vacuo and MeOH (5 mL) and H_2O (20 mL) were added. The resulting suspension was filtered and the residue was diluted with MeOH (5 mL) and H_2O (20 mL) once again. The filtrate was purified by RP-chromatography (RP-18, MeOH–H_2O + 0.5% HCO_2H, 1:4) to give **16**-HCO_2H (66 mg, 66%).

1-(2-Amino-1*H*-imidazol-4-yl)-3-hydroxypropan-1-one Trifluoroacetic Acid Salt (16-TFA)

R_f = 0.68 (RP-18, MeOH–H_2O + 0.5% TFA, 1:5).

IR (ATR): 3310, 3149, 1787, 1698, 1654, 1614, 1428, 1392, 1308, 1177, 1123, 1044, 1020, 927, 830, 798, 721 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 2.94 (t, *J* = 6.0 Hz, 2 H, CH_2CO), 3.91 (t, *J* = 6.0 Hz, 2 H, CH_2OH), 7.79 (s, 1 H, NCCHN).

^{13}C NMR (150.8 MHz, CD_3OD): δ = 41.9, 58.5, 122.7, 129.1, 150.4, 189.2.

MS (ESI+): *m/z* (%) = 156 (100) $[M + H]^+$.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_6H_{10}N_3O_2$: 156.0773; found: 156.0766.

1-(2-Amino-1*H*-imidazol-4-yl)-3-hydroxypropan-1-one (16)

To obtain the free base, a small portion of **16** was purified by chromatography (silica gel, $CHCl_3$–MeOH–NH_4OH, 40:10:1).

^1H NMR (400 MHz, CD_3OD): δ = 2.86 (t, *J* = 6.3 Hz, 2 H, CH_2CO), 3.88 (t, *J* = 6.3 Hz, 2 H, CH_2OH), 7.51 (s, 1 H, NCCHN).

^{13}C NMR (100.5 MHz, CD_3OD): δ = 41.6, 59.5, 130.5, 136.5, 155.5, 188.8.

3-(2-Amino-1*H*-imidazol-4-yl)prop-2-yn-1-ol Trifluoroacetic Acid Salt (15-TFA)

R_f = 0.63 (RP-18, MeOH–H_2O + 0.5% TFA, 1:5).

IR (ATR): 3288, 3154, 3025, 2769, 2238, 1788, 1667, 1435, 1356, 1187, 1133, 1043, 1008, 914, 839, 796, 721 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 4.38 (s, 2 H, CH_2), 7.01 (s, 1 H, NCCHN).

^{13}C NMR (150.8 MHz, CD_3OD): δ = 51.0, 72.1, 94.7, 110.6, 118.7, 148.7.

MS (ESI+): *m/z* (%) = 138 (100) $[M + H]^+$.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_6H_8N_3O$: 138.0667; found: 138.0661.

4,5-Dibromo-*N*-[3-(2-amino-1*H*-imidazol-4-yl)-3-oxopropyl]-1*H*-pyrrole-2-carboxamide Hydrochloric Acid Salt (19-HCl)

A soln of **18** (445 mg, 0.50 mmol) in THF–6 M HCl (2:1, 30 mL) was refluxed for 24 h (monitored by TLC). After cooling to r.t., H_2O (250 mL), MeOH (50 mL), and Et_2O (400 mL) were added. The phases were separated and the aqueous layer was washed with Et_2O (2 × 200 mL). The mixture was concentrated in vacuo and the residue was dissolved in MeOH (20 mL) and H_2O (20 mL). Purification by chromatography (RP-18, H_2O + 0.5% AcOH–MeOH, 2:1) gave **19**-HCl (115 mg, 52%) as a pale yellow solid; mp 242–244 °C (dec.); R_f = 0.33 (RP-18, MeOH–H_2O + 0.5% AcOH, 4:3).

IR (ATR): 3301, 3116, 2897, 1699, 1657, 1612, 1578, 1533, 1420, 1396, 1339, 1243, 1202, 1082, 980, 947, 810, 750, 685 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 3.05 (t, *J* = 6.7 Hz, 2 H, $COCH_2$), 3.65 (t, *J* = 6.7 Hz, 2 H, CH_2NH), 6.77 (s, 1 H, BrCCH), 7.79 (s, 1 H, NCCHN).

^{13}C NMR (100.5 MHz, CD_3OD): δ = 36.1, 38.9, 100.0, 106.2, 114.3, 122.6, 128.66, 128.68, 150.2, 161.8, 188.7.

MS (ESI+): *m/z* (%) = 404/406/408 (36/100/56) $[M + H]^+$.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{11}H_{12}{}^{79}Br_2N_5O_2$: 403.9358; found: 403.9340.

UV/Vis (MeOH): λ_{max} (log ε) = 280 nm (4.26).

4,5-Dibromo-*N*-[3-(2-amino-1*H*-imidazol-4-yl)-3-oxopropyl]-1*H*-pyrrole-2-carboxamide

To obtain the free base, a small portion of **19** was purified by chromatography (silica gel, CH_2Cl_2–MeOH–NH_4OH, 20:10:1).

^1H NMR (400 MHz, CD_3OD): δ = 3.00 (t, *J* = 6.7 Hz, 2 H, $COCH_2$), 3.64 (t, *J* = 6.7 Hz, 2 H, CH_2NH), 6.77 (s, 1 H, BrCCH), 7.66 (s, 1 H, NCCHN).

^{13}C NMR (100.5 MHz, CD_3OD): δ = 36.5, 38.7, 100.0, 106.2, 114.4, 128.8, 129.3, 145.6, 147.4, 161.8, 188.7.

4,5-Dibromo-*N*-[3-(3-methyl-3*H*-imidazol-4-yl)prop-2-ynyl]-1*H*-pyrrole-2-carboxamide (21)

5-Iodo-1-methyl-1*H*-imidazole (**20**, 416 mg, 2.00 mmol, 1.0 equiv),[17] $PdCl_2(PPh_3)_2$ (70.0 mg, 0.10 mmol, 5 mol%), CuI (39.0 mg, 0.20 mmol, 10 mol%), and *i*-Pr_2NH (0.6 mL, 4.3 mmol, 2 equiv) were dissolved in THF (50 mL). Alkyne **17** (857 mg, 2.80 mmol, 1.4 equiv) in THF (20 mL) was added. After 48 h at r.t. the mixture was filtered, concentrated in vacuo, and purified by chromatography (silica gel, $CHCl_3$–MeOH, 25:1) to give **21** (580 mg, 75%) as a colorless solid; mp 215 °C (dec.); R_f = 0.12 (EtOAc).

IR (ATR): 3148, 3108, 3060, 2950, 2851, 2769, 2653, 2357, 2335, 1652, 1568, 1530, 1487, 1429, 1416, 1402, 1347, 1310, 1281, 1240, 1223, 1117, 1059, 971, 919, 832, 760, 753 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.61 (s, 3 H, NCH_3), 4.32 (d, *J* = 5.5 Hz, 2 H, CH_2NH), 6.97 (s, 1 H, BrCCH), 7.20 (s, 1 H, NCCHN), 7.72 (s, 1 H, NCHN), 8.69 (t, *J* = 5.5 Hz, 1 H, CH_2NH), 12.78 (br s, 1 H, BrCNH).

^{13}C NMR (100.5 MHz, DMSO-d_6): δ = 28.8, 31.5, 70.2, 93.8, 97.9, 105.0, 112.9, 114.9, 127.5, 133.3, 139.0, 158.5.

MS (ESI+): *m/z* (%) = 385/387/389(38/100/50) $[M + H]^+$.

HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{12}H_{11}{}^{79}Br_2N_4O$: 384.9300; found: 384.9285.

UV/Vis (DMSO): λ_{max} (log ε) = 274 nm (3.23).

***N*-[3-(2-Azido-3-methyl-3*H*-imidazol-4-yl)prop-2-ynyl]-4,5-dibromo-1*H*-pyrrole-2-carboxamide (22)**

A 2.5 M soln of BuLi in hexane (1.6 mL, 4.0 mmol, 4.0 equiv) was added to a soln of *i*-Pr_2NH (0.59 mL, 4.2 mmol, 4.2 equiv) in anhyd THF (5 mL) at 0 °C and the soln was stirred for 15 min. At –78 °C,

the LDA soln was added to a soln of **21** (386 mg, 1.00 mmol, 1.0 equiv) in anhyd THF (70 mL). The mixture was stirred for 0.5 h and TsN_3 (296 mg, 1.50 mmol, 1.5 equiv)[15] was added dropwise. After 10 min, the reaction was quenched by addition of aq buffer (pH 7, 15 mL) and brine (20 mL). The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography (silica gel, $CHCl_3$–EtOAc, 1:1) to give **22** (278 mg, 65%) as a yellow solid; R_f = 0.76 (EtOAc).

IR (ATR): 3122, 2950, 2851, 2653, 2357, 2138, 1628, 1555, 1563, 1407, 1385, 1308, 1210, 1152, 1084, 974, 823, 749 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.35 (s, 3 H, NCH_3), 4.31 (d, J = 5.5 Hz, 2 H, CH_2NH), 6.96 (s, 1 H, BrCCH), 7.14 (s, 1 H, NCCHN), 8.68 (t, J = 5.5 Hz, 1 H, CH_2NH), 12.77 (br s, 1 H, BrC-NH).

^{13}C NMR (100.5 MHz, DMSO-d_6): δ = 28.8, 29.8, 70.0, 94.1, 97.9, 105.1, 112.9, 114.4, 127.4, 131.5, 140.1, 158.5.

MS (ESI–): m/z (%) = 424/426/428 (47/100/45) $[M - H]^-$.

HRMS (ESI–): m/z $[M - H]^-$ calcd for $C_{12}H_8{}^{79}Br_2N_7O$: 423.9157; found: 423.9152.

UV/Vis (MeOH): λ_{max} (log ε) = 276 nm (3.33).

N-[3-(2-Amino-3-methyl-3*H*-imidazol-4-yl)prop-2-ynyl]-4,5-dibromo-1*H*-pyrrole-2-carboxamide (23)

A soln of azide **22** (200 mg, 0.47 mmol, 1.0 equiv) and $Na_2S·9\ H_2O$ (1.13 g, 4.7 mmol, 10 equiv) in MeOH (20 mL) was stirred at r.t. for 18 h. BuOH (150 mL) and brine (50 mL) were added. The organic layer was separated, washed with brine (3 × 50 mL), concentrated in vacuo, and purified by chromatography (silica gel, $CHCl_3$–MeOH–NH_4OH, 70:10:1) to give **23** (162 mg, 86%) as a yellow solid; mp 190–193 °C (dec.); R_f = 0.28 ($CHCl_3$–MeOH–NH_4OH, 70:10:1).

IR (ATR): 3411, 3148, 3104, 3049, 2945, 2851, 2665, 2356, 2330, 2214, 1644, 1559, 1516, 1432, 1405, 1396, 1350, 1309, 1241, 1215, 1056, 977, 922, 812, 752 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 3.40 (s, 3 H, NCH_3), 4.33 (s, 2 H, CH_2NH), 6.81 (s, 1 H, BrCCH), 6.90 (s, 1 H, NCCHN).

^{13}C NMR (100.5 MHz, CD_3OD): δ = 30.2, 30.3, 70.8, 94.4, 100.1, 106.6, 113.0, 114.7, 123.8, 128.4, 149.7, 161.4.

MS (ESI+): m/z (%) = 400/402/404(33/100/47) $[M + H]^+$.

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{12}H_{12}{}^{79}Br_2N_5O$: 399.9409; found: 399.9389.

UV/Vis (MeOH): λ_{max} (log ε) = 275 nm (3.28).

N-[3-(2-Amino-3-methyl-3*H*-imidazol-4-yl)-3-oxopropyl]-4,5-dibromo-1*H*-pyrrole-2-carboxamide (26)

To a soln of alkyne **23** (40 mg, 0.10 mmol) in MeOH (1 mL) was added HCO_2H (0.1 mL) and the soln was concentrated in vacuo. The formate was dissolved in H_2O–EtOH (4:1, 40 mL) and heated for 24 h in a sealed tube. The mixture was filtered and concentrated in vacuo to give **26** (38 mg, 90%) as a slightly brown solid; R_f = 0.30 ($CHCl_3$–MeOH–NH_4OH, 70:10:1).

IR (ATR): 3114, 3039, 1713, 1680, 1655, 1560, 1519, 1390, 1318, 1235, 1191, 1135, 1096, 1000, 827, 758, 615 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.86 (t, J = 6.8 Hz, 2 H, CH_2CH_2NH), 3.36 (br s, 2 H, NH_2), 3.47 (dt, J = 5.6, 6.8 Hz, 2 H, CH_2CH_2NH), 3.58 (s, 3 H, NCH_3), 6.88 (s, 1 H, BrCCH), 7.72 (s, 1 H, NCCHN), 8.24 (t, J = 5.6 Hz, 1 H, CH_2NH), 12.68 (s, 1 H, BrC-NH).

^{13}C NMR (100.5 MHz, DMSO-d_6): δ = 30.7, 35.3, 37.9, 97.7, 104.3, 112.5, 125.9, 128.0, 136.1, 153.7, 158.7, 185.9.

MS (ESI+): m/z (%) = 418/420/422 (42/100/52) $[M + H]^+$.

HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{12}H_{14}{}^{79}Br_2N_5O_2$: 417.9514; found: 417.9488.

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