Synthesis of Poly-functionalized Imidazoles via Vinyl Azides Participated Annulation

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General Information

All solvents were purified according to standard methods prior to use. Purifications of products were carried out by chromatography using silica gel (200-300 mesh). Melting points were recorded on a Büchi B-540 melting point apparatus. NMR spectra were recorded on a Bruker DRX-500 [Bruker Biospin, Germany] and Mercury plus Varian 300MHz. NMR spectra were recorded for $^1$H NMR at 500 MHz and for $^{13}$C NMR at 125 MHz. For $^1$H NMR, tetramethylsilane (TMS) served as internal standard ($\delta=0$) and data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant(s) in Hz. For $^{13}$C NMR, TMS ($\delta=0$) or CDCl$_3$ ($\delta=77.26$) was used as internal standard and spectra were obtained with complete proton decoupling. HPLC analysis and the HRMS of all biologically evaluated compounds was confirmed on a Agilent 1290 HPLC-6224 Time of Flight Mass Spectrometer using PhenomenexLuna 5µ C18, 100 Å, 150 × 4.60 mm 5 micron column at a flow rate of 0.5 mL/min using liner gradients buffer B in A (B: CH$_3$OH containing 0.1 % formic acid, A: H$_2$O containing 0.1% formic acid). Mobile phase B was increased linearly from 5% to 95% over 7 min and 95% over the next 2 min, after which the column was equilibrated to 5% for 1 min.

The starting material 1 and 2 were prepared according to literature methods.$^{1,2}$

References:

General Procedure for the Synthesis of 3

A mixture of vinyl azide 1 (0.1 mmol), imidate or thioamidium 2 (0.11 mmol, 1.1 equiv) was stirred in t-BuOH (1.0 mL) in a sealed tube at 110 °C for 8 h. After the completeness of the reaction, the mixture was cooled down to room temperature and diluted with water, extracted three times with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, concentrated and purified by flash chromatography (DCM/MeOH) on silica gel to afford 3.

Characterization Data

Ethyl 2, 4-diphenyl-1H-imidazole-5-carboxylate (3a)

Yellow solid, m.p. 158.9-159.1 °C; Yield: 269 mg (92%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$10.43 (s, 1H), 7.97 (m, 4H), 7.48-7.36 (m, 6H), 4.33 (q, $J = 6.4$ Hz, 2H), 1.30 (t, $J = 6.4$ Hz, 3H); $^{13}$C NMR
(125 MHz, CDCl$_3$) $\delta$ 160.8, 148.1, 133.6, 130.0, 129.6, 129.2, 129.0, 128.7, 128.0, 126.3, 119.0, 61.2, 14.3. HRMS (ESI) calcd. for C$_{10}$H$_7$N$_2$O$_2$ [M+H]$^+$ = 293.1285, found 293.1285.

**Ethyl 2-methyl-4-phenyl-1H-imidazole-5-carboxylate (3b)**

![Chemical structure of 3b](image)

Yellow oil; Yield: 159 mg (69%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.59 (dd, $J = 7.7$, 1.7 Hz, 2H), 7.22-7.16 (m, 3H), 4.10 (q, $J = 7.1$ Hz, 2H), 2.09 (s, 3H), 1.07 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.1, 146.4, 142.5, 131.5, 129.2, 128.3, 127.8, 122.0, 60.4, 14.0, 13.3. HRMS (ESI) calcd. for C$_{13}$H$_{15}$N$_2$O$_2$[M+H]$^+$ = 231.1128, found 231.1128.

**Ethyl 4-(4-methoxyphenyl)-2-phenyl-1H-imidazole-5-carboxylate (3c):**

![Chemical structure of 3c](image)

Yellow solid, m.p. 122.9-123.3 °C; Yield: 258 mg (80%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 10.18 (s, 1H), 7.97 (m, 3H), 7.48-7.36 (m, 6H), 4.35 (q, $J = 7.1$ Hz, 2H), 1.69 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 164.2, 162.1, 158.8, 138.0, 131.2, 126.4, 123.3, 121.8, 114.1, 112.2, 109.0, 93.7, 60.8, 55.4, 14.4. HRMS (ESI) calcd for C$_{19}$H$_{19}$N$_2$O$_3$ [M+H]$^+$ = 323.1390, found 323.1391.

**Ethyl 4-(4-methoxyphenyl)-2-methyl-1H-imidazole-5-carboxylate (3d):**

![Chemical structure of 3d](image)

Yellow oil; Yield: 177 mg (68%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.70 (d, $J = 8.7$ Hz, 2H), 6.88-6.83 (m, 2H), 4.24 (q, $J = 7.1$ Hz, 2H), 3.78 (s, 3H), 2.28 (s, 3H), 1.23 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 161.9, 159.9, 146.2, 130.6, 124.5, 113.4, 60.6, 55.4, 14.3, 13.9. HRMS (ESI) calcd. for C$_{14}$H$_{17}$N$_2$O$_3$[M+H]$^+$ = 261.1234, found 261.1234;
Ethyl 4-(benzo[d][1,3]dioxol-5-yl)-2-phenyl-1H-imidazole-5-carboxylate (3e):

Yellow solid, m.p. 202.5-202.8 °C; Yield: 221 mg (66%); ¹H NMR (500 MHz, CDCl₃) δ 10.01 (s, 1H), 7.95 (d, J = 6.8 Hz, 2H), 7.49-7.43 (m, 5H), 6.87 (d, J = 8.1 Hz, 1H), 6.00 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 148.1, 147.5, 123.0, 129.2, 129.1, 126.1, 123.8, 118.3, 110.2, 108.1, 101.3, 61.2, 14.5. HRMS (ESI) calcd. for C₁₉H₁₇N₂O₄ [M+H]+ = 337.1183, found 337.1184.

Ethyl 4-(4-bromophenyl)-2-phenyl-1H-imidazole-5-carboxylate (3f):

Yellow solid, m.p. 159.0-159.3 °C; Yield: 344 mg (93%); ¹H NMR (500 MHz, CDCl₃) δ 10.23 (s, 1H), 7.96 (d, J = 6.7 Hz, 2H), 7.88 (m, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 7.3 Hz, 3H), 4.36 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 163.0, 148.1, 132.0, 130.3, 130.1, 129.7, 129.1, 128.4, 126.0, 124.2, 123.5, 123.1, 61.5, 14.3. HRMS (ESI) calcd. for C₁₈H₁₆BrN₂O₂ [M+H]+ = 371.0390, found 371.0392.

Ethyl 4-(4-bromophenyl)-2-methyl-1H-imidazole-5-carboxylate (3g):

Yellow solid, m.p. 137.3-137.5 °C. Yield: 271 mg (88%); ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.47-7.45 (m, 2H), 7.41-7.38 (m, 2H), 7.35-7.33 (m, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.15-7.13 (m, 1H), 7.08 (d, J = 8.0 Hz, 2H), 5.11 (s, 2H), 3.73 (s, 2H), 3.59 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 168.4, 158.3, 147.2, 146.0, 142.1, 136.8, 130.4, 130.0, 129.3, 128.9, 128.6, 128.0, 127.8, 127.7, 127.6, 127.4, 124.2, 119.1, 115.3, 70.0, 51.9. HRMS (ESI) calcd. for C₂₇H₂₃N₂O₅ [M+H]+ = 455.1601, found 455.1601.
Ethyl 4-(furan-2-yl)-2-phenyl-1H-imidazole-5-carboxylate (3i):

Yellow solid, m.p. 117.7-118.0 °C; Yield: 155 mg (55%); \(^{1}H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 10.19 (s, 1H), 7.98 (m, 3H), 7.44 (m, 5H), 4.35 (q, \(J = 7.1\) Hz, 2H), 1.33 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 160.4, 148.3, 147.7, 133.3, 129.9, 129.4, 129.0, 128.9, 128.5, 127.8, 126.0, 118.5, 61.1, 14.2. HRMS (ESI) calcd. for C\(_{16}\)H\(_{15}\)N\(_2\)O\(_3\) [M+H]\(^+\) 283.1077, found 283.1077.

2-Methyl-4-phenyl-1H-imidazole-5-carbaldehyde (3k):

Yellow solid, m.p. 164.9-165.2 °C; Yield: 52 mg (28%); \(^{1}H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 10.04 (s, 1H), 8.19-8.09 (m, 2H), 7.46-7.37 (m, 3H), 7.09 (s, 1H), 2.40 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.6, 161.2, 139.7, 134.1, 132.4, 130.6, 129.0, 128.0, 16.8. HRMS (ESI) calcd. for C\(_{11}\)H\(_{11}\)N\(_2\)O [M+H]\(^+\) = 187.0866, found 187.0866.

(4-Isopropyl-2-methyl-1H-imidazol-5-yl)(phenyl)methanone (3l):

Yellow solid, m.p. 95.8-96.2 °C; Yield: 217 mg (95%); \(^{1}H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.87 (s, 2H), 7.53 (t, \(J = 7.3\) Hz, 1H), 7.45 (t, \(J = 7.4\) Hz, 2H), 3.71 (d, \(J = 7.0\) Hz, 1H), 2.42 (s, 3H), 1.21 (d, \(J = 6.8\) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 188.7, 145.8, 139.4, 132.0, 129.3, 128.2, 26.2, 22.3, 14.2. HRMS (ESI) calcd. for C\(_{14}\)H\(_{17}\)N\(_2\)O [M+H]\(^+\) = 229.1335, found 229.1337.

(2-Methyl-1H-imidazol-5-yl)(morpholino)methanone (3m):
Yellow solid, m.p. 174.1-174.3 °C; Yield: 176 mg (90%); $^1$H NMR (500 MHz, DMSO-d$_6$) δ 12.21 (s, 1H), 7.46 (s, 1H), 4.11 - 4.51 (m, 8H), 2.28 (s, 3H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) δ 171.9, 162.3, 162.2, 144.3, 66.9, 22.9, 14.20. HRMS (ESI) calcd. for C$_9$H$_{14}$N$_3$O$_2$ [M+H]$^+$ = 196.1081, found 196.1083.

**Ethyl 2-amino-4-phenyl-$^1$H-imidazole-5-carboxylate (3n):**

![Structure](image1.png)

Yellow oil. Yield: 169 mg (73%); $^1$H NMR (500 MHz, DMSO-d$_6$) δ 10.86 (s, 1H), 7.86 (d, $J$ = 7.4 Hz, 2H), 7.32-7.24 (m, 3H), 5.73 (s, 2H), 4.13 (q, $J$ = 7.1 Hz, 2H), 1.19 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) δ 164.8, 156.6, 139.0, 137.0, 133.9, 132.8, 132.6, 64.5, 19.5. HRMS (ESI) calcd. for C$_{12}$H$_{14}$N$_3$O$_2$ [M+H]$^+$ = 232.1081, found 232.1082.

**Ethyl 2-(2-ethoxy-2-oxoethyl)-4-phenyl-$^1$H-imidazole-5-carboxylate (3o):**

![Structure](image2.png)

Yellow solid, m.p. 116.3-116.7 °C. Yield: 193 mg (64%); $^1$H NMR (500 MHz, CDCl$_3$) δ 9.22 (s, 1H), 7.24-7.16 (m, 5H), 5.14 (s, 2H), 4.26 (q, $J$ = 7.1 Hz, 2H), 4.16 (t, $J$ = 7.1 Hz, 2H), 1.26 (t, $J$ = 7.1 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 168.5, 165.6, 147.1, 131.2, 128.8, 127.3, 126.3, 125.1, 111.6, 93.3, 61.6, 59.7, 14.6, 14.2. HRMS (ESI) calcd. for C$_{16}$H$_{19}$N$_2$O$_4$ [M+H]$^+$ = 303.1339, found 303.1339.

**Ethyl 2-(2-fluorobenzyl)-4-phenyl-$^1$H-imidazole-5-carboxylate (3p):**

![Structure](image3.png)

Yellow oil; Yield: 185 mg (57%); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.79 (s, 2H), 7.40-7.33 (m, 3H), 7.26 (s, 2H), 7.12-7.04 (m, 2H), 4.27 (q, $J$ = 7.1 Hz, 2H), 4.15 (s, 2H), 1.27 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 159.6 (d, $J$ = 245.1 Hz), 159.4, 146.8, 131.1, 130.2, 130.0 (d, $J$ = 3.8 Hz), 128.3, 128.2, 126.8, 123.7, 123.6, 122.1 (d, $J$ = 15.6 Hz), 120.7, 114.5 (d, $J$ = 21.6 Hz), 60.1, 27.2 (d, $J$ = 3.3 Hz), 13.1. HRMS (ESI) calcd. for C$_{19}$H$_{18}$FN$_2$O$_2$ [M+H]$^+$ = 325.1347, found 325.1348.
Ethyl 2-(2-ethoxy-2-oxoethyl)-4-(p-tolyl)-1H-imidazole-5-carboxylate (3q):

Yellow oil. Yield: 250 mg (79%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.07 (s, 1H), 7.16 (d, $J = 8.1$ Hz, 2H), 7.03 (d, $J = 8.0$ Hz, 2H), 5.15 (s, 2H), 4.28 (d, $J = 7.2$ Hz, 2H), 4.19 (d, $J = 7.1$ Hz, 2H), 2.31 (s, 3H), 1.32-1.26 (m, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 168.4, 165.6, 146.8, 137.3, 129.5, 128.4, 126.3, 125.3, 111.2, 93.1, 61.5, 59.6, 21.3, 14.6, 14.2. HRMS (ESI) calcd. for C$_{17}$H$_{21}$N$_2$O$_4$ [M+H]$^+$ =317.1496, found 317.1498.

Ethyl 2-amino-4-(4-methoxyphenyl)-1H-imidazole-5-carboxylate (3r):

Yellow oil. Yield: 178 mg (68%); $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 10.68 (s, 1H), 7.86 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 9.0$ Hz, 2H), 5.68 (s, 2H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.73 (s, 3H), 1.20 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) $\delta$ 160.2, 159.3, 151.8, 130.4, 113.3, 59.6, 55.5, 14.8. HRMS (ESI) calcd. for C$_{13}$H$_{16}$N$_3$O$_3$ [M+H]$^+$ = 262.1186, found 262.1188.

Ethyl 2-(2-fluorobenzyl)-4-(4-methoxyphenyl)-1H-imidazole-5-carboxylate (3s):

Yellow oil; Yield: 163 mg (46%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.58 (s, 1H), 7.87 (s, 1H), 7.31-7.25 (m, 2H), 7.09 (d, $J = 6.8$ Hz, 2H), 6.92 (d, $J = 8.8$ Hz, 2H), 4.34-4.24 (m, 2H), 4.15 (s, 2H), 3.83 (s, 3H), 1.30 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 161.7, 159.8, 159.8, 131.2, 131.2, 130.5, 129.3, 129.2, 124.7, 124.7, 115.7, 115.5, 113.3, 60.7, 55.2, 28.5, 14.2. HRMS (ESI) calcd. for C$_{20}$H$_{20}$FN$_2$O$_3$ [M+H]$^+$ = 355.1452, found 355.1452.
Ethyl 2-amino-4-(3-bromophenyl)-1H-imidazole-5-carboxylate (3t):

Yellow solid, m.p. 182.6-182.9 °C; Yield: 273 mg (88%); 1H NMR (500 MHz, DMSO-d6) δ 10.86 (s, 1H), 7.86 (d, J = 7.4 Hz, 2H), 7.32-7.24 (m, 3H), 5.73 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H); 13C NMR (125 MHz, DMSO-d6) δ 164.8, 156.6, 139.0, 137.0, 133.9, 132.8, 132.6, 64.5, 19.5; HRMS (ESI) calcd. for C_{12}H_{13}BrN_{3}O_{2}[M+H]^{+} = 310.0186, found 310.0186.

Ethyl 4-(3-bromophenyl)-2-(2-fluorobenzyl)-1H-imidazole-5-carboxylate (3u):

Yellow oil; Yield: 330 mg (88%); 1H NMR (500 MHz, CDCl_{3}) δ 9.89 (s, 1H), 7.93 (s, 1H), 7.93 (s, 1H), 7.40 (m, 1H), 7.39 (m, 1H), 7.20-7.16 (m, 2H), 7.06-6.99 (m, 2H), 4.22 (q, J = 7.1 Hz, 2H), 4.10 (s, 2H), 1.23 (t, J = 7.1 Hz, 3H); 13C NMR (75 MHz, CDCl_{3}) δ 159.6 (d, J = 245.1 Hz), 159.4, 146.8, 131.1, 130.2, 130.0 (d, J = 3.8 Hz), 128.3, 128.2, 126.8, 123.7, 123.6, 122.1 (d, J = 15.6 Hz), 120.7, 114.5 (d, J = 21.6 Hz), 60.1, 27.2 (d, J = 3.3 Hz), 13.1. HRMS (ESI) calcd. for C_{19}H_{17}BrF_{2}N_{2}O_{2} [M+H]^+ = 403.0452, found 403.0452.
X-ray crystallography Data of 3g (CCDC No: 1045551):

Single crystals of compound 3g were measured on a Rigaku RAXIS-RAPID single-crystal diffractometer. The recrystallization solvent of 3g was EtOH.

Table S1 X-ray crystallography data of 3g

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$^1$H NMR (500 MHz) and $^{13}$C NMR (125 MHz) Spectra of 3: