

1 *Supplementary Information*

2
3 **Tetrasubstituted Imidazoles as Incognito Toll-like**
4 **Receptor 8 A(nta)gonists**

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17 [#] These authors contributed equally to this work.

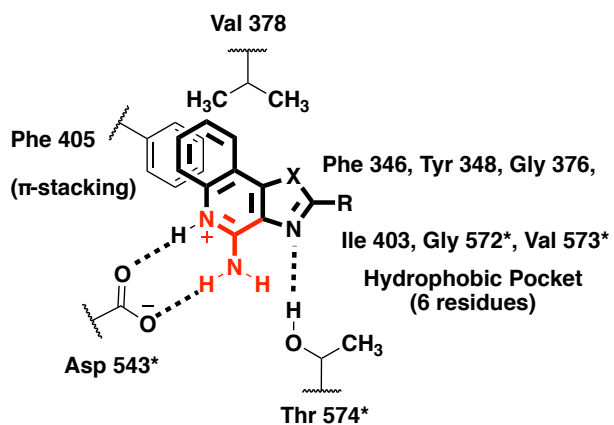
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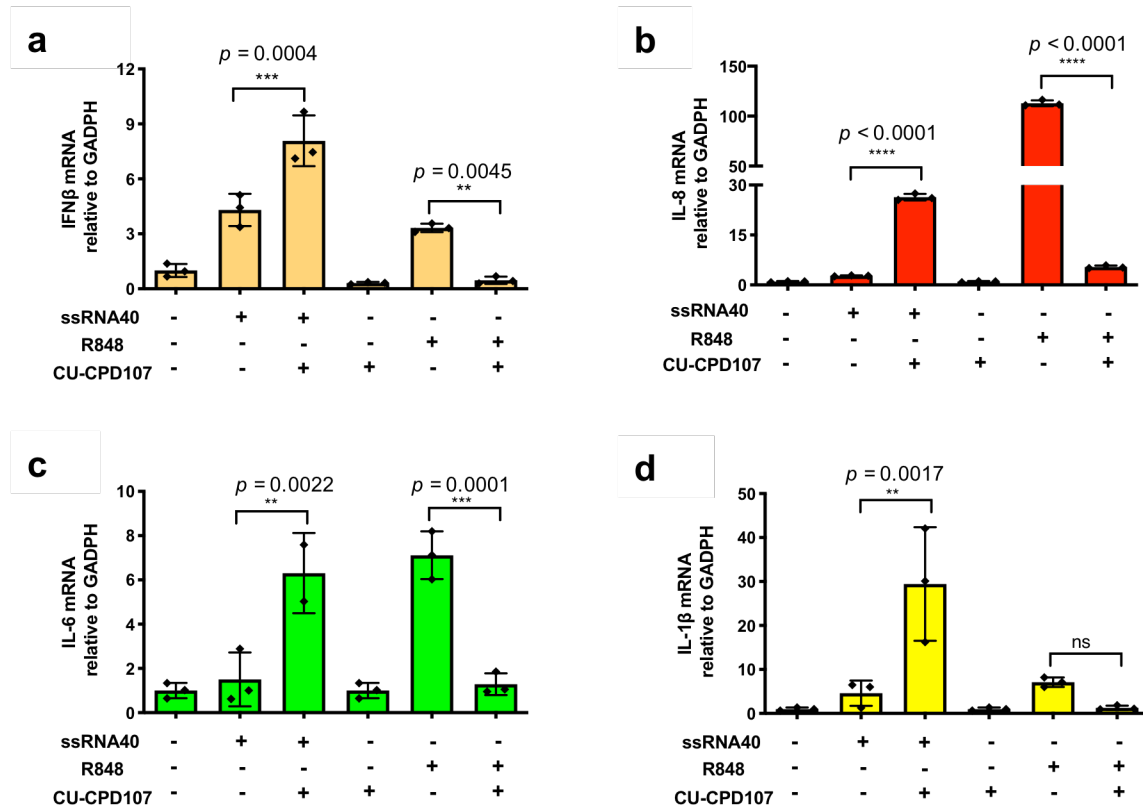
- 21 **Supplementary Fig. 1** Key interactions of imidazoquinolines binding to TLR8.
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23 cytokines by RT-qPCR in HEK-Blue hTLR8 cells.
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25 of IL-8 and TNF- α with the presence of 5 $\mu\text{g}/\text{mL}$ ORN06.
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- 30 **Supplementary Fig. 6** **CU-CPD107** showed neglected toxicity in human PBMCs.
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- 39 **General Chemistry Methods**
- 40 **Supplementary Fig. 10-20** Chemical synthetic routes of compounds.
- 41 **Compounds synthesis and characterization**



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43 **Supplementary Fig. 1** Key interactions of imidazoquinolines binding to TLR8 are
44 shown (residues marked with * indicate that they are located on a different TLR8 protein
45 in the dimer complex from unmarked residues).

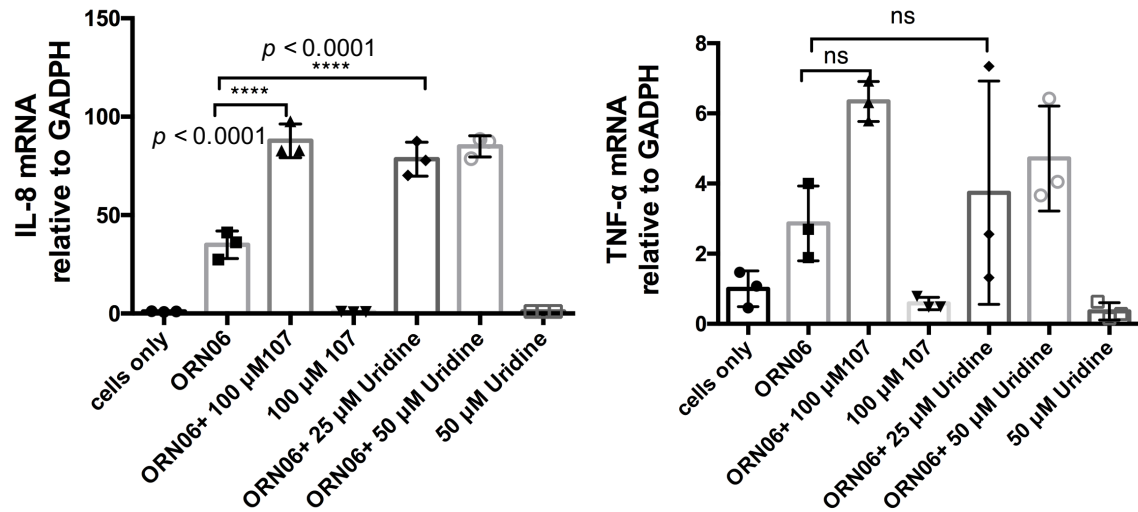
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48 **Supplementary Fig. 2** The effects of **CU-CPD107** on the mRNA level of downstream
 49 cytokines by RT-qPCR in HEK-Blue hTLR8 cells. **CU-CPD107** could synergistically
 50 upregulate the mRNA levels of IFN- β (**a**), IL-8 (**b**), IL-6 (**c**), and IL-1 β (**d**) in the
 51 presence of 5 μ g/mL ssRNA40, while it could inhibit R848-induced activation and itself
 52 had no effect in HEK-Blue hTLR8 cells. Data are mean \pm s.d.; the data shown are
 53 representative of three independent experiments. A one-way analysis of variance with
 54 Bonferroni's multiple comparisons test for multiple comparisons was used for statistical
 55 analysis. Statistical significance of the data is indicated as follows: * $p < 0.05$, ** $p < 0.01$,
 56 *** $p < 0.001$, **** $p < 0.0001$; ns = not significant. Source data are provided as a Source
 57 data file.

58



59

60 **Supplementary Fig. 3** CU-CPD107 could synergistically upregulate the mRNA levels

61 of IL-8 and TNF- α with the presence of 5 μ g/mL ORN06. Uridine was used as a positive

62 control and itself has no effects on TLR8 signaling in HEK-Blue TLR8 cells. Data are

63 mean \pm s.d.; the data shown are representative of three independent experiments. A one-

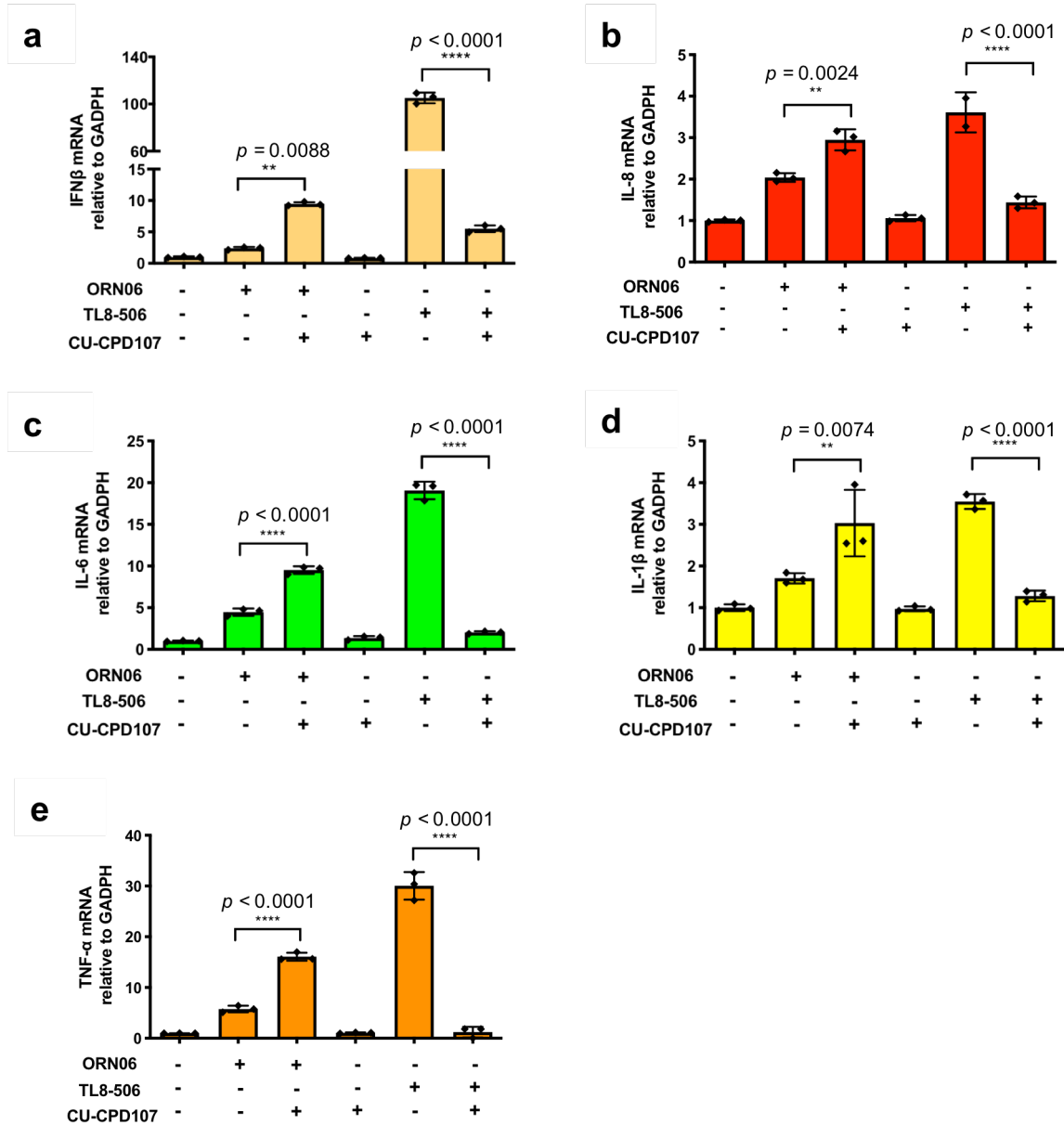
64 way analysis of variance with Bonferroni's multiple comparisons test for multiple

65 comparisons was used for statistical analysis. Statistical significance of the data is

66 indicated as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; ns = not

67 significant. Source data are provided as a Source data file.

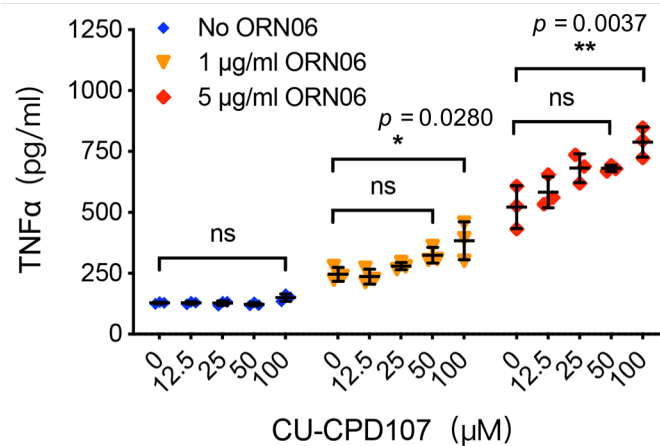
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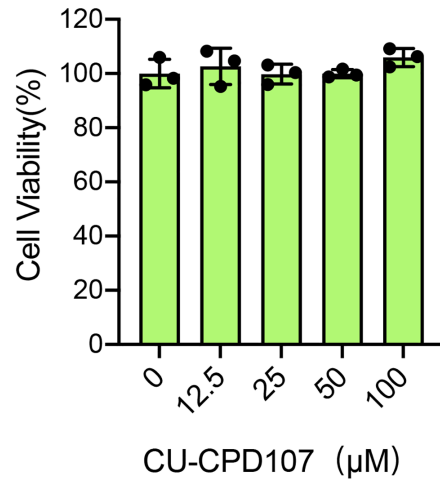
70 **Supplementary Fig. 4** The effects of **CU-CPD107** on the mRNA level of downstream
 71 cytokines by RT-qPCR in human PBMCs. **CU-CPD107** could synergistically upregulate
 72 the mRNA levels of IFN- β (a), IL-8 (b), IL-6 (c), IL-1 β (d), and TNF- α (e) in the
 73 presence of 2 $\mu\text{g}/\text{mL}$ ORN06, while it could inhibit 1 $\mu\text{g}/\text{mL}$ TL8-506-induced activation
 74 whereas itself had no effect in PBMCs. Data are mean \pm s.d.; the data shown are
 75 representative of three independent experiments with three independent blood donors. A

76 one-way analysis of variance with Bonferroni's multiple comparisons test for multiple
77 comparisons was used for statistical analysis. Statistical significance of the data is
78 indicated as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; ns = not
79 significant. Source data are provided as a Source data file.



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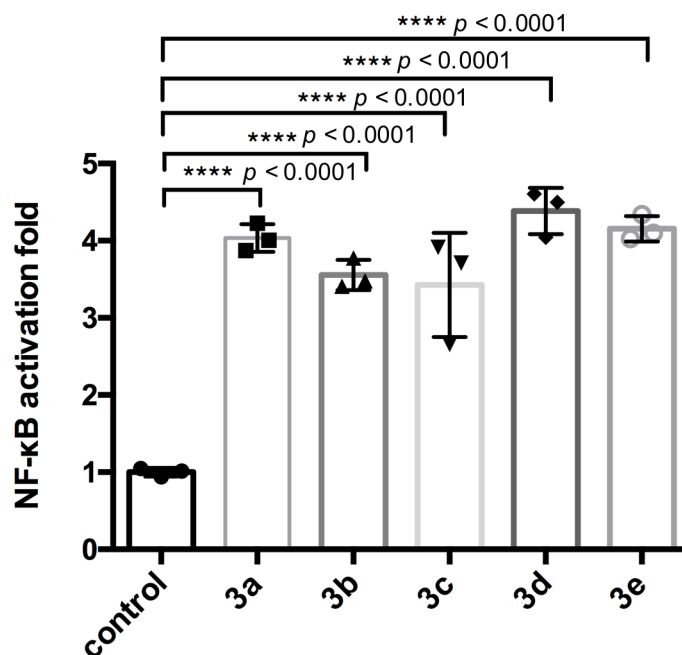
81 **Supplementary Fig. 5** The effects of **CU-CPD107** in induction of TNF- α in human
 82 PBMCs in the presence of ORN06. The production of TNF- α were measured 6 hours
 83 after treatment of ORN06. Data are mean \pm s.d.; the data shown are representative of six
 84 independent experiments with six independent blood donors. A one-way analysis of
 85 variance with Bonferroni's multiple comparisons test for multiple comparisons was used
 86 for statistical analysis. Statistical significance of the data is indicated as follows:
 87 * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$; ns = not significant. Source data are
 88 provided as a Source data file.



89

90 **Supplementary Fig. 6** CU-CPD107 showed neglected toxicity in human PBMCs. Data
91 are normalized to CU-CPD107 untreated cells as 100%. Data are mean \pm s.d.; n = 3
92 biologically independent experiments. Source data are provided as a Source data file.

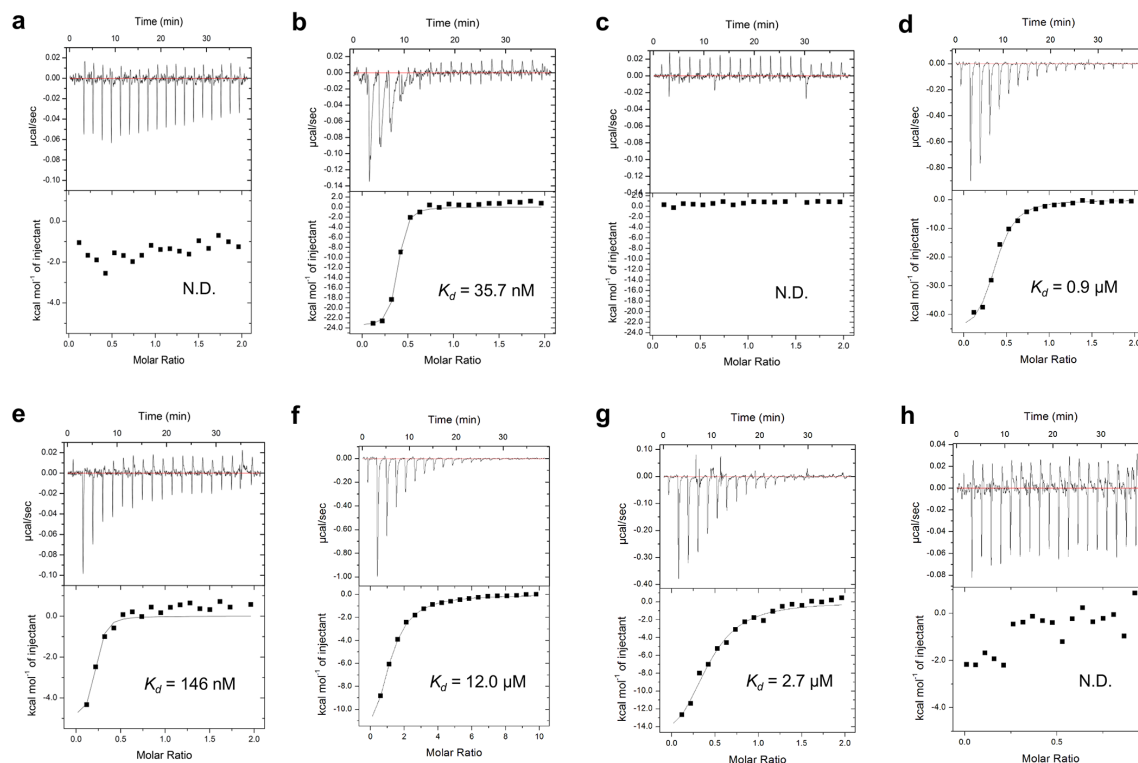
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94

95 **Supplementary Fig. 7** The activities of the compounds in the presence of 5 μg/mL
 96 ssRNA40. The TLR8 activation fold induced by **3a**, **3b**, **3c**, **3d** and **3e** at 100 μM in the
 97 presence of ssRNA (5 μg/mL) compared to ssRNA (5 μg/mL) control. Data are mean ±
 98 s.d.; n = 3 biologically independent experiments. A one-way analysis of variance with
 99 Bonferroni's multiple comparisons test for multiple comparisons was used for statistical
 100 analysis. Statistical significance of the data is indicated as follows: *p < 0.05, **p < 0.01,
 101 ***p < 0.001, ****p < 0.0001; ns = not significant. Source data are provided as a Source
 102 data file.

103

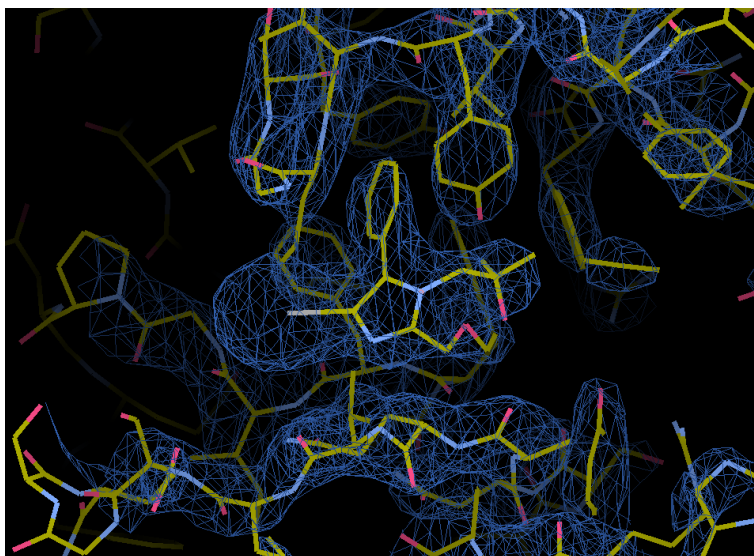


104

105 **Supplementary Fig. 8 ITC experiments with TLR8.** **a** CU-CPD107 (100 µM) was
 106 titrated into TLR8 (10 µM), showing little heat change. **b** R848 (100 µM) was titrated
 107 into TLR8 (10 µM), showing a binding curve with a $K_d = 35.7$ nM. **c** R848 (100 µM) was
 108 titrated into TLR8 (10 µM) with CU-CPD107 (100 µM), showing inhibited binding by
 109 no heat change. **d** ORN06 (200 µM) was titrated to TLR8 (20 µM) with a $K_d = 0.9$ µM. **e**
 110 CU-CPD107 (100 µM) was titrated into TLR8 (10 µM) with ORN06 (20 µM), showing
 111 a binding curve with a $K_d = 146$ nM. **f** Uridine (1 mM) was titrated to TLR8 (20 µM)
 112 with a $K_d = 12$ µM. **g** Uridine (200 µM) was titrated to TLR8 (20 µM) and ORN06 (40
 113 µM) with a $K_d = 2.7$ µM. **h** CU-CPD107 (100 µM) was titrated to ORN06 (40 µM) which
 114 could not evaluate a K_d -value due to little heat change.

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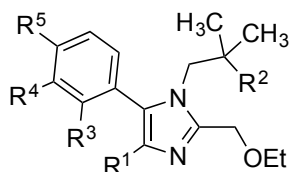
118 **Supplementary Fig. 9** Electron density map around **CU-CPD107**.

119 **Supplementary Table 1** Toxicity of the tetrasubstituted imidazoles analogues.

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121

122



compounds	R ¹	R ²	R ³	R ⁴	R ⁵	Cell viability ^[a]
1a	-CN	-OH	-H	-H	-H	0.7 ± 0.3
1b		-OH	-H	-H	-H	0.7 ± 0.2
1c	-CONH ₂	-OH	-H	-H	-H	0.8 ± 0.3
1d	-CHO	-OH	-H	-H	-H	0.7 ± 0.2
1e	-COOCH ₃	-OH	-H	-H	-H	0.9 ± 0.1
1f	-CH ₂ OH	-OH	-H	-H	-H	0.8 ± 0.1
1g	-CH ₂ OCH ₃	-OH	-H	-H	-H	0.8 ± 0.2
1h	-CH ₃	-OH	-H	-H	-H	0.8 ± 0.3
1i	-CH ₂ F	-OH	-H	-H	-H	0.9 ± 0.3
1j	-C(CH ₃) ₂ OH	-OH	-H	-H	-H	TBD
1k	-CH(CH ₃) ₂	-OH	-H	-H	-H	0.8 ± 0.3
1l	-Ph	-OH	-H	-H	-H	TBD
1m	-H	-OH	-H	-H	-H	0.9 ± 0.2
1n	-Cl	-OH	-H	-H	-H	0.9 ± 0.2
1o	-Br	-OH	-H	-H	-H	1.1 ± 0.3
1p (CU-CPD107)	-I	-OH	-H	-H	-H	0.9 ± 0.2
1q	-COOH	-OH	-H	-H	-H	1.1 ± 0.3
2a	-H	-H	-H	-H	-H	0.9 ± 0.3

2b	-Cl	-H	-H	-H	-H	0.7 ± 0.2
2c	-Br	-H	-H	-H	-H	0.7 ± 0.1
2d	-I	-H	-H	-H	-H	0.3 ± 0.2
3a	-I	-OH	-H	-H	-Ph	0.8 ± 0.1
3b	-I	-OH	-H	-Ph	-H	0.8 ± 0.0
3c	-I	-OH	-CH ₃	-H	-H	0.8 ± 0.0
3d	-I	-OH	-H	-CH ₃	-H	0.8 ± 0.0
3e	-I	-OH	-H	-H	-CH ₃	0.9 ± 0.1

123 ^[a]Cell viability was measured by WST1 as compared to uninhibited R848 signaling, which was
 124 normalized to 1.0. Data are representative of the average and standard deviation of at least three
 125 independent experiments.

126

127 **Supplementary Table 2** Primer lists.

Primer Name	Sequence (5' to 3')
TNF- α F	CCCAGGGACCTCTCTCTAATC
TNF- α R	ATGGGCTACAGGCTTGTCCT
IL-1 β F	AACCTCTTCGAGGCACAAG
IL-1 β R	GTTTAGGGCCATCAGCTTCA
IL-6 F	GTACATCCTCGACGGCATCTC
IL-6 R	GGCAAGTCTCCTCATTGAATC
IL-8 F	CCAGGAAGAAACCACCGGAAG
IL-8 R	TGGTCCACTCTCAATCACTCTCAG
IFN- β F	AGGACAGGATGAACTTTGAC
IFN- β R	TGATAGACATTAGCCAGGAG
GAPDH F	CCCACTCCTCCACCTTTGACG
GAPDH R	CACCACCCTGTTGCTGTAGCCA

128

129 **Supplementary Table 3** Data collection and refinement statistic for hTLR8/CU-
 130 **CPD107.**

131

132

hTLR8/CU-CPD107

133

Data collection

134

Space group

*C*2

135

Cell dimensions

136

a, *b*, *c* (Å)

144.3, 100.0, 140.9

137

α , β , γ (°)

90.0, 105.6, 90.0

138

Resolution (Å)

2.89

139

R_{sym} or R_{merge}

0.071 (0.678)

140

$I / \sigma I$

17.0 (2.8)

141

Completeness (%)

99.9 (100.0)

142

Redundancy

6.9 (6.6)

143

Total No. of reflections

298,805

144

No. of unique reflections

43,396

145

Refinement

146

Resolution (Å)

40.71-2.89

147

No. of reflections

41,017

148

$R_{\text{work}} / R_{\text{free}}$

0.210/0.268

149

No. of atoms

150

Protein

12,036

151

Glycan

682

152

CU-CPD107

42

153

B-factors

Protein

79.5

Glycan

99.1

CU-CPD107

70.7

R.m.s. deviations

Bond lengths (Å)

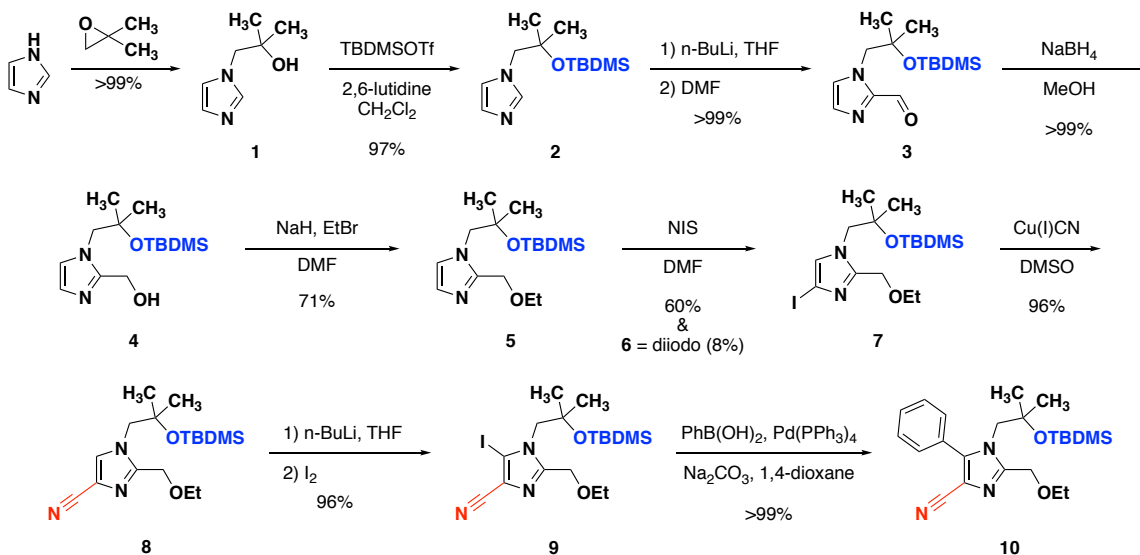
0.005

Bond angles (°)

1.48

154 **General Chemistry Methods**

155 NMR spectra were acquired on Bruker 400 spectrometer, running at 400 MHz for ^1H and
156 101 MHz for ^{13}C respectively. ^1H NMR spectra were recorded at 400 MHz in $\text{DMSO-}d_6$
157 using residual DMSO (2.50 ppm) as the internal standard. ^{13}C NMR spectra were
158 recorded at 101 MHz in $\text{DMSO-}d_6$ using residual DMSO (39.52 ppm) as internal
159 reference. Thin layer chromatography was performed on Merck Kieselgel 60 Å F254
160 plates eluting with the solvent indicated, visualized by a 254 nm UV lamp. Compounds
161 were purified using flash chromatography, (Silica gel 60Å, 230-400 mesh, Sorbent
162 Technologies). Mass spectrometry was performed at the mass spectrometry facility of the
163 Department of Chemistry at University of Colorado at Boulder on a double focusing high
164 resolution mass spectrometer. Unless otherwise noted, analytical grade solvents and
165 commercially available reagents were used without further purification. The purity of
166 tested compounds was evaluated via ^1H NMR (>95% sample purity). All compounds
167 tested in the SEAP assay were confirmed via high-resolution mass spectrometry. All
168 other intermediate compounds were confirmed with either high-resolution or standard
169 resolution mass spectrometry, and all compounds were characterized via ^{13}C and/or ^1H
170 NMR.



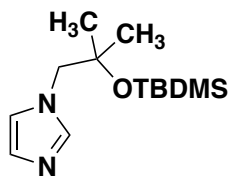
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173 **Supplementary Fig. 10 Key intermediate synthesis:** Key intermediate **10** was

174 synthesized from imidazole in 38% yield over nine steps.

175



176

177 **1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-1H-imidazole (2)**

178 To a solution of 1-(1H-imidazol-1-yl)-2-methylpropan-2-ol (10.3 g, 73.5 mmol, prepared

179 as previously reported in *Tetrahedron*, 63(2), **2007**, 469-473) and 2,6-lutidine (60.0 mL,

180 515 mmol) in dichloromethane (900 mL) at room temperature was added *tert*-

181 butyldimethylsilyl trifluoromethanesulfonate (84.5 mL, 368 mmol) via addition funnel

182 over 10 min. The resulting solution was allowed to stir for 16 hours at room temperature.

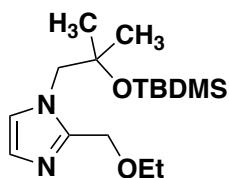
183 After this time, the reaction mixture was concentrated to roughly 400 mL, washed with

184 water (5 × 400 mL), washed with saturated aqueous sodium chloride (400 mL), dried

185 over sodium sulfate, filtered and concentrated to dryness. The residue obtained was

186 azeotroped with toluene (3 × 400 mL) and was purified via flash SiO₂ chromatography
187 (100 g silica gel, gradient of dichloromethane to 4% methanol/96% dichloromethane) to
188 give 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-1H-imidazole (**2**) (18.1 g, 97%)
189 as a red oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.51 (s, 1H), 7.06 (t, *J* = 1.1 Hz, 1H), 6.86
190 (s, 1H), 3.88 (s, 2H), 1.15 (s, 6H), 0.83 (s, 9H), 0.01 (s, 6H); ¹³C NMR (101 MHz
191 DMSO-*d*₆) δ 138.30, 127.41, 120.76, 72.90, 57.87, 26.96, 25.74, 17.71, -2.31; MS (ESI⁺),
192 calcd C₁₃H₂₆N₂OSi (M+H) = 255.1893, found = 255.1885.

193



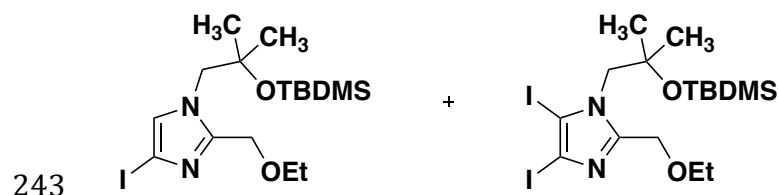
195 **1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl) 1H-imidazole**
196 **(5)**

197 A solution of 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-1H-imidazole (15.35 g,
198 60.33 mmol) in tetrahydrofuran (735 mL) was cooled in a dry ice/isopropyl alcohol bath
199 (~ -78 °C). *n*-Butyllithium (36 mL, 91 mmol, 2.5 M solution in hexanes) was added
200 slowly over 20 min (keeping internal temperature at -55 °C or lower) and the resulting
201 solution was allowed to stir at the same temperature for 40 min. After this time, the
202 reaction flask was transferred to a warmer dry ice/isopropyl alcohol bath (maintained
203 between -40 °C and -25 °C) and was allowed to stir for 1 hour. After this time, the
204 reaction flask was placed back into the original -78 °C bath and was allowed to stir until
205 the internal temperature reached -65 °C. At this time *N,N*-dimethylformamide (9.40 mL,
206 121 mmol) was added and allowed to stir at the same temperature for 30 min. After this

207 time, the dry ice bath was removed and the reaction was allowed to stir at room
208 temperature for 18 hours. After this time, saturated aqueous ammonium chloride (100 mL)
209 and water (100 mL) was added. The entire biphasic mixture was concentrated via rotary
210 evaporation to remove roughly 500 mL of tetrahydrofuran. The resulting biphasic
211 mixture was further diluted with saturated aqueous ammonium chloride (300 mL) and
212 extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed
213 with saturated aqueous sodium chloride (300 mL), dried over magnesium sulfate, filtered
214 and concentrated to dryness to give crude 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-
215 methylpropyl}-1H-imidazole-2-carbaldehyde (**3**) as a yellow oil. This oil was taken up
216 into methanol (450 mL) and cooled in an ice bath. Sodium borohydride (3.42 g, 90.5
217 mmol) was added and the ice bath was kept for 5 min. After this time, the ice bath was
218 removed and the reaction was allowed to stir at room temperature for 18.5 hours. After
219 this time, saturated aqueous ammonium chloride (300 mL) was added and the resulting
220 mixture was extracted with dichloromethane (3 × 200 mL). The combined organic layers
221 were washed with saturated aqueous sodium chloride (400 mL), dried over sodium
222 sulfate, filtered and concentrated to dryness. The off-white solid obtained was azeotroped
223 with toluene (400 mL), then left on a high-vacuum pump for several hours to give crude
224 (1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-1H-imidazol-2-yl)methanol (**4**). The
225 white solid was taken up into *N,N*-dimethylformamide (450 mL) and cooled in an ice
226 bath. Sodium hydride (3.62 g, 90.5 mmol, 60% dispersion in mineral oil) was added and
227 allowed to stir in the ice bath for 30 min. After this time, bromoethane (9.0 mL, 120
228 mmol) was added. The ice bath was then removed and the reaction was allowed to stir for
229 18 hours. After this time, saturated aqueous ammonium chloride (100 mL) and water

230 (150 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 200
 231 mL). The combined organic layers were then washed with 5% aqueous lithium chloride
 232 (3 × 200 mL), washed with saturated aqueous sodium chloride (300 mL), dried over
 233 magnesium sulfate, filtered and concentrated to dryness. The resulting residue was
 234 purified via flash SiO₂ chromatography (340 g silica gel, gradient of dichloromethane to
 235 5% methanol/95% dichloromethane) to give 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-
 236 methylpropyl}-2-(ethoxymethyl) 1H-imidazole (**5**) (13.45 g, 71% over three steps) as an
 237 orange oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.11 (d, *J* = 1.2 Hz, 1H), 6.82 (d, *J* = 1.2 Hz,
 238 1H), 4.46 (s, 2H), 3.92 (s, 2H), 3.42 (q, *J* = 7.0 Hz, 2H), 1.19 (s, 6H), 1.08 (t, *J* = 7.0 Hz,
 239 3H), 0.82 (s, 9H), 0.04 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 144.76, 126.18, 121.86,
 240 73.53, 64.74, 63.80, 56.56, 27.22, 25.77, 17.70, 14.90, -2.23; MS (ESI⁺), calcd
 241 C₁₆H₃₃N₂O₂Si (M+H) = 313.2311, found = 313.2316.

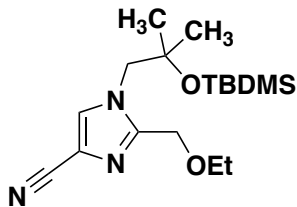
242



244 **1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-iodo-1H-**
 245 **imidazole (7) and 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-**
 246 **(ethoxymethyl)-4,5-diiodo-1H-imidazole (6)**

247 A solution of 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl) 1H-
 248 imidazole (3.00 g, 9.60 mmol) in *N,N*-dimethylformamide (60 mL) was heated to 80 °C.
 249 A separate solution of *N*-iodosuccinimide (4.32 g, 19.2 mmol) in *N,N*-
 250 dimethylformamide (30 mL) was prepared and slowly added to the original reaction flask

251 over 5 min. The reaction was allowed to stir at 80 °C for 16 hours. After this time, the
252 reaction was allowed to cool to room temperature and water (100 mL) was added. Solid
253 sodium thiosulfate pentahydrate was added until no further color change was observed,
254 resulting in a pale yellow suspension. The resulting mixture was extracted with ethyl
255 acetate (3 × 70 mL). The combined organic layers were then washed with 5% aqueous
256 lithium chloride (3 × 150 mL), washed with saturated aqueous sodium chloride (200 mL),
257 dried over magnesium chloride, filtered and concentrated to dryness. The resulting
258 residue was purified via flash SiO₂ chromatography (100 g silica gel, gradient of hexanes
259 to 25% ethyl acetate/75% hexanes), to give 1-{2-[(*tert*-butyldimethylsilyloxy]-2-
260 methylpropyl}-2-(ethoxymethyl)-4-iodo-1H-imidazole (**7**) (2.44 g, 58%) as pale yellow
261 oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.25 (s, 1H), 4.44 (s, 2H), 3.91 (s, 2H), 3.42 (q, *J* =
262 7.0 Hz, 2H), 1.17 (s, 6H), 1.08 (t, *J* = 7.0 Hz, 3H), 0.83 (s, 9H), 0.04 (s, 6H); ¹³C NMR
263 (101 MHz DMSO-*d*₆) δ 147.02, 127.62, 80.04, 73.43, 64.94, 63.11, 56.66, 27.05, 25.77,
264 17.75, 14.90, -2.26; MS (ESI⁺), calcd C₁₆H₃₂IN₂O₂Si (M+H) = 439.1278, found =
265 439.1274. Chromatography also gave 1-{2-[(*tert*-butyldimethylsilyloxy]-2-
266 methylpropyl}-2-(ethoxymethyl)-4,5-diiodo-1H-imidazole (**6**) (0.434 g, 8%) as an off-
267 white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.58 (s, 2H), 4.09 (s, 2H), 3.40 (q, *J* = 7.0
268 Hz, 2H), 1.29 (s, 6H), 1.08 (t, *J* = 7.0 Hz, 3H), 0.75 (s, 9H), 0.05 (s, 6H); ¹³C NMR (101
269 MHz DMSO-*d*₆) δ 150.27, 96.31, 89.26, 74.14, 65.14, 64.68, 58.01, 28.83, 25.92, 17.80,
270 14.92, -2.02; MS (ESI⁺), calcd C₁₆H₃₁I₂N₂O₂Si (M+H) = 565.0244, found = 565.0242.
271

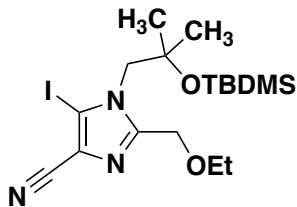


272

273 **1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl) 1H-imidazole-**
 274 **4-carbonitrile (8)**

275 A solution of 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-
 276 iodo-1H-imidazole (2.00 g, 4.56 mmol) in dimethyl sulfoxide (60 mL) was degassed and
 277 backfilled with nitrogen gas (3×). Copper (I) cyanide (0.817 g, 9.12 mmol) was added
 278 and the resulting mixture was degassed and backfilled with nitrogen (3×) again. The
 279 reaction was heated at 150 °C for 17 hours and then allowed to cool to room temperature.
 280 ethyl acetate (300 mL) was added and filtered through a plug of silica gel (~ 70 g). The
 281 filtrate was washed with water (3 × 200 mL), washed with saturated aqueous sodium
 282 chloride (200 mL), dried over magnesium sulfate, and filtered through an additional plug
 283 of silica gel (~ 70 g, eluting with ethyl acetate) to give 1-{2-[(*tert*-
 284 butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl) 1H-imidazole-4-carbonitrile
 285 **(8)** (1.467 g, 95%) as a yellow oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.98 (s, 1H), 4.52 (s,
 286 2H), 4.02 (s, 2H), 3.45 (q, *J* = 7.0 Hz, 2H), 1.21 (s, 6H), 1.09 (t, *J* = 7.0 Hz, 3H), 0.79 (s,
 287 9H), 0.03 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 147.38, 131.98, 115.47, 109.95,
 288 73.14, 65.25, 63.21, 57.05, 27.16, 25.74, 17.69, 14.85, -2.28; MS (ESI⁺), calcd
 289 C₁₇H₃₂N₃O₂Si (M+H) = 338.2264, found = 338.2257.

290



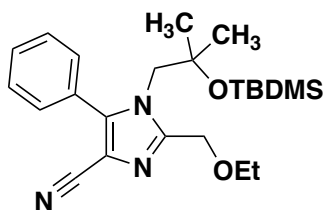
291

292 **1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl) 5-iodo-1H-**
 293 **imidazole-4-carbonitrile (9)**

294 A solution of 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl) 1H-
 295 imidazole-4-carbonitrile (1.467 g, 4.346 mmol) in tetrahydrofuran (60 mL) was prepared
 296 in an oven-dried flask and cooled in a dry ice/isopropyl alcohol bath (~ -78 °C). *n*-
 297 Butyllithium (3.0 mL, 4.8 mmol, 1.6 M solution in hexanes) was added slowly over 5
 298 min and the reaction was allowed to stir in the ice bath for 30 min. After this time, a
 299 solution of iodine (2.21 g, 8.69 mmol) in tetrahydrofuran (9 mL) was added slowly over
 300 10 min. The reaction was allowed to stir in the dry ice bath for an additional 30 min.
 301 After this time, the dry ice bath was removed and the reaction was allowed to stir at room
 302 temperature for 17 hours. After this time, saturated aqueous ammonium chloride (60 mL)
 303 was added and the resulting mixture was extracted with ethyl acetate (3 × 40 mL). The
 304 combined organic layers were washed with aqueous sodium thiosulfate pentahydrate (100
 305 mL, 1 M), washed with saturated aqueous sodium chloride (100 mL), dried over
 306 magnesium sulfate, filtered and concentrated to dryness. The residue obtained was
 307 purified via flash SiO₂ chromatography (100 g silica gel, gradient of dichloromethane to
 308 6% ethyl acetate/94% dichloromethane) to give 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-
 309 methylpropyl}-2-(ethoxymethyl) 5-iodo-1H-imidazole-4-carbonitrile (**9**) (1.928 g, 96%)
 310 as an orange solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.63 (s, 2H), 4.10 (s, 2H), 3.43 (q, *J*
 311 = 7.0 Hz, 2H), 1.32 (s, 6H), 1.09 (t, *J* = 7.0 Hz, 3H), 0.72 (s, 9H), 0.06 (s, 6H); ¹³C NMR

312 (101 MHz DMSO-*d*₆) δ 150.64, 119.51, 115.66, 91.76, 73.93, 65.38, 64.55, 57.23, 28.93,
313 25.87, 17.75, 14.87, -2.05; MS (ESI⁺), calcd C₁₇H₃₁IN₃O₂Si (M+H) = 464.1230, found =
314 464.1225.

315

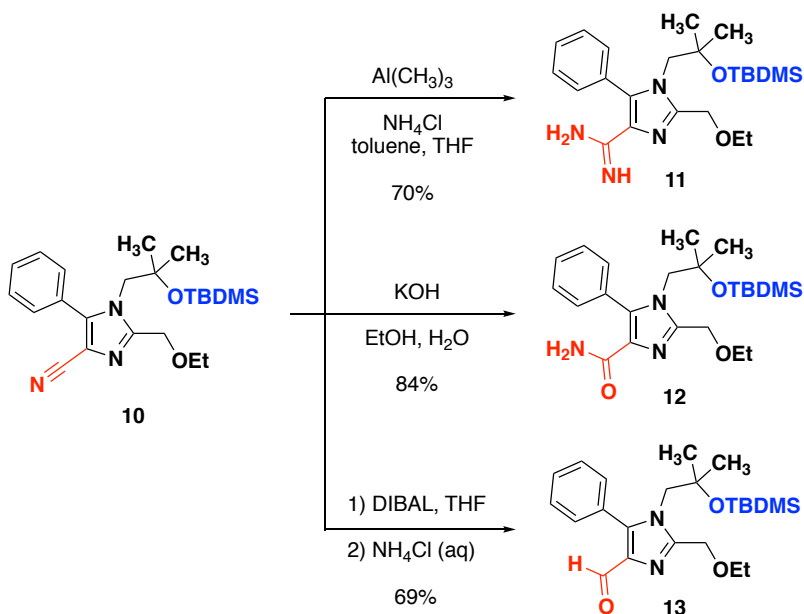


316

317 **1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-1H-**
318 **imidazole-4-carbonitrile (10)**

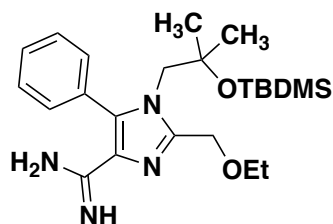
319 A mixture of 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl) 5-
320 iodo-1H-imidazole-4-carbonitrile (2.239 g, 4.831 mmol), phenylboronic acid (0.647 g,
321 5.31 mmol), and aqueous sodium carbonate (32 mL, 1 M) in 1,4-dioxane (63 mL) was
322 degassed and backfilled with nitrogen gas (4x). Tetrakis(triphenylphosphine)palladium(0)
323 was added and the resulting mixture was degassed and backfilled with nitrogen gas (4x)
324 again. The mixture was heated at 80 °C for 20 hours. After this time, the reaction was
325 allowed to cool to room temperature, diluted with water (200 mL), and extracted with
326 ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated
327 aqueous sodium chloride (200 mL), dried over magnesium sulfate, filtered and
328 concentrated to dryness. The residue obtained was purified via flash SiO₂
329 chromatography (100 g silica gel, gradient of hexanes to 15% ethyl acetate/85% hexanes)
330 to give 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-
331 1H-imidazole-4-carbonitrile (**10**) (1.99 g, >99%) as a yellow oil; ¹H NMR (400 MHz,
332 DMSO-*d*₆) δ 7.61-7.51 (m, 5H), 4.64 (s, 2H), 4.23 (s, 2H), 3.52 (q, *J* = 7.0 Hz, 2H), 1.15

333 (t, $J=7.0$ Hz, 3H), 0.86 (s, 6H), 0.70 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (101 MHz DMSO- d_6)
 334 δ 148.97, 142.61, 129.76, 129.36, 129.17, 127.49, 115.81, 110.52, 73.60, 65.51, 64.56,
 335 54.77, 28.19, 25.72, 17.65, 14.91, -2.27; MS (ESI $^+$), calcd $\text{C}_{23}\text{H}_{36}\text{N}_3\text{O}_2\text{Si}$ (M+H) =
 336 414.2577, found = 414.2569.



338 **Supplementary Fig. 11 Amidine, amide, and aldehyde analog synthesis:** Key
 339 intermediate **10** was used to synthesize amidine **11**, primary amide **12**, and aldehyde **13**.

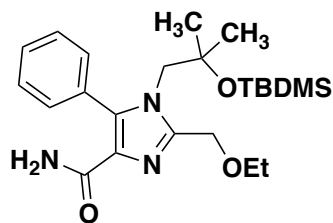
340



342 **1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-1H-**
 343 **imidazole-4-carboximidamide (11)**

344 A mixture of solid ammonium chloride (0.026 g, 0.48 mmol) in toluene (4 mL) was
 345 cooled in an ice bath. Trimethylaluminum (0.73 mL, 0.73 mmol, 1 M solution in heptane)

346 was added over 2 min, and the resulting mixture was allowed to stir in the ice bath for 30
347 min. After this time, the ice bath was removed and the resulting mixture was allowed to
348 stir at room temperature for 90 min. After this time, 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-
349 methylpropyl}-2-(ethoxymethyl)-5-phenyl-1H-imidazole-4-carbonitrile (0.100 g, 0.242
350 mmol) in tetrahydrofuran (1.5 mL) was added and the solution was heated at 80 °C for 17
351 hours. After this time, the solution was allowed to cool to room temperature and saturated
352 aqueous sodium bicarbonate (10 mL) was added, followed by saturated aqueous
353 potassium sodium tartrate (30 mL), and the resulting mixture was extracted with ethyl
354 acetate (3 × 30 mL). The combined organic layers were washed with saturated aqueous
355 sodium chloride (50 mL), dried over magnesium sulfate, filtered and concentrated to
356 dryness. The residue obtained was purified via flash SiO₂ chromatography (10 g silica gel,
357 gradient of dichloromethane to 20% [1% triethylamine/99% methanol]/80%
358 dichloromethane) to give 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-
359 (ethoxymethyl)-5-phenyl-1H-imidazole-4-carboximidamide (**11**) (0.075 g, 72%) as a
360 white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.38 (br s, 3H), 7.60–7.55 (m, 3H), 7.54-
361 7.50 (m, 2H), 4.70 (s, 2H), 4.12 (s, 2H), 3.55 (q, *J* = 7.0 Hz, 2H), 1.16 (t, *J* = 7.0 Hz, 3H),
362 0.83 (s, 6H), 0.75 (s, 9H), -0.01 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 159.50,
363 147.67, 137.48, 130.84, 130.05, 129.33, 127.37, 125.33, 73.57, 65.60, 64.54, 54.50, 28.21,
364 25.84, 17.73, 14.96, -2.17; MS (ESI⁺), calcd C₂₃H₃₉N₄O₂Si (M+H) = 431.2842, found =
365 431.2841.
366

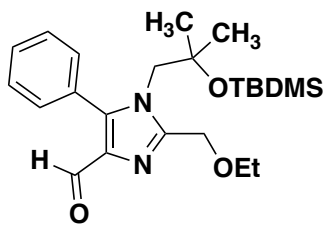


367

368 **1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-1H-**
 369 **imidazole-4-carboxamide (12)**

370 To a solution of 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
 371 phenyl-1H-imidazole-4-carbonitrile (0.100 g, 0.242 mmol) in ethanol (3 mL) was added a
 372 solution of potassium hydroxide (0.135 g, 2.42 mmol) in water (3 mL), and the resulting
 373 mixture was heated at reflux for 18 hours. After this time, the mixture was allowed to
 374 cool to room temperature, added hydrochloric acid (0.2 mL, 12.1 M), then saturated
 375 aqueous sodium bicarbonate was added until neutral, and the resulting mixture was then
 376 extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with
 377 saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and
 378 concentrated to dryness. The resulting solid was triturated with a diethyl ether/hexanes
 379 mixture to give 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
 380 phenyl-1H-imidazole-4-carboxamide (**12**) (0.085 g, 82%) as an off-white solid; ¹H NMR
 381 (400 MHz, DMSO-*d*₆) δ 7.44-7.38 (m, 5H), 7.26 (s, 1H), 6.96 (s, 1H), 4.63 (s, 2H), 4.07
 382 (s, 2H), 3.52 (q, *J* = 7.0 Hz, 2H), 1.15 (t, *J* = 7.0 Hz, 3H), 0.81 (s, 6H), 0.73 (s, 9H), -0.03
 383 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 164.09, 145.29, 135.40, 131.22, 130.95,
 384 130.04, 128.15, 127.76, 73.65, 65.34, 64.86, 54.05, 28.26, 25.81, 17.71, 15.01, -2.20; MS
 385 (ESI⁺), calcd C₂₃H₃₈N₃O₃Si (M+H) = 432.2682, found = 432.2688.

386

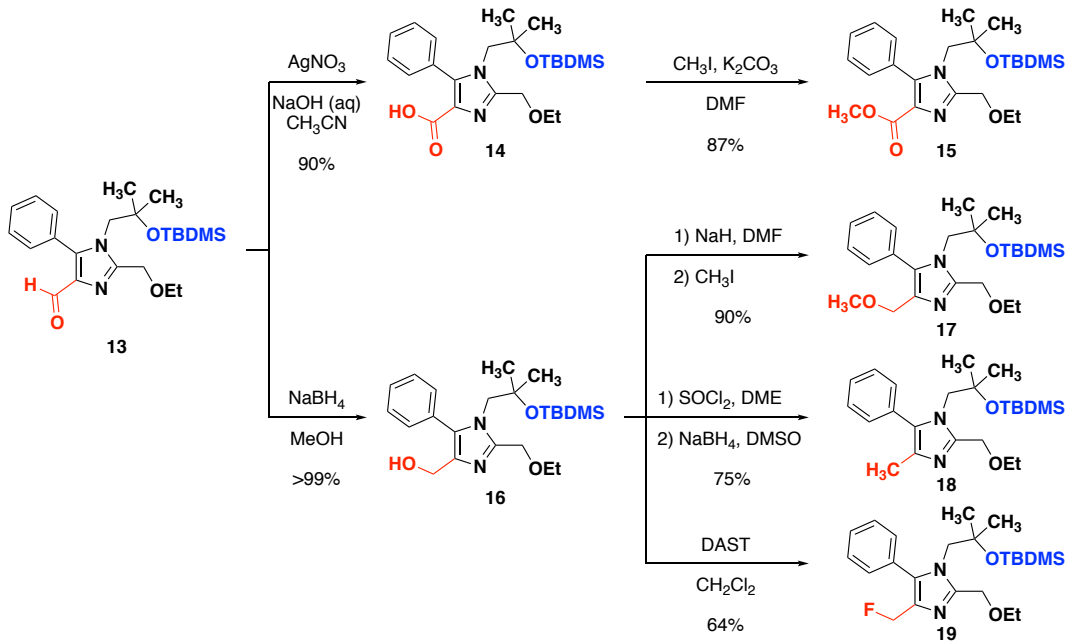


387

388 **1-{2-[(tert-butyldimethylsilyloxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-1H-**
 389 **imidazole-4-carbaldehyde (13)**

390 A solution of 1-{2-[(*tert*-butyldimethylsilyloxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
 391 phenyl-1H-imidazole-4-carbonitrile (1.70 g, 4.11 mmol) was cooled in a dry
 392 ice/isopropanol bath (~ -78 °C). Diisobutylaluminum hydride (8.2 mL, 8.2 mmol, 1 M in
 393 hexanes) was slowly added over 10 min. The solution was allowed to stir in the dry ice
 394 bath for 3.5 hours. While still in the dry ice bath, saturated aqueous ammonium chloride
 395 (100 mL) was added, the mixture was allowed to warm to room temperature and was
 396 extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with
 397 saturated aqueous potassium sodium tartrate (150 mL), washed with saturated aqueous
 398 sodium chloride (150 mL), dried over magnesium sulfate, filtered and concentrated to
 399 dryness. The residue obtained was purified via flash SiO₂ chromatography (100 g silica
 400 gel, gradient of hexanes to 50% ethyl acetate/50% hexanes) to give 1-{2-[(*tert*-
 401 butyldimethylsilyloxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-1H-imidazole-4-
 402 carbaldehyde (**13**) (1.21 g, 71%) as an off-white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ
 403 9.56 (s, 1H), 7.55-7.51 (m, 5H), 4.68 (s, 2H), 4.18 (s, 2H), 3.53 (q, *J* = 7.0 Hz, 2H), 1.16
 404 (t, *J* = 7.0 Hz, 3H), 0.85 (s, 6H), 0.72 (s, 9H), -0.02 (s, 6H); ¹³C NMR (101 MHz DMSO-
 405 *d*₆) δ 184.32, 148.29, 142.59, 136.24, 130.59, 129.36, 128.78, 127.95, 73.69, 65.43, 64.92,
 406 54.18, 28.24, 25.76, 17.67, 14.94, -2.23; MS (ESI⁺), calcd C₂₃H₃₇N₂O₃Si (M+H) =
 407 417.2574, found = 417.2570.

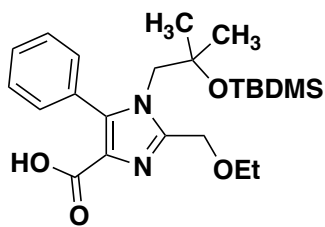
408



409

410 **Supplementary Fig. 12 Carboxylic acid, ester, alcohol, ether, methyl, and**
 411 **fluoromethyl analog synthesis:** Aldehyde **13** was used to synthesize carboxylic acid **14**,
 412 which was used to make methyl ester **15**. Aldehyde **13** was also used to make primary
 413 alcohol **16**, which was used to make methyl ether **17**, methyl **18**, and fluoromethyl **19**.

414



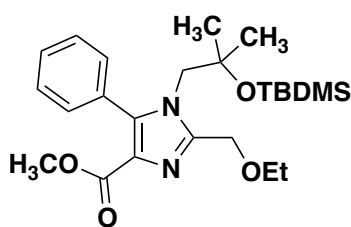
415

416 **1-{2-[(tert-butyldimethylsilyloxy)-2-methylpropyl]-2-(ethoxymethyl)-5-phenyl-1H-**
 417 **imidazole-4-carboxylic acid (14)**

418 To a solution of 1-{2-[(tert-butyldimethylsilyloxy)-2-methylpropyl]-2-(ethoxymethyl)-5-
 419 phenyl-1H-imidazole-4-carbaldehyde (0.537 g, 1.29 mmol) in acetonitrile (5.4 mL) was

420 added 10% aqueous sodium hydroxide (6.4 mL), followed by silver (I) nitrate (0.438 g,
421 2.58 mmol), and the resulting mixture was allowed to stir at room temperature for 24
422 hours. After this time, the mixture was neutralized with sodium phosphate monobasic
423 monohydrate (80 mL, 1 M in water), diluted with saturated aqueous sodium chloride (50
424 mL), and the resulting mixture was extracted with ethyl acetate (4 × 50 mL). The
425 combined organic layers were washed with saturated aqueous sodium chloride (100 mL),
426 dried over magnesium sulfate, filtered and concentrated to dryness to give 1-{2-[(tert-
427 butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-1H-imidazole-4-
428 carboxylic acid (**14**) (0.490 g, 88%) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ
429 12.0 (br s, 1H), 7.47-7.38 (m, 5H), 4.64 (s, 2H), 4.06 (s, 2H), 3.50 (q, *J* = 7.0 Hz, 2H),
430 1.15 (t, *J* = 7.0 Hz, 3H), 0.82 (s, 6H), 0.73 (s, 9H), -0.03 (s, 6H); ¹³C NMR (101 MHz
431 DMSO-*d*₆) δ 163.78, 146.21, 138.53, 131.04, 129.88, 128.70, 128.48, 127.95, 73.61,
432 65.26, 64.94, 54.17, 28.29, 25.79, 17.70, 14.98, -2.21; MS (ESI⁺), calcd C₂₃H₃₇N₂O₄Si
433 (M-H) = 431.2366, found = 431.2375.

434



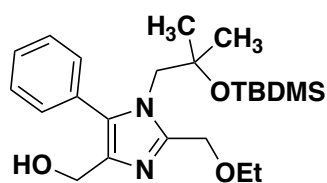
435

436 **methyl 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-**
437 **phenyl-1H-imidazole-4-carboxylate (15)**

438 To a mixture of potassium carbonate (0.363 g, 2.62 mmol), in *N,N*-dimethylformamide
439 (8.5 mL) was added 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-
440 (ethoxymethyl)-5-phenyl-1H-imidazole-4-carboxylic acid (0.283 g, 0.654 mmol), and the

441 resulting mixture was allowed to stir for 15 min. After this time, iodomethane (61 μ L,
442 0.98 mmol) was added and allowed to stir for 17 hours. After this time, water (20 mL)
443 was added and the resulting mixture was extracted with ethyl acetate (3 \times 10 mL). The
444 combined organic layers were washed with 5% aqueous lithium chloride (3 \times 30 mL),
445 washed with saturated aqueous sodium chloride (30 mL), dried over magnesium sulfate,
446 filtered and concentrated to dryness. The residue obtained was purified via flash SiO₂
447 chromatography (10 g silica gel, gradient of hexanes to 35% ethyl acetate/65% hexanes)
448 to give methyl 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
449 phenyl-1H-imidazole-4-carboxylate (**15**) (0.254 g, 87%) as a colorless oil; ¹H NMR (400
450 MHz, DMSO-*d*₆) δ 7.49-7.43 (m, 3H), 7.43-7.39 (m, 2H), 4.64 (s, 2H), 4.08 (s, 2H), 3.59
451 (s, 3H), 3.50 (q, *J* = 7.0 Hz, 2H), 1.14 (t, *J* = 7.0 Hz, 3H), 0.83 (s, 6H), 0.72 (s, 9H), -0.03
452 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 162.84, 146.60, 139.09, 130.92, 129.49,
453 128.66, 128.02, 127.81, 73.60, 65.25, 64.91, 54.20, 50.74, 28.26, 25.77, 17.67, 14.94, -
454 2.22; MS (ESI⁺), calcd C₂₄H₃₉N₂O₄Si (M+H) = 447.2679, found = 447.2677.

455



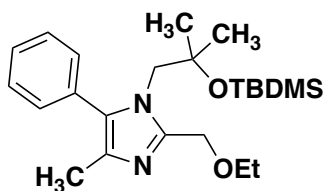
456

457 **(1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-1H-**
458 **imidazol-4-yl)methanol (16)**

459 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
460 phenyl-1H-imidazole-4-carbaldehyde (0.458 g, 1.10 mmol) in methanol (17 mL) was
461 added sodium borohydride (0.064 g, 1.7 mmol). The mixture was allowed to stir at room

462 temperature for 3 hours, and then saturated aqueous ammonium chloride (50 mL) was
463 added. The mixture was extracted with dichloromethane (4 × 25 mL). The combined
464 organic layers were washed with saturated aqueous sodium chloride (100 mL), dried over
465 sodium sulfate, filtered and concentrated to dryness. The residue obtained was purified
466 via flash SiO₂ chromatography (50 g silica gel, gradient of dichloromethane to 7%
467 methanol/93% dichloromethane) to give (1-{2-[(tert-butyldimethylsilyl)oxy]-2-
468 methylpropyl}-2-(ethoxymethyl)-5-phenyl-1H-imidazol-4-yl)methanol (**16**) (0.413 g,
469 90%) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.48-7.45 (m, 2H), 7.41–7.36
470 (m, 3H), 4.78 (t, *J* = 5.4, 1H), 4.60 (s, 2H), 4.17 (d, *J* = 5.2, 2H), 4.11 (s, 2H), 3.50 (q, *J* =
471 7.0 Hz, 2H), 1.14 (t, *J* = 7.0 Hz, 3H), 0.81 (s, 6H), 0.74 (s, 9H), 0.04 (s, 6H); ¹³C NMR
472 (101 MHz DMSO-*d*₆) δ 145.30, 138.16, 130.81, 130.61, 129.93, 128.61, 127.61, 74.00,
473 65.14, 65.08, 56.09, 54.24, 28.15, 25.82, 17.71, 15.01, -2.19.

474



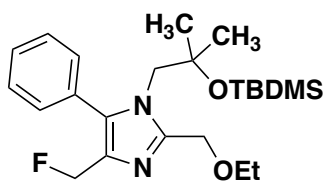
475

476 **1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-methyl-5-**
477 **phenyl-1H-imidazole (18)**

478 A solution of (1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
479 phenyl-1H-imidazol-4-yl)methanol (0.050 g, 0.12 mmol) in 1,2-dichloroethane (2 mL)
480 was cooled in an ice bath. Thionyl chloride (18 μL, 0.24 mmol) was added and the
481 solution was allowed to stir in the ice bath for an additional 10 min. After this time, the
482 solution was allowed to warm to room temperature and then heated at 60 °C for 2.5 hours.

483 After this time, the solution was allowed to cool to room temperature, diluted with
484 dichloromethane (10 mL). The resulting organic solution was neutralized with saturated
485 aqueous sodium bicarbonate (10 mL), washed with saturated aqueous sodium chloride
486 (30 mL), dried over sodium sulfate, filtered and concentrated to dryness. The resulting
487 residue was further dried on a high-vacuum pump for 1 hour. The resulting residue was
488 dissolved in dimethyl sulfoxide (2 mL). Sodium borohydride (0.042 g, 1.1 mmol) was
489 added. Additional dimethyl sulfoxide (1 mL) was immediately used to rinse the sides of
490 the reaction flask. The mixture was allowed to stir at room temperature for 24 hours.
491 After this time, water was added (10 mL) and the resulting mixture was extracted with
492 diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated
493 aqueous sodium chloride (30 mL), dried over magnesium sulfate, filtered and
494 concentrated to dryness. The resulting residue was purified via flash SiO₂
495 chromatography (10 g silica gel, gradient of hexanes to 14% ethyl acetate/86% hexanes)
496 to give 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-methyl-
497 5-phenyl-1H-imidazole (**18**) (0.033 g, 75%) as a white solid; ¹H NMR (400 MHz,
498 DMSO-*d*₆) δ 7.55-7.51 (m, 2H), 7.49-7.42 (m, 3H), 4.93 (s, 2H), 4.18 (s, 2H), 3.55 (q, *J* =
499 7.0 Hz), 2.13 (s, 3H), 1.16 (t, *J* = 7.0 Hz, 3H), 0.86 (s, 6H), 0.71 (s, 9H), -0.04 (s, 6H);
500 ¹³C NMR (101 MHz DMSO-*d*₆) δ 144.11, 131.26, 130.43, 129.21, 129.03, 128.77,
501 128.57, 73.36, 65.75, 60.67, 54.59, 28.26, 25.73, 17.64, 14.96, 10.92, -2.29; MS (ESI⁺),
502 calcd C₂₃H₃₉N₂O₂Si (M+H) = 403.2781, found = 403.2779.

503



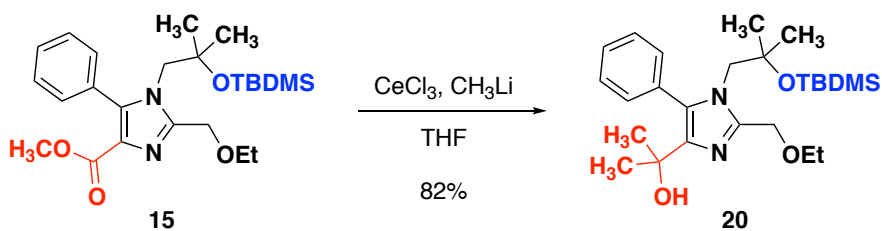
504

505 **1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-**

506 **(fluoromethyl)-5-phenyl-1H-imidazole (19)**

507 A solution of (1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
 508 phenyl-1H-imidazol-4-yl)methanol (0.113 g, 0.270 mmol) in dichloromethane (6 mL)
 509 was cooled in an ice bath. (Diethylamino)sulfur trifluoride (0.35 mL, 0.35 mmol, 1 M
 510 solution in dichloromethane) was added and the solution was allowed to stir in the ice
 511 bath for 1 hour. After this time, saturated aqueous sodium bicarbonate (10 mL) was
 512 added and the resulting mixture was extracted with dichloromethane (3 × 10 mL). The
 513 combined organic layers were washed with saturated aqueous sodium chloride (30 mL),
 514 dried over sodium sulfate, filtered and concentrated to dryness. The residue obtained was
 515 purified via flash SiO₂ chromatography (10 g silica gel, gradient of hexanes to 30% ethyl
 516 acetate/70% hexanes) to give 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-
 517 (ethoxymethyl)-4-(fluoromethyl)-5-phenyl-1H-imidazole (**19**) (0.073 g, 64%) as an off-
 518 white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.54–7.50 (m, 2H), 7.47-7.40 (m, 3H),
 519 5.08 (d, *J* = 50.0 Hz, 2H), 4.62 (s, 2H), 4.15 (s, 2H), 3.50 (q, *J* = 7.0 Hz, 2H), 1.15 (t, *J* =
 520 7.0 Hz, 3H), 0.84 (s, 6H), 0.72 (s, 9H), -0.05 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ
 521 146.40, 134.22, 134.16, 132.88, 132.70, 129.75, 129.73, 129.70, 128.93, 128.33, 78.38,
 522 76.80, 73.76, 65.23, 64.97, 54.36, 28.21, 25.76, 17.67, 14.97, -2.25; MS (ESI⁺), calcd
 523 C₂₃H₃₈FN₂O₂Si (M+H) = 421.2686, found = 421.2696.

524



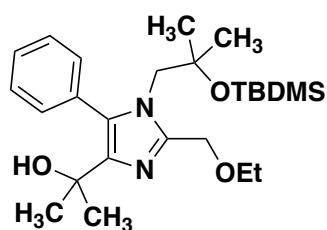
525

15

20

526 **Supplementary Fig. 13 Tertiary alcohol analog synthesis:** Methyl ester **15** was used to
 527 make tertiary alcohol **20**.

528



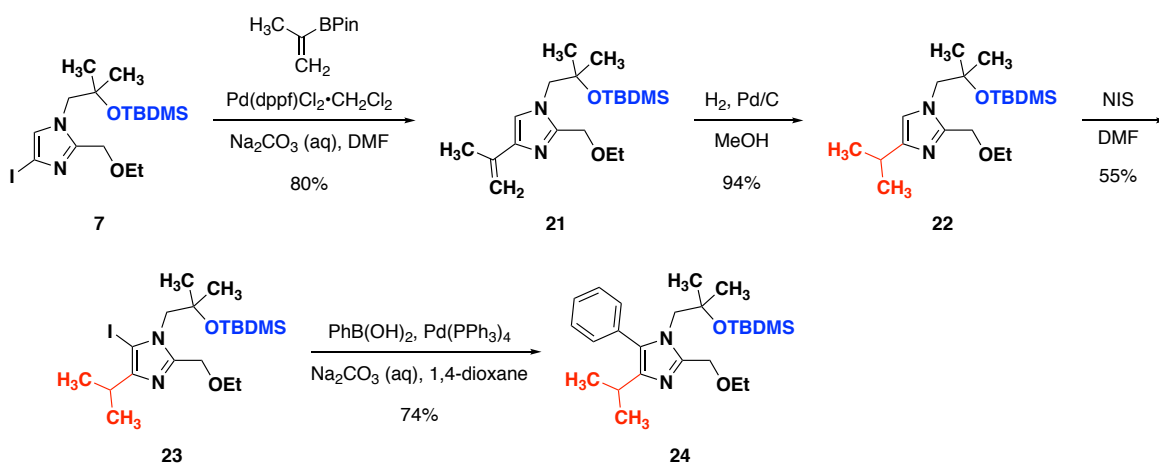
529

530 **2-(1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-**
 531 **1H-imidazol-4-yl)propan-2-ol (20)**

532 In an oven-dried flask, cerium (III) chloride (0.054 g, 0.22 mmol) was taken up into
 533 tetrahydrofuran (2 mL) and stirred at room temperature for 2.5 hours. After this time, the
 534 mixture was cooled in a dry ice/isopropyl alcohol bath (~ -78 °C). Methyl lithium (0.24
 535 mL, 0.39 mmol, 1.6 M solution in diethyl ether) and was allowed to stir in the dry ice
 536 bath for 30 min. In a second oven-dried flask solution of 1-{2-[(tert-
 537 butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-1H-imidazole-4-
 538 carboxylate (0.051 g, 0.11 mmol) in tetrahydrofuran (1 mL) was prepared, cannulated
 539 into the first, cooled flask and stirred in the dry ice bath for 30 min. The mixture was
 540 removed from the dry ice bath and allowed to stir at room temperature for 17 hours. After
 541 this time, saturated aqueous ammonium chloride (10 mL) was added and the resulting
 542 mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were

543 washed with saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate,
 544 filtered and concentrated to dryness. The residue obtained was purified via flash SiO₂
 545 chromatography (10 g silica gel, gradient of dichloromethane to 80% ethyl acetate/20%
 546 dichloromethane) to give 2-(1-{2-[(tert-butyldimethylsilyloxy]-2-methylpropyl}-2-
 547 (ethoxymethyl)-5-phenyl-1H-imidazol-4-yl)propan-2-ol (**20**) (0.037 g, 76%) as a white
 548 solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.43–7.33 (m, 5H), 4.57 (s, 2H), 4.40 (s, 1H),
 549 3.92 (s, 2H), 3.50 (q, *J* = 7.0 Hz, 2H), 1.27 (s, 6H), 1.14 (t, *J* = 7.0 Hz, 3H), 0.82 (s, 6H),
 550 0.74 (s, 9H), -0.04 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 144.20, 143.26, 132.16,
 551 131.97, 127.73, 127.65, 127.39, 73.66, 69.17, 65.22, 65.16, 53.88, 31.32, 28.46, 25.83,
 552 17.73, 15.05, -2.17; MS (ESI⁺), calcd C₂₅H₄₃N₂O₃Si (M+H) = 447.3043, found =
 553 447.3035.

554

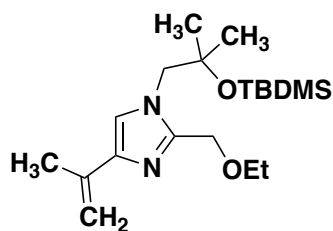


555

556 **Supplementary Fig. 14 iso-Propyl analog synthesis:** Iso-propyl **24** was made from iodo

557 **7** in 31% yield over four steps.

558



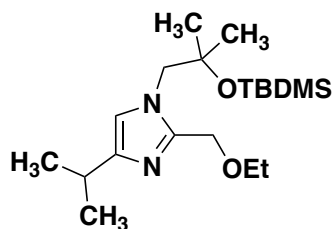
559

560 **1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-(prop-1-en-2-**
 561 **yl)-1H-imidazole (21)**

562 A mixture of 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-
 563 iodo-1H-imidazole (0.300 g, 0.684 mmol), and aqueous sodium carbonate (2.5 mL, 2 M)
 564 in *N,N*-dimethylformamide (5 mL) was degassed and backfilled with nitrogen gas (4 ×).
 565 (1,1'-Bis(diphenylphosphino)ferrocene)palladium(II) dichloride•dichloromethane (0.028
 566 g, 0.034 mmol) was added and the resulting mixture was degassed and backfilled with
 567 nitrogen gas (4 ×) again. Isopropenylboronic acid pinacol ester (0.14 mL, 0.75 mmol)
 568 was added and the resulting mixture was heated at 65 °C for 17 hours. After this time, the
 569 mixture was allowed to cool to room temperature, diluted with water (30 mL), and
 570 extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with
 571 5% aqueous lithium chloride (2 × 40 mL), washed with saturated aqueous sodium
 572 chloride (50 mL), dried over magnesium sulfate, filtered and concentrated to dryness. The
 573 residue obtained was purified via flash SiO₂ chromatography (25 g silica gel, gradient of
 574 hexanes to 30% ethyl acetate/70% hexanes) to give 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-
 575 methylpropyl}-2-(ethoxymethyl)-4-(prop-1-en-2-yl)-1H-imidazole (**21**) (0.193 g, 80%) as
 576 a yellow oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.14 (s, 1H), 5.48 (dd, *J* = 2.8, 0.57 Hz,
 577 1H), 4.77 (dd, *J* = 2.8, 1.5 Hz, 1H), 4.45 (s, 2H), 3.89 (s, 2H), 3.44 (q, *J* = 7.0 Hz, 2H),
 578 1.93 (s, 3H), 1.19 (s, 6H), 1.09 (t, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ¹³C NMR

579 (101 MHz DMSO-*d*₆) δ 144.92, 139.48, 136.06, 118.69, 108.09, 73.63, 64.89, 63.78,
580 56.65, 27.01, 25.77, 19.95, 17.74, 14.95, -2.22.

581

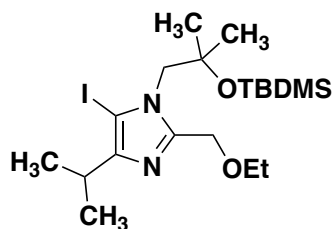


583 **1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-(propan-2-**
584 **yl)-1H-imidazole (22)**

585 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-
586 (prop-1-en-2-yl)-1H-imidazole (0.190 g, 0.539 mmol) in methanol (9 mL) was added
587 palladium on carbon (0.010 g, 5% basis). The mixture was degassed and backfilled with
588 nitrogen gas (4 ×), then degassed and backfilled with hydrogen gas (4 ×). The reaction
589 was then allowed to stir under hydrogen atmosphere (balloon) for 17 hours. After this
590 time, the mixture was degassed and backfilled with nitrogen gas (4 ×), diluted with
591 dichloromethane (20 mL), and filtered through Celite (rinsing with additional
592 dichloromethane). The filtrate was concentrated to dryness. The residue obtained was
593 purified via flash SiO₂ chromatography (10 g silica gel, gradient of hexanes to 50% ethyl
594 acetate/40% hexanes) to give 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-
595 (ethoxymethyl)-4-(propan-2-yl)-1H-imidazole (**22**) (0.180 g, 94%) as a colorless oil; ¹H
596 NMR (400 MHz, DMSO-*d*₆) δ 6.81 (d, *J* = 0.7 Hz, 1H), 4.40 (s, 2H), 3.83 (s, 2H), 3.42 (q,
597 *J* = 7.0 Hz, 2H), 2.70 (dsep, *J* = 6.9, 0.7 Hz, 1H), 1.17 (s, 6H), 1.13 (d, *J* = 6.9 Hz, 6H),
598 1.08 (t, *J* = 7.0 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ

599 145.53, 143.67, 115.95, 73.63, 64.79, 63.87, 56.52, 27.22, 27.09, 25.77, 22.38, 17.72,
600 14.95, -2.24.

601

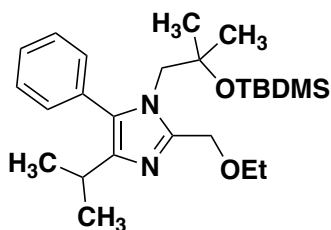


602

603 **1-{2-[(tert-butyldimethylsilyloxy)-2-methylpropyl]}-2-(ethoxymethyl)-5-iodo-4-**
604 **(propan-2-yl)-1H-imidazole (23)**

605 To a solution of 1-{2-[(tert-butyldimethylsilyloxy)-2-methylpropyl]}-2-(ethoxymethyl)-4-
606 (propan-2-yl)-1H-imidazole (0.175 g, 0.493 mmol) in *N,N*-dimethylformamide (5 mL)
607 was added *N*-iodosuccinimide (0.166 g, 0.740 mmol) and the resulting solution was
608 heated at 80 °C for 17 hours. After this time, the solution was allowed to cool to room
609 temperature, diluted with water (30 mL), and solid sodium thiosulfate pentahydrate was
610 added until no further color change was observed. The resulting mixture was extracted
611 with ethyl acetate (3 × 20 mL). The combined organic layers were washed with 5%
612 aqueous lithium chloride (3 × 40 mL), washed with saturated aqueous sodium chloride
613 (50 mL), dried over magnesium sulfate, filtered and concentrated to dryness. The residue
614 obtained was purified via flash SiO₂ chromatography (10 g silica gel, gradient of hexanes
615 to 20% ethyl acetate/80% hexanes) to give 1-{2-[(tert-butyldimethylsilyloxy)-2-
616 methylpropyl]}-2-(ethoxymethyl)-5-iodo-4-(propan-2-yl)-1H-imidazole (**23**) (0.130 g,
617 55%) as a colorless oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.57 (s, 2H), 3.97 (s, 2H), 3.43
618 (q, *J* = 7.0 Hz, 2H), 2.81 (sep, *J* = 6.9 Hz, 1H), 1.30 (s, 6H), 1.12 (d, *J* = 6.9 Hz, 6H),

619 1.10 (t, $J = 7.0$ Hz, 3H), 0.74 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (101 MHz DMSO- d_6) δ
620 149.15, 147.72, 74.05, 73.65, 65.31, 65.07, 56.16, 29.05, 27.45, 25.92, 22.27, 17.77,
621 14.96, -2.05 ; MS (ESI $^+$), calcd $\text{C}_{19}\text{H}_{38}\text{IN}_2\text{O}_2\text{Si}$ (M+H) = 481.1747, found = 481.1745.
622

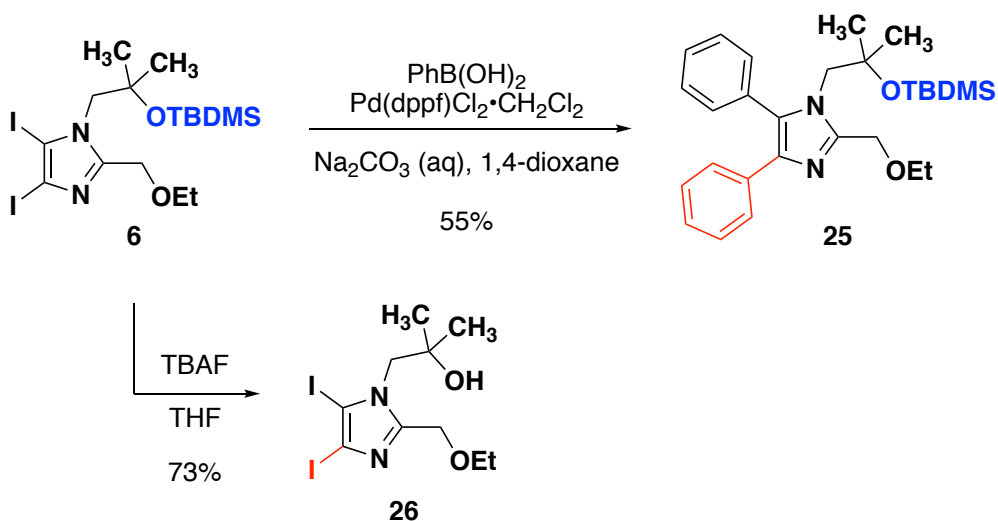


623

624 **1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-4-**
625 **(propan-2-yl)-1H-imidazole (24)**

626 A mixture of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
627 iodo-4-(propan-2-yl)-1H-imidazole (0.120 g, 0.250 mmol), phenylboronic acid (0.034 g,
628 0.28 mmol), and aqueous sodium carbonate (1.7 mL, 1 M) in 1,4-dioxane (3.4 mL) was
629 degassed and backfilled with nitrogen gas (4 \times). Tetrakis(triphenylphosphine)palladium(0)
630 (0.015 g, 0.013 mmol) was added, the mixture was degassed and backfilled with nitrogen
631 gas (4 \times) again, and the mixture was heated at 80 $^{\circ}\text{C}$ for 18 hours. After this time, the
632 mixture was allowed to cool to room temperature, diluted with water (10 mL), and the
633 resulting mixture was extracted with ethyl acetate (3 \times 5 mL). The combined organic
634 layers were washed with saturated aqueous sodium chloride (10 mL), dried over
635 magnesium sulfate, filtered and concentrated to dryness. The residue obtained was
636 purified via flash SiO_2 chromatography (10 g silica gel, gradient of hexanes to 25% ethyl
637 acetate/75% hexanes) to give 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-
638 (ethoxymethyl)-5-phenyl-4-(propan-2-yl)-1H-imidazole (**24**) (0.080 g, 74%) as a colorless

639 oil; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.49–7.45 (m, 2H), 7.38–7.34 (m, 1H), 4.56 (s,
 640 2H), 4.03 (s, 2H), 3.50 (q, $J = 7.0$ Hz, 2H), 2.76 (sep, $J = 6.8$ Hz, 1H), 1.15 (t, $J = 7.0$ Hz,
 641 3H), 1.11 (d, $J = 6.2$ Hz, 6H), 0.82 (s, 6H), 0.70 (s, 9H), -0.06 (s, 6H); ^{13}C NMR (101
 642 MHz $\text{DMSO-}d_6$) δ 145.31, 143.19, 131.37, 129.92, 128.74, 127.35, 127.03, 73.62, 65.28,
 643 65.20, 54.05, 28.43, 25.78, 25.43, 23.17, 17.67, 15.01, -2.26 ; MS (ESI^+), calcd
 644 $\text{C}_{25}\text{H}_{43}\text{N}_2\text{O}_2\text{Si}$ ($\text{M}+\text{H}$) = 431.3094, found = 431.3090.

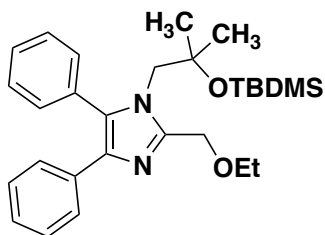


645

646 **Supplementary Fig. 15 4,5-Diphenyl and 4,5-diiodo analog synthesis:** Diphenyl

647 intermediate 25 and final diiodo target 26 were made from diiodo intermediate 6.

648



649

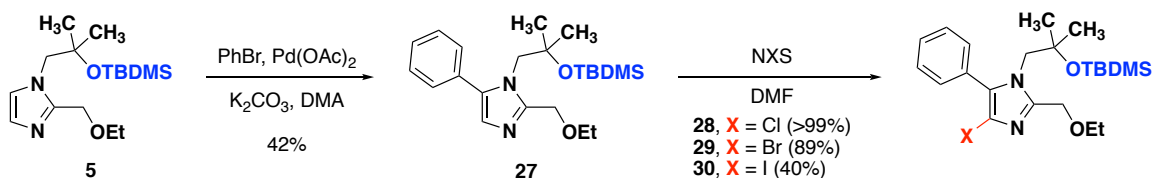
650 **1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4,5-diphenyl-**

651 **1H-imidazole (25)**

673 **1-[2-(ethoxymethyl)-4,5-diiodo-1H-imidazol-1-yl]-2-methylpropan-2-ol (26)**

674 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-
675 4,5-diiodo-1H-imidazole (0.100 g, 0.177 mmol) in tetrahydrofuran (4.5 mL) was added
676 tetrabutylammonium fluoride (0.53 mL, 0.53 mmol, 1 M solution in tetrahydrofuran).
677 The reaction was allowed to stir at room temperature for 16 hours. After this time,
678 saturated aqueous ammonium chloride (10 mL) was added and the resulting mixture was
679 extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with
680 saturated aqueous sodium chloride (20 mL), dried over magnesium sulfate, filtered and
681 concentrated to dryness. The residue obtained was purified via flash SiO₂
682 chromatography (10 g silica gel, gradient of hexanes to 70% ethyl acetate/30% hexanes)
683 to give 1-[2-(ethoxymethyl)-4,5-diiodo-1H-imidazol-1-yl]-2-methylpropan-2-ol (**26**)
684 (0.058 g, 73%) as an off-white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.88 (s, 1H), 4.65
685 (s, 2H), 4.03 (s, 2H), 3.41 (q, *J* = 7.0 Hz, 2H), 1.13 (s, 6H), 1.08 (t, *J* = 7.0 Hz, 3H); ¹³C
686 NMR (101 MHz DMSO-*d*₆) δ 150.77, 95.89, 89.07, 70.17, 65.08, 64.77, 57.36, 28.14,
687 14.98; MS (ESI⁺), calcd C₁₀H₁₇I₂N₂O₂ (M+H) = 450.9379, found = 450.9389.

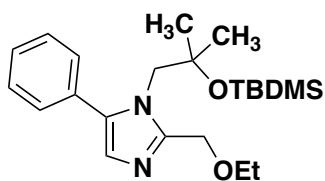
688



690 **Supplementary Fig. 16 4-Chloro, 4-bromo, and 4-iodo analog synthesis:** Halogenated
691 compounds **28**, **29**, and **30** were made from imidazole intermediate **5**.

692

693



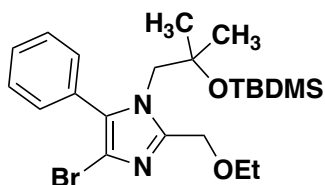
694

695 **1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-1H-**
 696 **imidazole (27)**

697 A mixture of 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl) 1H-
 698 imidazole (7.00 g, 22.4 mmol), bromobenzene (3.9 mL, 37 mmol), and potassium
 699 carbonate (10.2 g, 74.0 mmol) in *N,N*-dimethylacetamide (180 mL) was degassed and
 700 backfilled with nitrogen gas (4 ×). Palladium (II) acetate (0.831 g, 3.70 mmol) was added
 701 and the mixture was degassed and backfilled with nitrogen gas (4×) again. The mixture
 702 was heated at 150 °C for 21 hours, and after this time the reaction was allowed to cool to
 703 room temperature. Water (200 mL) was added and the resulting mixture was extracted
 704 with ethyl acetate (3 × 200 mL). The combined organic layers were washed with 5%
 705 aqueous lithium chloride (3 × 400 mL), washed with saturated aqueous sodium chloride
 706 (400 mL), dried over magnesium sulfate, filtered and concentrated to dryness. The
 707 residue obtained was purified via flash SiO₂ chromatography (340 g silica gel, gradient of
 708 dichloromethane to 4% methanol/96% dichloromethane) to give 1-{2-[(*tert*-
 709 butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-phenyl-1H-imidazole (**27**)
 710 (2.88 g, 20%) as a red oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.47-7.40 (m, 4H), 7.38-
 711 7.33 (m, 1H), 6.91 (s, 1H), 4.60 (s, 2H), 4.20 (s, 2H), 3.49 (q, *J* = 7.0 Hz, 2H), 1.14 (t, *J* =
 712 7.0 Hz, 3H), 0.86 (s, 6H), 0.72 (s, 9H), -0.05 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ
 713 147.32, 133.86, 131.35, 128.88, 128.30, 127.49, 126.83, 73.90, 65.16, 65.04, 54.23, 28.21,

714 25.75, 17.66, 14.97, -2.26; MS (ESI⁺), calcd C₂₂H₃₇N₂O₂Si (M+H) = 389.2624, found =
715 389.2622.

716

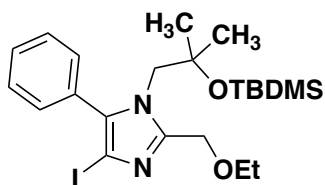


718 **4-bromo-1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-**
719 **phenyl-1H-imidazole (29)**

720 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
721 phenyl-1H-imidazole (0.300 g, 0.772 mmol) in *N,N*-dimethylformamide (11 mL) was
722 added a solution of *N*-bromosuccinimide (0.144 g, 0.811 mmol) in *N,N*-
723 dimethylformamide (4 mL), and the solution was allowed to stir for 18 hours. After this
724 time, the solution was diluted with water (15 mL), and solid sodium thiosulfate
725 pentahydrate was added until no further color change was observed, resulting in a pale
726 yellow suspension. The resulting mixture was extracted with ethyl acetate (3 × 20 mL).
727 The combined organic layers were washed with 5% aqueous lithium chloride (3 × 40 mL),
728 washed with saturated aqueous sodium chloride (40 mL), dried over magnesium sulfate,
729 filtered and concentrated to dryness. The residue obtained was purified via flash SiO₂
730 chromatography (25 g silica gel, gradient of dichloromethane to 5% methanol/95%
731 dichloromethane) to give 4-bromo-1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-
732 (ethoxymethyl)-5-phenyl-1H-imidazole (**29**) (0.320 g, 89%) as an off white solid; ¹H
733 NMR (400 MHz, DMSO-*d*₆) δ 7.52–7.48 (m, 2H), 7.45–7.40 (m, 3H), 4.56 (s, 2H), 4.13
734 (s, 2H), 3.50 (q, *J* = 7.0 Hz, 2H), 1.15 (t, *J* = 7.0 Hz, 3H), 0.84 (s, 6H), 0.72 (s, 9H), -0.04

735 (s, 6H); ^{13}C NMR (101 MHz DMSO- d_6) δ 146.45, 130.39, 130.09, 129.26, 128.79,
736 128.40, 113.50, 73.62, 65.25, 64.61, 54.90, 28.18, 25.75, 17.66, 14.94, -2.25; MS (ESI $^+$),
737 calcd $\text{C}_{22}\text{H}_{36}\text{BrN}_2\text{O}_2\text{Si}$ (M+H) = 353.0866, found = 353.0868.

738



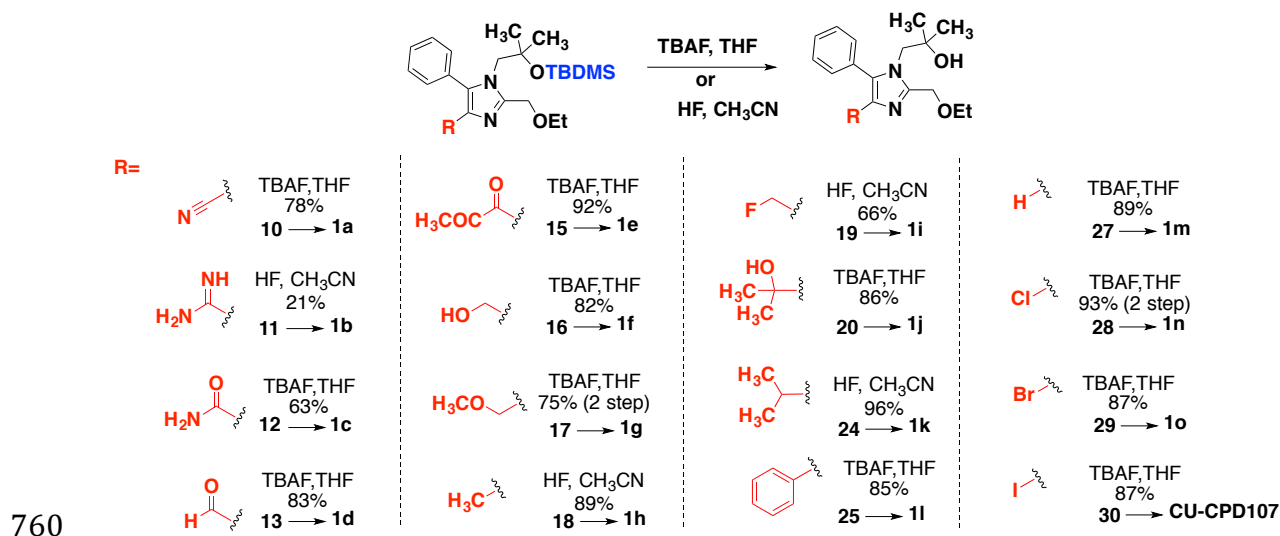
739

740 **1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-iodo-5-**

741 **phenyl-1H-imidazole (30)**

742 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
743 phenyl-1H-imidazole (0.178 g, 0.458 mmol) in *N,N*-dimethylformamide (5 mL) at 60 °C
744 was added a solution of *N*-iodosuccinimide (0.113 g, 0.504 mmol) in *N,N*-
745 dimethylformamide (1 mL) and the solution was allowed to stir 60 °C for 17 hours. After
746 this time, water (10 mL) was added, solid sodium thiosulfate pentahydrate was added
747 until no further color change was observed, and the resulting mixture was extracted with
748 ethyl acetate (3 × 10 mL). The combined organic layers were washed with 5% aqueous
749 lithium chloride (3 × 30 mL), washed with saturated aqueous sodium chloride (30 mL),
750 dried over magnesium sulfate, filtered and concentrated to dryness. The residue obtained
751 was purified via flash SiO_2 chromatography (10 g silica gel, gradient of hexanes to 20%
752 ethyl acetate/80% hexanes) to give 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-
753 2-(ethoxymethyl)-4-iodo-5-phenyl-1H-imidazole (**30**) (0.094 g, 40%) as a colorless oil;
754 ^1H NMR (400 MHz, DMSO- d_6) δ 7.52–7.48 (m, 2H), 7.44–7.40 (m, 3H), 4.57 (s, 2H),
755 4.13 (s, 2H), 3.50 (q, $J = 7.0$ Hz, 2H), 1.15 (t, $J = 7.0$ Hz, 3H), 0.84 (s, 6H), 0.73 (s, 9H),

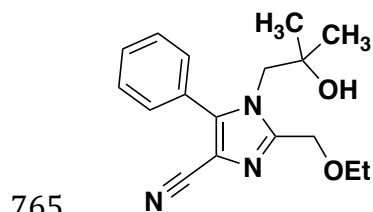
756 -0.03 (s, 6H); ^{13}C NMR (101 MHz DMSO- d_6) δ 146.46, 130.40, 130.10, 129.27, 128.80,
 757 128.41, 113.50, 73.62, 65.26, 64.61, 54.90, 28.18, 25.76, 17.67, 14.95, -2.24 ; MS (ESI $^+$),
 758 calcd $\text{C}_{22}\text{H}_{36}\text{IN}_2\text{O}_2\text{Si}$ (M+H) = 515.1591, found = 515.1609.
 759



761 **Supplementary Fig. 17 TBDMS deprotections:** TBDMS deprotections were carried out
 762 with either TBAF or hydrofluoric acid to yield a variety of tertiary alcohols.

763

764

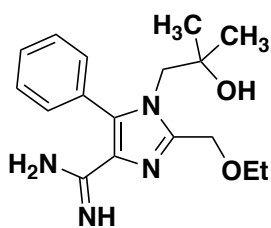


766 **2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-5-phenyl-1H-imidazole-4-**
 767 **carbonitrile (31, also called as 1a)**

768 To a solution of 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
 769 phenyl-1H-imidazole-4-carbonitrile (0.050 g, 0.12 mmol) in tetrahydrofuran (2 mL) was

770 added tetrabutylammonium fluoride (0.36 mL, 0.36 mmol, 1 M solution in
771 tetrahydrofuran). The solution was allowed to stir at room temperature for 18 hours. After
772 this time, saturated aqueous ammonium chloride (5 mL) was added and the resulting
773 mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were
774 washed with saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate,
775 filtered and concentrated to dryness. The residue obtained was purified via flash SiO₂
776 chromatography (10 g silica gel, gradient of hexanes to 70% ethyl acetate/30% hexanes)
777 to give 2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-5-phenyl-1H-imidazole-4-
778 carbonitrile (**31**) (0.028 g, 78%) as an off-white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ
779 7.59–7.50 (m, 5H), 4.80 (s, 1H), 4.72 (s, 2H), 4.13 (s, 2H), 3.52 (q, *J* = 7.0 Hz, 2H), 1.15
780 (t, *J* = 7.0 Hz, 3H), 0.75 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 149.06, 142.88,
781 129.58, 129.43, 129.13, 127.50, 115.87, 110.36, 69.65, 65.38, 64.47, 53.94, 27.57, 14.95;
782 MS (ESI⁺), calcd C₁₇H₂₂N₃O₂ (M+H) = 300.1712, found = 300.1717.

783

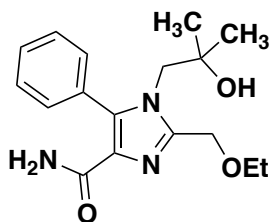


784

785 **2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-5-phenyl-1H-imidazole-4-**
786 **carboximidamide (32, also called as 1b)**

787 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
788 phenyl-1H-imidazole-4-carboximidamide (0.098 g, 0.23 mmol) in acetonitrile (5 mL, in
789 an HDPE scintillation vial) was added hydrofluoric acid (5 mL, 48 wt % in water) and the
790 solution was allowed to stir at room temperature for 21 hours. After this time, the solution

791 was added to a mixture of sodium carbonate (50.0 g, 472 mmol) in acetonitrile (100 mL,
792 cooled in an ice bath to ~ 0 °C) and stirred for 30 min. After this time, the solution was
793 filtered and the filtrate was concentrated to dryness. The residue obtained was purified
794 via flash SiO₂ chromatography (10 g silica gel, gradient of dichloromethane to 20%[1%
795 triethylamine/99% methanol]/80% dichloromethane, performed 3×) to give 2-
796 (ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-5-phenyl-1H-imidazole-4-
797 carboximidamide (**32**) (0.015 g, 21%) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ
798 8.44 (br s, 3H), 7.58–7.47 (m, 5H), 4.88 (s, 1H), 4.77 (s, 2H), 4.03 (s, 2H), 3.55 (q, *J* =
799 7.0 Hz, 2H), 1.16 (t, *J* = 7.0 Hz, 3H), 0.74 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ
800 159.95, 148.05, 137.53, 130.92, 129.86, 129.15, 127.46, 125.27, 69.50, 65.49, 64.58,
801 53.57, 27.76, 15.05; MS (ESI⁺), calcd C₁₇H₂₅N₄O₂ (M+H) = 317.1978, found = 317.1970.
802



803

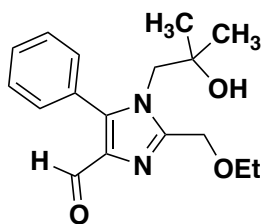
804 **2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-5-phenyl-1H-imidazole-4-**

805 **carboxamide (33, also called as 1c)**

806 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
807 phenyl-1H-imidazole-4-carboxamide (0.041 g, 0.095 mmol) in tetrahydrofuran (4 mL)
808 was added tetrabutylammonium fluoride (95 μL, 0.095 mmol, 1 M solution in
809 tetrahydrofuran), and the solution was allowed to stir at room temperature for 18 hours.
810 After this time, saturated aqueous ammonium chloride (10 mL) was added and the
811 resulting mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic

812 layers were washed with saturated aqueous sodium chloride (10 mL), dried over
813 magnesium sulfate, filtered and concentrated to dryness. The solid obtained was
814 recrystallized from ethyl acetate and hexanes to give 2-(ethoxymethyl)-1-(2-hydroxy-2-
815 methylpropyl)-5-phenyl-1H-imidazole-4-carboxamide (**33**) (0.019 g, 63%) as a white
816 solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.43–7.34 (m, 5H), 7.24 (d, *J* = 2.1 Hz, 1H),
817 6.94 (d, *J* = 2.1 Hz, 1H), 4.75 (s, 1H), 4.71 (s, 2H), 3.98 (s, 2H), 3.52 (q, *J* = 7.0 Hz, 2H),
818 1.15 (t, *J* = 7.0 Hz, 3H), 0.71 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 164.15, 145.52,
819 135.59, 131.28, 130.77, 130.08, 128.03, 127.63, 69.61, 65.20, 64.76, 53.13, 27.77, 15.05;
820 MS (ESI⁺), calcd C₁₇H₂₄N₃O₃ (M+H) = 318.1818, found = 318.1825.

821



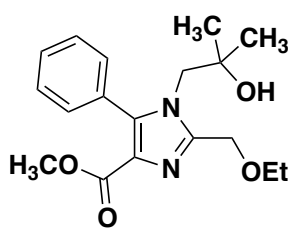
822

823 **2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-5-phenyl-1H-imidazole-4-**
824 **carbaldehyde (34, also called as 1d)**

825 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
826 phenyl-1H-imidazole-4-carbaldehyde (0.075 g, 0.18 mmol) in tetrahydrofuran (6 mL)
827 was added tetrabutylammonium fluoride (0.54 mL, 0.54 mmol, 1 M solution in
828 tetrahydrofuran). The solution was allowed to stir at room temperature for 16 hours. After
829 this time, saturated aqueous ammonium chloride (10 mL) was added and the resulting
830 mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were
831 washed with saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate,
832 filtered and concentrated to dryness. The residue obtained was purified via flash SiO₂

833 chromatography (10 g silica gel, gradient of dichloromethane to 7% methanol/93%
834 dichloromethane) to give 2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-5-phenyl-1H-
835 imidazole-4-carbaldehyde (**34**) (0.083 g, 83%) as a white solid; ¹H NMR (400 MHz,
836 DMSO-*d*₆) δ 9.53 (s, 1H), 7.57–7.47 (m, 5H), 4.80 (s, 1H), 4.76 (s, 2H), 4.09 (s, 2H),
837 3.53 (q, *J* = 7.0 Hz, 2H), 1.16 (t, *J* = 7.0 Hz, 3H), 0.75 (s, 6H); ¹³C NMR (101 MHz
838 DMSO-*d*₆) δ 145.30, 138.16, 130.81, 130.61, 129.93, 128.61, 127.61, 74.00, 65.14, 65.08,
839 56.09, 54.24, 28.15, 25.82, 17.71, 15.01, –2.19; MS (ESI⁺), calcd C₁₇H₂₃N₂O₃ (M+H) =
840 303.1709, found = 303.1711.

841



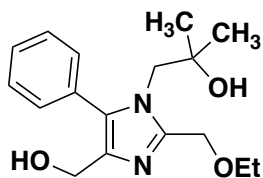
842

843 **methyl 2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-5-phenyl-1H-imidazole-4-**
844 **carboxylate (**35**, also called as **1e**)**

845 To a solution of methyl 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-
846 (ethoxymethyl)-5-phenyl-1H-imidazole-4-carboxylate (0.050 g, 0.11 mmol) in
847 tetrahydrofuran (3 mL) was added tetrabutylammonium fluoride (0.33 mL, 0.33 mmol, 1
848 M solution in tetrahydrofuran), and the solution was allowed to stir at room temperature
849 for 16 hours. After this time, saturated aqueous ammonium chloride (10 mL) was added
850 and the resulting mixture was extracted with ethyl acetate (3 × 5 mL). The combined
851 organic layers were washed with saturated aqueous sodium chloride, dried over
852 magnesium sulfate, filtered and concentrated to dryness. The residue obtained was
853 purified via flash SiO₂ chromatography (10 g silica gel, gradient of dichloromethane to 8%

854 methanol/92% dichloromethane) to give methyl 2-(ethoxymethyl)-1-(2-hydroxy-2-
855 methylpropyl)-5-phenyl-1H-imidazole-4-carboxylate (**35**) (0.034 g, 92%) as an off-white
856 solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.49–7.45 (m, 2H), 7.41–7.34 (m, 3H), 4.67 (2 x
857 s, 3H), 4.09 (s, 2H), 4.03 (s, 2H), 3.50 (q, *J* = 7.0 Hz, 2H), 3.16 (s, 3H), 1.14 (t, *J* = 7.0
858 Hz, 3H), 0.71 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 145.78, 134.30, 132.45, 130.45,
859 130.03, 128.58, 127.79, 69.82, 66.77, 65.02, 64.87, 56.94, 53.39, 27.72, 15.06; MS (ESI⁺),
860 calcd C₁₈H₂₅N₂O₄ (M+H) = 319.2022, found = 319.2020.

861



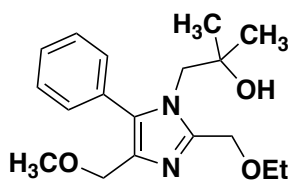
862

863 **1-[2-(ethoxymethyl)-4-(hydroxymethyl)-5-phenyl-1H-imidazol-1-yl]-2-methylpropan-**
864 **2-ol (36, also called as 1f)**

865 To a solution of (1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-
866 5-phenyl-1H-imidazol-4-yl)methanol (0.030 g, 0.072 mmol) in tetrahydrofuran (2 mL)
867 was added tetrabutylammonium fluoride (0.22 mL, 0.22 mmol, 1 M solution in
868 tetrahydrofuran). The solution was allowed to stir at room temperature for 16 hours. After
869 this time, saturated aqueous ammonium chloride (10 mL) was added and the resulting
870 mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were
871 washed with saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate,
872 filtered and concentrated to dryness. The residue obtained was purified via flash SiO₂
873 chromatography (10 g silica gel, gradient of hexanes to 70% ethyl acetate/30% hexanes)
874 to give 1-[2-(ethoxymethyl)-4-(hydroxymethyl)-5-phenyl-1H-imidazol-1-yl]-2-

875 methylpropan-2-ol (**36**) (0.018 g, 82%) as a white solid; ^1H NMR (400 MHz, $\text{DMSO-}d_6$)
876 δ 7.48–7.44 (m, 2H), 7.39–7.35 (m, 3H), 4.74 (t, $J = 5.4$ Hz, 1H), 4.66 (s, 2H), 4.64 (s,
877 1H), 4.16 (d, $J = 5.4$ Hz, 2H), 4.03 (s, 2H), 3.51 (q, $J = 7.0$ Hz, 2H), 1.14 (t, $J = 7.0$ Hz,
878 3H), 0.71 (s, 6H); ^{13}C NMR (101 MHz $\text{DMSO-}d_6$) δ 145.53, 137.69, 130.86, 130.76,
879 130.09, 128.45, 127.52, 69.82, 65.01, 64.91, 56.15, 53.30, 27.72, 15.04; MS (ESI^+), calcd
880 $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_3$ (M+H) = 305.1865, found = 305.1873 .

881



882

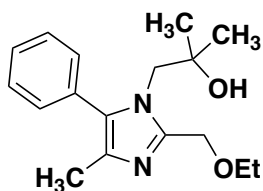
883 **1-[2-(ethoxymethyl)-4-(methoxymethyl)-5-phenyl-1H-imidazol-1-yl]-2-**

884 **methylpropan-2-ol (**37**, also called as **1g**)**

885 A solution of (1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
886 phenyl-1H-imidazol-4-yl)methanol (0.050 g, 0.12 mmol) in *N,N*-dimethylformamide (2
887 mL) was cooled in an ice bath (~ 0 °C). Sodium hydride (0.008 g, 0.2 mmol, 60
888 dispersion in mineral oil) was added and the resulting mixture was allowed to stir in the
889 ice bath for 20 min. After this time, iodomethane (15 μL , 0.24 mmol) was added. The ice
890 bath was removed and the solution was allowed to stir at room temperature for 19 hours.
891 After this time, saturated aqueous ammonium chloride (10 mL) was added and the
892 resulting mixture was extracted with ethyl acetate (3×5 mL). The combined organic
893 layers were washed with 5% aqueous lithium chloride (3×10 mL), washed with
894 saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate, filtered and
895 concentrated to dryness. The residue obtained was filtered through a plug of silica gel, (\approx

896 10 g, eluting with ethyl acetate) and the filtrate was concentrated to dryness to give crude
897 1-{2-[(tert-butyl(dimethyl)silyloxy]-2-methylpropyl}-2-(ethoxymethyl)-4-
898 (methoxymethyl)-5-phenyl-1H-imidazole (**17**) (0.051 g, 98%) as a colorless oil, which
899 was used in the next reaction without further purification. The colorless oil obtained
900 (0.045 g, 0.10 mmol) was dissolved in tetrahydrofuran (3 mL), and tetrabutylammonium
901 fluoride (0.30 mL, 0.30 mmol, 1 M solution in tetrahydrofuran) was added. The solution
902 was allowed to stir for 18 hours at room temperature. After this time, saturated aqueous
903 ammonium chloride (10 mL) was added and the resulting mixture was extracted with
904 ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated
905 aqueous sodium chloride (10 mL), dried over magnesium sulfate, filtered and
906 concentrated to dryness. The residue obtained was purified via flash SiO₂
907 chromatography (10 g silica gel, gradient of hexanes to ethyl acetate to 10% methanol/90%
908 ethyl acetate to give 1-[2-(ethoxymethyl)-4-(methoxymethyl)-5-phenyl-1H-imidazol-1-
909 yl]-2-methylpropan-2-ol (**37**) (0.024 g, 75%) as a white solid; ¹H NMR (400 MHz,
910 DMSO-*d*₆) δ 7.48–7.41 (m, 3H), 7.39–7.35 (m, 2H), 4.78 (s, 1H), 4.72 (s, 2H), 3.98 (s,
911 2H), 3.57 (s, 3H), 3.50 (q, *J* = 7.0 Hz, 2H), 1.14 (t, *J* = 7.0 Hz, 3H), 0.72 (s, 6H); ¹³C
912 NMR (101 MHz DMSO-*d*₆) δ 130.88, 129.89, 128.75, 127.60, 73.89, 65.20, 54.25, 28.24,
913 25.82, 17.71, 15.03, –2.19; MS (ESI⁺), calcd C₁₈H₂₇N₂O₃ (M+H) = 319.2022, found =
914 319.2020.

915

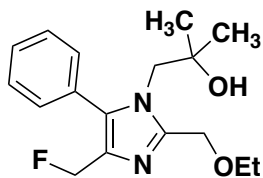


916

917 **1-[2-(ethoxymethyl)-4-methyl-5-phenyl-1H-imidazol-1-yl]-2-methylpropan-2-ol (38,**
918 **also called as 1h)**

919 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-
920 methyl-5-phenyl-1H-imidazole (0.025 g, 0.062 mmol), in acetonitrile (1.3 mL, in an
921 HDPE scintillation vial) was added hydrofluoric acid (1.3 mL, 48 wt % in water). The
922 solution was allowed to stir at room temperature for 16 hours. After this time, saturated
923 aqueous sodium carbonate was added until pH \approx 10, and the resulting mixture was
924 extracted with ethyl acetate (3 \times 20 mL). The combined organic layers were washed with
925 saturated aqueous sodium chloride (40 mL), dried over magnesium sulfate, filtered and
926 concentrated to dryness. The residue obtained was purified via flash SiO₂
927 chromatography (10 g silica gel, gradient of dichloromethane to 7% methanol/93%
928 dichloromethane) to give 1-[2-(ethoxymethyl)-4-methyl-5-phenyl-1H-imidazol-1-yl]-2-
929 methylpropan-2-ol (**38**) (0.016, 89%) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ
930 7.47–7.44 (m, 2H), 7.37–7.33 (m, 1H), 7.30–7.28 (m, 2H), 4.62–4.62 (m, 3H), 3.98 (s,
931 2H), 3.49 (q, *J* = 7.0 Hz, 2H), 2.03 (s, 3H), 1.13 (t, *J* = 7.0 Hz, 3H), 0.70 (s, 6H); ¹³C
932 NMR (101 MHz DMSO-*d*₆) δ 145.20, 132.93, 131.36, 130.05, 129.13, 128.63, 127.30,
933 69.83, 64.97, 64.81, 53.38, 27.76, 15.08, 13.13; MS (ESI⁺), calcd C₁₇H₂₅N₂O₂ (M+H) =
934 289.1916, found = 289.1905.

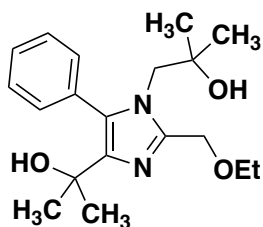
935



937 **1-[2-(ethoxymethyl)-4-(fluoromethyl)-5-phenyl-1H-imidazol-1-yl]-2-methylpropan-2-**
938 **ol (39, also called as 1i)**

939 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-
940 (fluoromethyl)-5-phenyl-1H-imidazole (0.040 g, 0.095 mmol) in acetonitrile (2 mL, in an
941 HDPE scintillation vial) was added hydrofluoric acid (2 mL, 48 wt % in water), and the
942 solution was allowed to stir at room temperature for 17 hours. After this time, saturated
943 aqueous sodium carbonate was added until pH ~ 10, and the resulting mixture was
944 extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with
945 saturated aqueous sodium chloride (50 mL), dried over magnesium sulfate, filtered and
946 concentrated to dryness. The residue obtained was purified via flash SiO₂
947 chromatography (10 g silica gel, gradient of dichloromethane to 6% methanol/94%
948 dichloromethane) to give 1-[2-(ethoxymethyl)-4-(fluoromethyl)-5-phenyl-1H-imidazol-1-
949 yl]-2-methylpropan-2-ol (**39**) (0.019 g, 66%) as a colorless oil; ¹H NMR (400 MHz,
950 DMSO-*d*₆) δ 7.53–7.49 (m, 2H), 7.46–7.42 (m, 1H), 7.39–7.37 (m, 2H), 5.07 (d, *J* = 50.4
951 Hz, 2H), 4.73 (s, 1H), 4.69 (s, 2H), 4.06 (s, 2H), 3.51 (q, *J* = 7.0 Hz, 2H), 1.14 (t, *J* = 7.0
952 Hz, 3H), 0.72 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 146.59, 134.55, 134.48, 132.52,
953 132.33, 130.06, 130.04, 129.67, 129.64, 128.82, 128.33, 78.49, 76.91, 69.79, 65.18, 64.84,
954 53.50, 27.73, 15.07; MS (ESI⁺), calcd C₁₇H₂₄FN₂O₂ (M+H) = 307.1822, found =
955 307.1819.

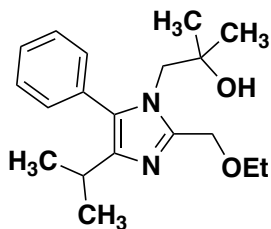
956



958 **1-[2-(ethoxymethyl)-4-(2-hydroxypropan-2-yl)-5-phenyl-1H-imidazol-1-yl]-2-**
959 **methylpropan-2-ol (40, also called as 1j)**

960 To a solution of 2-(1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-
961 (ethoxymethyl)-5-phenyl-1H-imidazol-4-yl)propan-2-ol (0.030 g, 0.067 mmol) in
962 tetrahydrofuran (2 mL) was added tetrabutylammonium fluoride (0.20 mL, 0.20 mmol, 1
963 M solution in tetrahydrofuran), and the solution was allowed to stir at room temperature
964 for 22 hours. After this time, saturated aqueous ammonium chloride (10 mL) was added
965 and the resulting mixture was extracted with ethyl acetate (3 × 5 mL). The combined
966 organic layers were washed with saturated aqueous sodium chloride (10 mL), dried over
967 magnesium sulfate, filtered and concentrated to dryness. The residue obtained was
968 purified via flash SiO₂ chromatography (10 g silica gel, gradient of dichloromethane to 5%
969 methanol/95% dichloromethane) to give 1-[2-(ethoxymethyl)-4-(2-hydroxypropan-2-yl)-
970 5-phenyl-1H-imidazol-1-yl]-2-methylpropan-2-ol (**40**) (0.019 g, 86%) as a colorless oil;
971 ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.47–7.30 (m, 5H), 4.69 (s, 1H), 4.66 (s, 2H), 4.50 (s,
972 2H), 3.83 (s, 2H), 3.51 (q, *J* = 7.0 Hz, 2H), 1.25 (s, 6H), 1.14 (t, *J* = 7.0 Hz, 3H), 0.74 (s,
973 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 143.40, 143.27, 132.18, 131.87, 127.86, 127.82,
974 127.68, 69.59, 68.90, 65.17, 64.86, 53.05, 31.16, 27.94, 15.09; MS (ESI⁺), calcd
975 C₁₉H₂₉N₂O₃ (M+H) = 333.2178, found = 333.2191.

976

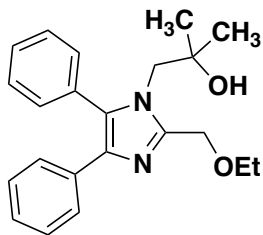


977

978 **1-[2-(ethoxymethyl)-5-phenyl-4-(propan-2-yl)-1H-imidazol-1-yl]-2-methylpropan-2-ol**
979 **(41, also called as 1k)**

980 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
981 phenyl-4-(propan-2-yl)-1H-imidazole (0.075 g, 0.17 mmol) in acetonitrile (3.5 mL, in an
982 HDPE scintillation vial) was added hydrofluoric acid (3.5 mL, 48 wt % in water), and the
983 solution was allowed to stir at room temperature for 17 hours. After this time, saturated
984 aqueous sodium carbonate was added until pH ~ 10, and the resulting mixture was
985 extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with
986 saturated aqueous sodium chloride (30 mL), dried over magnesium sulfate, filtered and
987 concentrated to dryness. The residue obtained was purified via flash SiO₂
988 chromatography (10 g silica gel, gradient of dichloromethane to 7% methanol/93%
989 dichloromethane) to give 1-[2-(ethoxymethyl)-5-phenyl-4-(propan-2-yl)-1H-imidazol-1-
990 yl]-2-methylpropan-2-ol (**41**) (0.052 g, 96%) as a white solid; ¹H NMR (400 MHz,
991 DMSO-*d*₆) δ 7.47–7.44 (m, 2H), 7.38–7.34 (m, 1H), 7.28–7.25 (m, 2H), 4.64 (s, 3H),
992 3.95 (s, 2H), 3.51 (q, *J* = 7.0 Hz, 2H), 2.72 (sep, *J* = 6.8 Hz, 1H), 1.14 (t, *J* = 7.0 Hz, 3H),
993 1.10 (d, *J* = 6.8 Hz, 6H), 0.70 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 145.08, 142.72,
994 131.29, 130.39, 128.59, 127.64, 127.45, 69.82, 65.11, 65.04, 53.19, 27.81, 25.54, 23.22,
995 15.10; MS (ESI⁺), calcd C₁₉H₂₉N₂O₂ (M+H) = 317.2229, found = 317.2223.

996

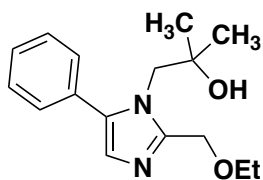


997

998 **1-[2-(ethoxymethyl)-4,5-diphenyl-1H-imidazol-1-yl]-2-methylpropan-2-ol (42, also**
999 **called as 1l)**

1000 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-
1001 4,5-diphenyl-1H-imidazole (0.035 g, 0.075 mmol) in tetrahydrofuran (2 mL) was added
1002 tetrabutylammonium fluoride (0.23 mL, 0.23 mmol, 1 M solution in tetrahydrofuran).
1003 The solution was allowed to stir at room temperature for 17 hours. After this time,
1004 saturated aqueous ammonium chloride (5 mL) was added and the resulting mixture was
1005 extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with
1006 saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate, filtered and
1007 concentrated to dryness. The residue obtained was purified via flash SiO₂
1008 chromatography (10 g silica gel, gradient of hexanes to ethyl acetate) to give 1-[2-
1009 (ethoxymethyl)-4,5-diphenyl-1H-imidazol-1-yl]-2-methylpropan-2-ol (**42**) (0.022 g, 85%)
1010 as an off-white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.50–7.42 (m, 3H), 7.34–7.29 (m,
1011 4H), 7.19–7.15 (m, 2H), 7.12–7.08 (m, 1H), 4.76 (s, 1H), 4.75 (s, 2H), 3.07 (s, 2H), 3.53
1012 (q, *J* = 7.0 Hz, 2H), 1.15 (t, *J* = 7.0 Hz, 3H), 0.76 (s, 3H); MS (ESI⁺), calcd C₂₂H₂₇N₂O₂
1013 (M+H) = 351.2072, found = 315.2076.

1014

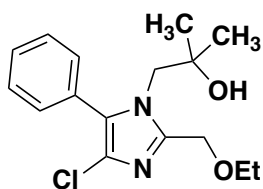


1015

1016 **1-[2-(ethoxymethyl)-5-phenyl-1H-imidazol-1-yl]-2-methylpropan-2-ol (43, also called**
1017 **as 1m)**

1018 To a mixture of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
1019 phenyl-1H-imidazole (0.050 g, 0.13 mmol) in tetrahydrofuran (3 mL) and
1020 tetrabutylammonium fluoride (0.39 mL, 0.39 mmol, 1 M solution in tetrahydrofuran) was
1021 added. The solution was allowed to stir at room temperature for 18 hours. After this time,
1022 saturated aqueous ammonium chloride (10 mL) was added and the resulting mixture was
1023 extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with
1024 saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and
1025 concentrated to dryness. The residue obtained was purified via flash SiO₂
1026 chromatography (10 g silica gel, gradient of dichloromethane to 10% methanol/90%
1027 dichloromethane) to give 1-[2-(ethoxymethyl)-5-phenyl-1H-imidazol-1-yl]-2-
1028 methylpropan-2-ol (**43**) (0.032 g, 89%) as a yellow oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ
1029 7.46–7.33 (m, 5H), 6.88 (s, 1H), 4.67 (s, 2H), 4.65 (s, 1H), 4.12 (s, 2H), 3.50 (q, *J* = 7.0
1030 Hz, 2 H), 1.14 (t, *J* = 7.0 Hz, 3H), 0.73 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 147.31,
1031 134.13, 131.29, 128.75, 128.68, 127.47, 126.49, 69.92, 64.96, 53.31, 27.72, 15.04; MS
1032 (ESI⁺), calcd C₁₆H₂₂N₂O₂ (M+H) = 275.2, found = 275.2.

1033



1034

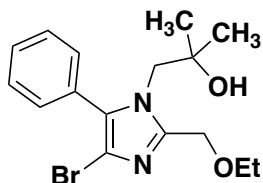
1035 **1-[4-chloro-2-(ethoxymethyl)-5-phenyl-1H-imidazol-1-yl]-2-methylpropan-2-ol** (**44**,
1036 **also called as 1n**)

1037 A solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-5-
1038 phenyl-1H-imidazole (0.050 g, 0.13 mmol) in *N,N*-dimethylformamide (2 mL) was

1039 heated at 60 °C. A solution of *N*-chlorosuccinimide (0.027 g, 0.20 mmol) in *N,N*-
1040 dimethylformamide (1 mL) was added, and the solution was allowed to stir at 60 °C for
1041 15 hours. After this time, the solution was allowed to cool to room temperature and water
1042 (20 mL) was added. Solid sodium thiosulfate pentahydrate was added until no further
1043 color change was observed, and the resulting mixture was extracted with ethyl acetate (3
1044 × 10 mL). The combined organic layers were washed with 5% aqueous lithium chloride
1045 (3 × 15 mL), washed with saturated aqueous sodium chloride (30 mL), dried over
1046 magnesium sulfate, filtered and concentrated to dryness. The residue obtained was
1047 filtered through a plug of silica gel (~ 10 g, eluting with ethyl acetate) and the filtrate was
1048 concentrated to dryness to give crude 1-{2-[(tert-butyldimethylsilyloxy]-2-
1049 methylpropyl}-4-chloro-2-(ethoxymethyl)-5-phenyl-1H-imidazole (**28**) (0.055 g, >99%).
1050 The residue was dissolved in tetrahydrofuran (5 mL) and tetrabutylammonium fluoride
1051 (0.39 mL, 0.39 mmol, 1 M solution in tetrahydrofuran) was added. The solution was
1052 allowed to stir at room temperature for 16 hours. After this time, saturated aqueous
1053 ammonium chloride (10 mL) was added and the resulting mixture was extracted with
1054 ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated
1055 aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated to
1056 dryness. The residue obtained was purified via flash SiO₂ chromatography (10 g silica gel,
1057 gradient of hexanes to 60% ethyl acetate/40% hexanes) to give 1-[4-chloro-2-
1058 (ethoxymethyl)-5-phenyl-1H-imidazol-1-yl]-2-methylpropan-2-ol (**44**) (0.037 g, 93%) as
1059 a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.51–7.47 (m, 2H), 7.44–7.39 (m, 3H),
1060 4.73 (s, 1H), 4.64 (s, 2H), 4.04 (s, 2H), 3.51 (q, *J* = 7.0 Hz, 2H), 1.14 (t, *J* = 7.0 Hz, 3H),
1061 0.73 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 145.27, 130.11, 128.78, 128.68, 128.27,

1062 127.91, 125.17, 69.63, 65.13, 64.45, 54.00, 27.60, 14.98; MS (ESI⁺), calcd C₁₆H₂₂ClN₂O₂
1063 (M+H) = 309.1370, found = 309.1376.

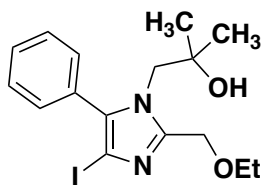
1064



1065

1066 **1-[4-bromo-2-(ethoxymethyl)-5-phenyl-1H-imidazol-1-yl]-2-methylpropan-2-ol (45,**
1067 **also called as 1o)**

1068 To a solution of 4-bromo-1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-
1069 (ethoxymethyl)-5-phenyl-1H-imidazole (0.050 g, 0.11 mmol) in tetrahydrofuran (5 mL)
1070 was added tetrabutylammonium fluoride (0.33 mL, 0.33 mmol, 1 M solution in
1071 tetrahydrofuran) and the solution was allowed to stir for 17 hours. After this time,
1072 saturated aqueous ammonium chloride (10 mL) was added and the resulting mixture was
1073 extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over
1074 magnesium sulfate, filtered and concentrated to dryness. The residue obtained was
1075 purified via flash SiO₂ chromatography (10 g silica gel, gradient of dichloromethane to 8%
1076 methanol/ 92% dichloromethane) to give 1-[4-bromo-2-(ethoxymethyl)-5-phenyl-1H-
1077 imidazol-1-yl]-2-methylpropan-2-ol (**45**) (0.034 g, 87%) as a white solid; ¹H NMR (400
1078 MHz, DMSO-*d*₆) δ 7.51–7.47 (m, 2H), 7.44–7.38 (m, 3H), 7.43 (s, 1H), 4.64 (s, 2H),
1079 4.04 (s, 2H), 3.50 (q, *J* = 7.0 Hz, 2H), 1.14 (t, *J* = 7.0 Hz, 3H), 0.73 (s, 6H); ¹³C NMR
1080 (101 MHz DMSO-*d*₆) δ 146.63, 130.67, 130.38, 129.25, 128.67, 128.37, 113.24, 69.67,
1081 65.19, 64.52, 54.10, 27.65, 15.03; MS (ESI⁺), calcd C₁₆H₂₂BrN₂O₂ (M+H) = 353.0865 &
1082 355.0846, found = 353.0868 & 355.0847.



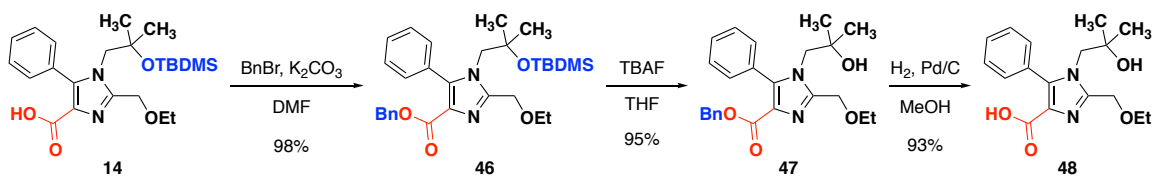
1083

1084 **1-[2-(ethoxymethyl)-4-iodo-5-phenyl-1H-imidazol-1-yl]-2-methylpropan-2-ol (CU-**
 1085 **CPD107)**

1086 To a solution of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl)-4-
 1087 iodo-5-phenyl-1H-imidazole (0.040 g, 0.078 mmol) in tetrahydrofuran (5 mL) was added
 1088 tetrabutylammonium fluoride (0.23 mL, 0.23 mmol, 1 M solution in tetrahydrofuran) and
 1089 the solution was allowed to stir at room temperature for 17 hours. After this time,
 1090 saturated aqueous ammonium chloride (10 mL) was added and the mixture was extracted
 1091 with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated
 1092 aqueous sodium chloride (10 mL), dried over magnesium sulfate, filtered and
 1093 concentrated to dryness. The residue obtained was purified via flash SiO₂
 1094 chromatography (10 g silica gel, gradient of hexanes to 70% ethyl acetate/30% hexanes)
 1095 to give 1-[2-(ethoxymethyl)-4-iodo-5-phenyl-1H-imidazol-1-yl]-2-methylpropan-2-ol
 1096 **(CU-CPD107)** (0.027 g, 87%) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.51–
 1097 7.47 (m, 2H), 7.44–7.38 (m, 3H), 4.74 (s, 2H), 4.65 (s, 2H), 4.04 (s, 2H), 3.50 (q, *J* = 7.0
 1098 Hz, 2H), 1.14 (t, *J* = 7.0 Hz, 3H), 0.73 (s, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 146.62,
 1099 130.65, 130.37, 129.25, 128.66, 128.35, 113.24, 69.66, 65.17, 64.52, 54.09, 27.64, 15.03;
 1100 MS (ESI⁺), calcd C₁₆H₂₂IN₂O₂ (M+H) = 401.0726, found = 401.0731.

1101

1102



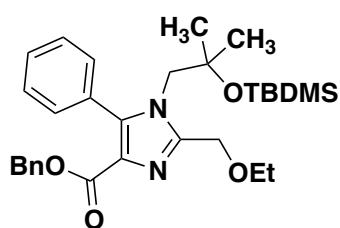
1103

1104 **Supplementary Fig. 18 Carboxylic acid analog deprotection:** Carboxylic acid **14** was

1105 deprotected over three steps to give **48**.

1106

1107



1108

1109 **benzyl 1-{2-[(tert-butyldimethylsilyloxy)-2-methylpropyl]-2-(ethoxymethyl)-5-**
 1110 **phenyl-1H-imidazole-4-carboxylate (46)**

1111 To a mixture of 1-{2-[(tert-butyldimethylsilyloxy)-2-methylpropyl]-2-(ethoxymethyl)-5-

1112 phenyl-1H-imidazole-4-carboxylic acid (0.100 g, 0.231 mmol), potassium carbonate

1113 (0.128 g, 0.924 mmol) in *N,N*-dimethylformamide (3 mL) was added benzyl bromide (42

1114 μ L, 0.35 mmol), and the resulting mixture was allowed to stir at room temperature for 17

1115 hours. After this time, the mixture was diluted with water (20 mL) and extracted with

1116 ethyl acetate (4×10 mL). The combined organic layers were washed with 5% aqueous

1117 lithium chloride (3×30 mL), washed with saturated aqueous sodium chloride (40 mL),

1118 dried over magnesium sulfate, filtered and concentrated to dryness. The residue obtained

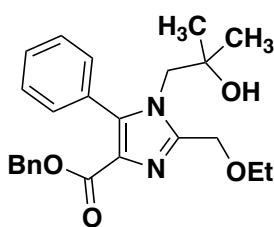
1119 was purified via flash SiO_2 chromatography (10 g silica gel, gradient of hexanes to 35%

1120 ethyl acetate/65% hexanes) to give benzyl 1-{2-[(tert-butyldimethylsilyloxy)-2-

1121 methylpropyl]-2-(ethoxymethyl)-5-phenyl-1H-imidazole-4-carboxylate (**46**) (0.118 g,

1122 98%) as a white solid; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.44–7.38 (m, 5H), 7.32–7.26
1123 (m, 3H), 7.17–7.12 (m, 2H), 5.10 (s, 2H), 4.65 (s, 2H), 4.07 (s, 2H), 3.49 (q, $J = 7.0$ Hz,
1124 2H), 1.14 (t, $J = 7.0$ Hz, 3H), 0.83 (s, 6H), 0.72 (s, 9H), -0.03 (s, 6H); ^{13}C NMR (101
1125 MHz $\text{DMSO-}d_6$) δ 162.21, 146.69, 139.36, 136.20, 131.01, 129.54, 128.69, 128.25,
1126 128.09, 127.86, 127.81, 127.78, 73.60, 65.32, 64.97, 64.91, 54.24, 28.32, 25.80, 17.71,
1127 14.98, -2.20 ; MS (ESI^+), calcd $\text{C}_{30}\text{H}_{43}\text{N}_2\text{O}_4\text{Si}$ ($\text{M}+\text{H}$) = 523.2992, found = 523.3004.

1128



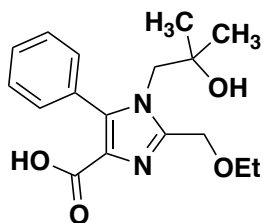
1129

1130 **benzyl 2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-5-phenyl-1H-imidazole-4-**
1131 **carboxylate (47)**

1132 To a solution of benzyl 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-
1133 (ethoxymethyl)-5-phenyl-1H-imidazole-4-carboxylate (0.108 g, 0.207 mmol) in
1134 tetrahydrofuran (3 mL) was added tetrabutylammonium fluoride (0.62 mL, 0.62 mmol, 1
1135 M in tetrahydrofuran), and the solution was allowed to stir for 15 hours. After this time,
1136 saturated aqueous ammonium chloride (10 mL) was added and the resulting mixture was
1137 extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with
1138 saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate, filtered and
1139 concentrated to dryness. The residue obtained was purified via flash SiO_2
1140 chromatography (10 g silica gel, gradient of hexanes to 95% ethyl acetate/5% hexanes) to
1141 give benzyl 2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-5-phenyl-1H-imidazole-4-
1142 carboxylate (**47**) (0.081 g, 95%) as a white solid; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.43–

1143 7.39 (m, 3H), 7.39–7.35 (m, 2H), 7.16–7.12 (m, 2H), 5.08 (s, 2H), 4.79 (s, 1H), 4.72 (s,
1144 2H), 3.97 (s, 2H), 3.49 (q, $J = 7.0$ Hz, 2H), 1.13 (t, $J = 7.0$ Hz, 3H), 0.73 (s, 6H); ^{13}C
1145 NMR (101 MHz DMSO- d_6) δ 162.28, 146.95, 139.65, 136.26, 131.11, 129.63, 128.60,
1146 128.27, 127.98, 127.79, 127.67, 69.59, 65.23, 64.90, 64.88, 53.40, 27.84, 15.06; MS
1147 (ESI $^+$), calcd $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_4$ (M+H) = 409.2127, found = 409.2134.

1148



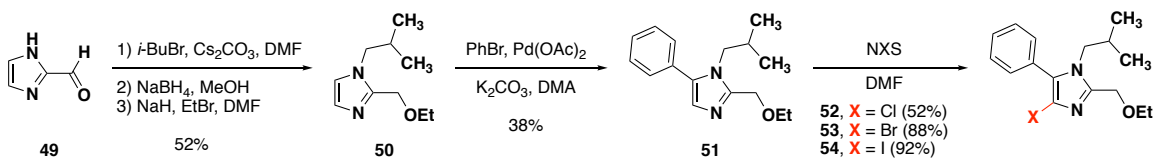
1149

1150 **2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-5-phenyl-1H-imidazole-4-carboxylic**
1151 **acid (48, also called as 1q)**

1152 To solution of benzyl 2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-5-phenyl-1H-
1153 imidazole-4-carboxylate (0.076 g, 0.19 mmol) in methanol (5 mL) was added palladium
1154 on carbon (0.008 g, 5% basis). The mixture was degassed and backfilled with nitrogen
1155 gas (4 \times), then degassed and backfilled with hydrogen gas (4 \times). The reaction was then
1156 allowed to stir under hydrogen atmosphere (balloon) for 17 hours. After this time, the
1157 mixture was degassed and backfilled with nitrogen gas (4 \times), diluted with
1158 dichloromethane (15 mL), and filtered through Celite (rinsing with additional
1159 dichloromethane). The filtrate was concentrated to dryness. The resulting solid was
1160 triturated with cold diethyl ether to give 2-(ethoxymethyl)-1-(2-hydroxy-2-methylpropyl)-
1161 5-phenyl-1H-imidazole-4-carboxylic acid (**48**) (0.056 g, 93%) as a white solid; ^1H NMR
1162 (400 MHz, DMSO- d_6) δ 11.9 (br s, 1H), 7.46–7.35 (m, 5H), 4.77–4.71 (2 x s, 3H), 3.97 (s,
1163 2H), 3.50 (q, $J = 7.0$ Hz, 2H), 1.14 (t, $J = 7.0$ Hz, 3H), 0.72 (s, 6H); ^{13}C NMR (101 MHz

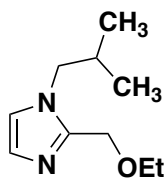
1164 DMSO-*d*₆) δ 163.88, 146.48, 138.83, 131.15, 129.97, 128.52, 128.39, 127.85, 69.61,
1165 65.18, 64.90, 53.31, 27.82, 15.07; MS (ESI⁺), calcd C₁₇H₂₃N₂O₄ (M-H) = 317.1501,
1166 found = 317.1517.

1167



1169 **Supplementary Fig. 19 R848/R837/CU-CPD107 hybrid synthesis:** Hybrid molecules
1170 **52, 53, and 54** were made from **49**.

1171



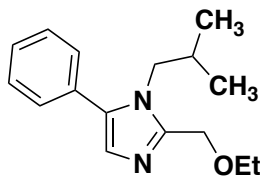
1172

1173 **2-(ethoxymethyl)-1-(2-methylpropyl)-1H-imidazole (50)**

1174 To a mixture of 2-imidazolecarboxaldehyde (**49**) (5.00 g, 52.0 mmol) and cesium
1175 carbonate (33.9 g, 104 mmol) in *N,N*-dimethylformamide (250 mL) was added 1-bromo-
1176 2-methylpropane (6.2 mL, 57 mmol), and was allowed to stir at room temperature for 18
1177 hours. After this time, the mixture was diluted with ethyl acetate (500 mL), washed with
1178 water (2 × 300 mL), washed with 5% aqueous lithium chloride (2 × 200 mL), washed
1179 with saturated aqueous sodium chloride (200 mL), dried over magnesium sulfate, filtered
1180 and concentrated to dryness to give crude 1-(2-methylpropyl)-1H-imidazole-2-
1181 carbaldehyde as a yellow oil. The oil obtained was dissolved in methanol (250 mL).
1182 Sodium borohydride was (2.95 g, 78.0 mmol) added and allowed to stir at room
1183 temperature for 17 hours. After this time, saturated aqueous ammonium chloride (200 mL)

1184 was added and the resulting mixture was extracted with dichloromethane (3 x 200 mL).
1185 The combined organic layers were washed with saturated aqueous sodium chloride (400
1186 mL), dried over sodium sulfate, filtered and concentrated to dryness. The resulting
1187 residue was azeotroped with additional dichloromethane and left on a high-vacuum pump
1188 for several hours to give crude [1-(2-methylpropyl)-1H-imidazol-2-yl]methanol as a clear,
1189 yellow oil. The yellow oil was dissolved in *N,N*-dimethylformamide (250 mL) and cooled
1190 in an ice bath (~ 0 °C). Sodium hydride (4.17 g, 104 mmol, 60% dispersion in mineral oil)
1191 was added and the mixture was allowed to stir in the ice bath for 45 min. After this time,
1192 bromoethane (9.7 mL, 130 mmol) was added and the mixture was allowed to stir in the
1193 ice bath for 1 hour. After this time, the ice bath was removed and the mixture was
1194 allowed to stir at room temperature for 15 hours. After this time, saturated aqueous
1195 ammonium chloride (200 mL) and water (50 mL) were added and the resulting mixture
1196 was extracted with ethyl acetate (500 mL). The organic layer was washed with water (2 ×
1197 400 mL), washed with 5% aqueous lithium chloride (400 mL), washed with saturated
1198 aqueous sodium chloride (400 mL), dried over magnesium sulfate, filtered and
1199 concentrated to dryness. The residue obtained was filtered through a plug of silica gel (~
1200 70 g). The filtrate was concentrated to give 2-(ethoxymethyl)-1-(2-methylpropyl)-1H-
1201 imidazole (**50**) (4.966 g, 52% over three steps) as a colorless oil; ¹H NMR (400 MHz,
1202 DMSO-*d*₆) δ 7.15 (d, *J* = 1.2 Hz, 1H), 6.81 (d, *J* = 1.2 Hz, 1H), 4.44 (s, 2H), 3.75 (d, *J* =
1203 7.5 Hz, 2H), 3.42 (q, *J* = 7.0 Hz, 2H), 2.05 (sep, *J* = 6.7 Hz, 1H), 1.09 (t, *J* = 7.0 Hz, 3H),
1204 0.84 (d, *J* = 6.7 Hz, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 144.17, 126.60, 121.37, 64.71,
1205 63.62, 52.46, 29.24, 19.66, 14.96; MS (ESI⁺), calcd C₁₀H₁₉N₂O (M+H) = 183.1497,
1206 found = 183.1498.

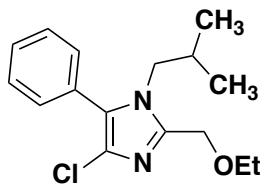
1207



1208

1209 **2-(ethoxymethyl)-1-(2-methylpropyl)-5-phenyl-1H-imidazole (51, also called as 2a)**

1210 A mixture of 2-(ethoxymethyl)-1-(2-methylpropyl)-1H-imidazole (1.00 g, 1.3 mmol),
1211 bromobenzene (0.44 mL, 4.2 mmol), and potassium acetate (1.16 g, 8.40 mmol) in *N,N*-
1212 dimethylacetamide (30 mL) was degassed and backfilled with nitrogen gas (4×).
1213 Palladium (II) acetate (0.094 g, 0.42 mmol) was added, the mixture was degassed and
1214 backfilled with nitrogen gas (4x) again and heated at 150 °C for 16 hours. After this time,
1215 the mixture was allowed to cool to room temperature, diluted with ethyl acetate (120 mL),
1216 washed with water (100 mL), washed with 5% aqueous lithium chloride (3 × 100 mL),
1217 washed with saturated aqueous sodium chloride (100 mL), dried over magnesium sulfate,
1218 filtered and concentrated to dryness. The residue obtained was purified via flash SiO₂
1219 chromatography (100 g silica gel, gradient of hexanes to 50% ethyl acetate/50% hexanes)
1220 to give 2-(ethoxymethyl)-1-(2-methylpropyl)-5-phenyl-1H-imidazole (**51**) (0.540 g, 38%)
1221 as a yellow oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.48–7.43 (m, 4H), 7.41–7.36 (m, 1H),
1222 6.92 (s, 1H), 4.52 (s, 2H), 3.94 (d, *J* = 7.7 Hz, 2H), 3.51 (q, *J* = 7.0 Hz, 2H), 1.64 (sep, *J*
1223 = 6.7 Hz, 1H), 1.13 (t, *J* = 7.0 Hz, 3H), 0.60 (d, *J* = 6.7 Hz, 6H); ¹³C NMR (101 MHz
1224 DMSO-*d*₆) δ 145.76, 133.60, 130.77, 128.79, 128.23, 127.75, 126.62, 64.90, 64.23, 50.62,
1225 28.48, 19.36, 14.96.
1226

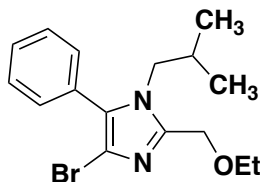


1227

1228 **4-chloro-2-(ethoxymethyl)-1-(2-methylpropyl)-5-phenyl-1H-imidazole (52, also called**
 1229 **as 2b)**

1230 To a solution of 2-(ethoxymethyl)-1-(2-methylpropyl)-5-phenyl-1H-imidazole (0.050 g,
 1231 0.19 mmol) in *N,N*-dimethylformamide (2 mL) at 60 °C was added a solution of *N*-
 1232 chlorosuccinimide (0.039 g, 0.29 mmol) in *N,N*-dimethylformamide (1 mL) and was
 1233 allowed to stir at 60 °C for 18 hours. After this time, the solution was allowed to cool to
 1234 room temperature, diluted with water (10 mL), added solid sodium thiosulfate
 1235 pentahydrate until the mixture was white, and extracted with ethyl acetate (10 mL). The
 1236 organic layer was washed with 5% aqueous lithium chloride (2 × 10 mL), washed with
 1237 saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate, filtered and
 1238 concentrated to dryness. The residue obtained was purified via flash SiO₂
 1239 chromatography (10 g silica gel, gradient of hexanes to 40% ethyl acetate/60% hexanes)
 1240 to give 4-chloro-2-(ethoxymethyl)-1-(2-methylpropyl)-5-phenyl-1H-imidazole (**52**) (0.029
 1241 g, 52%) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.53–7.41 (m, 5H), 4.50 (s,
 1242 2H), 3.86 (d, *J* = 7.7 Hz, 2H), 3.51 (q, *J* = q, 7.0 Hz, 2H), 1.57 (sep, *J* = 6.7 Hz, 1H), 1.14
 1243 (t, *J* = 7.0 Hz, 3H), 0.59 (d, *J* = 6.7 Hz, 6H); ¹³C NMR (101 MHz DMSO-*d*₆) δ 143.54,
 1244 129.73, 128.84, 128.67, 128.37, 127.64, 125.19, 65.08, 63.62, 51.31, 28.20, 19.28, 14.92.

1245

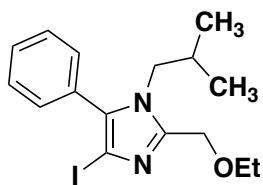


1246

1247 **4-bromo-2-(ethoxymethyl)-1-(2-methylpropyl)-5-phenyl-1H-imidazole (53, also**
 1248 **called as 2c)**

1249 To a solution of 2-(ethoxymethyl)-1-(2-methylpropyl)-5-phenyl-1H-imidazole (0.107 g,
 1250 0.414 mmol) in *N,N*-dimethylformamide (4 mL) was added a solution of *N*-
 1251 bromosuccinimide (0.077 g, 0.43 mmol) in *N,N*-dimethylformamide (2 mL), and was
 1252 allowed to stir at room temperature for 48 hours. After this time, the solution was diluted
 1253 with water (15 mL), added solid sodium thiosulfate pentahydrate until the mixture was
 1254 white, and extracted with ethyl acetate (20 mL). The organic layer was washed with 5%
 1255 aqueous lithium chloride (2 × 20 mL), washed with saturated aqueous sodium chloride
 1256 (20 mL), dried over magnesium sulfate, filtered and concentrated to dryness. The residue
 1257 obtained was purified via flash SiO₂ chromatography (25 g silica gel, gradient of hexanes
 1258 to 40% ethyl acetate/60% hexanes) to give 4-bromo-2-(ethoxymethyl)-1-(2-
 1259 methylpropyl)-5-phenyl-1H-imidazole (**53**) (0.123 g, 88%) as a white solid; ¹H NMR
 1260 (400 MHz, DMSO-*d*₆) δ 7.54–7.40 (m, 5H), 4.50 (s, 2H), 3.85 (d, *J* = 7.7 Hz, 2H), 3.51
 1261 (q, *J* = 7.0 Hz, 2H), 1.57 (sep, *J* = 6.7 Hz, 1H), 1.14 (t, *J* = 7.0 Hz, 3H), 0.59 (d, *J* = 6.7
 1262 Hz, 6H).

1263

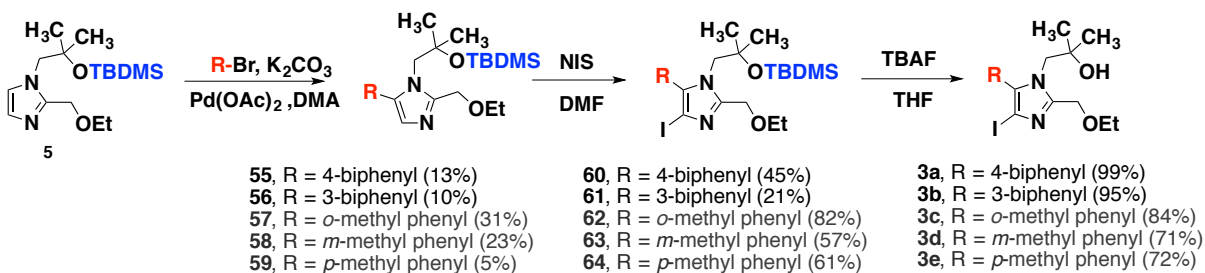


1264

1265 **2-(ethoxymethyl)-4-iodo-1-(2-methylpropyl)-5-phenyl-1H-imidazole (54, also called**
1266 **as 2d)**

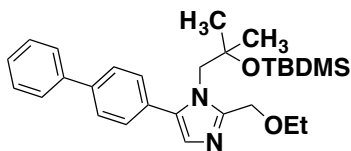
1267 To a solution of 2-(ethoxymethyl)-1-(2-methylpropyl)-5-phenyl-1H-imidazole (0.050 g,
1268 0.19 mmol) in *N,N*-dimethylformamide (2 mL) at 60 °C was added a solution of *N*-
1269 iodosuccinimide (0.065 g, 0.29 mmol) in *N,N*-dimethylformamide (1 mL), and was
1270 allowed to stir at 60 °C for 18 hours. After this time, the solution was allowed to cool to
1271 room temperature, diluted with water (10 mL), added solid sodium thiosulfate
1272 pentahydrate until the mixture was white, and extracted with ethyl acetate (20 mL). The
1273 organic layer was washed with 5% aqueous lithium chloride (2 × 20 mL), washed with
1274 saturated aqueous sodium chloride (20 mL), dried over magnesium sulfate, filtered and
1275 concentrated to dryness. The residue obtained was purified via flash SiO₂
1276 chromatography (10 g silica gel, gradient of hexanes to 40% ethyl acetate/60% hexanes)
1277 to give 2-(ethoxymethyl)-4-iodo-1-(2-methylpropyl)-5-phenyl-1H-imidazole (**54**) (0.067g,
1278 92%) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.52–7.43 (m, 3H), 7.39–7.36
1279 (m, 2H), 4.49 (s, 2H), 3.83 (d, *J* = 7.7 Hz, 2H), 3.51 (q, *J* = 7.0 Hz, 2H), 1.55 (sep, *J* = 6.7
1280 Hz, 1H), 1.13 (t, *J* = 7.0 Hz, 3H), 0.57 (d, *J* = 6.7 Hz, 6H); ¹³C NMR (101 MHz DMSO-
1281 *d*₆) δ 147.18, 135.52, 130.22, 129.89, 128.72, 128.68, 84.64, 65.07, 63.70, 51.40, 28.25,
1282 19.31, 14.94.

1283



1285 **Supplementary Fig. 20 Aromatic analogs synthesis: 3a, 3b, 3c, 3d, and 3e** were made
1286 from imidazole intermediate **5**.

1287



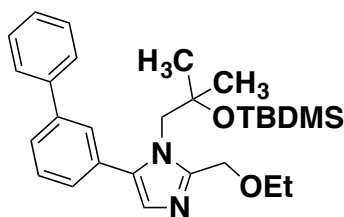
1288

1289 **5-([1,1'-biphenyl]-4-yl)-1-(2-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-2-**
1290 **(ethoxymethyl)-1H-imidazole (55)**

1291 A mixture of 1-{2-[(tert-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl) 1H-
1292 imidazole (312 mg, 1.00 mmol), 4-bromo-1,1'-biphenyl (466 mg, 2.00 mmol), and
1293 potassium carbonate (552mg, 4.00mmol) in N,N-dimethylacetamide (10 mL) was
1294 degassed and backfilled with nitrogen gas (4 ×). Palladium (II) acetate (38mg,
1295 0.17mmol) was added and the mixture was degassed and backfilled with nitrogen gas (4
1296 ×) again. The mixture was heated at 80 °C for 12 hours, and after this time the reaction
1297 was allowed to cool to room temperature. Water (20 mL) was added and the resulting
1298 mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were
1299 washed with 5% aqueous lithium chloride (3 x 100 mL), washed with saturated aqueous
1300 sodium chloride (300 mL), dried over magnesium sulfate, filtered and concentrated to
1301 dryness. The residue obtained was purified via flash SiO₂ chromatography (34 g silica gel,
1302 gradient of hexanes to 25% ethyl acetate/75% hexanes) to give 5-([1,1'-biphenyl]-4-yl)-1-
1303 (2-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-1H-
1304 imidazole(**55**)(60 mg, 13%) as a brown oil. ¹H NMR (400 MHz, CDCl₃) δ 7.66-7.62 (m,
1305 4H), 7.49-7.40 (m, 5H), 7.03 (s, 1H), 4.25 (s, 2H), 3.58 (q, *J* = 7.0 Hz, 2H), 1.25 (d, *J* =

1306 7.0 Hz, 3H), 0.95 (s, 6H), 0.78 (s, 9H), -0.02 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ
1307 147.87, 140.43, 134.25, 130.76, 129.26, 128.98, 127.74, 127.66, 127.53, 127.09, 77.16,
1308 74.54, 66.05, 65.89, 55.16, 28.72, 26.07, 18.14, 15.27, -1.92.

1309

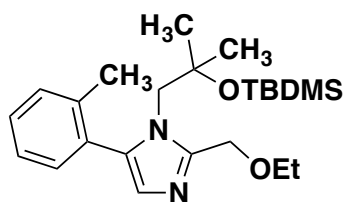


1310

1311 **5-([1,1'-biphenyl]-3-yl)-1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-**
1312 **(ethoxymethyl)-1*H*-imidazole (56)**

1313 A mixture of 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl) 1*H*-
1314 imidazole (312 mg, 1.00 mmol), 3-bromo-1,1'-biphenyl (466 mg, 2.00 mmol), and
1315 potassium carbonate (552mg, 4.00mmol) in *N,N*-dimethylacetamide (10 mL) was
1316 degassed and backfilled with nitrogen gas (4 ×). Palladium (II) acetate (38mg,
1317 0.17mmol) was added and the mixture was degassed and backfilled with nitrogen gas (4×)
1318 again. The mixture was heated at 80 °C for 12 hours, and after this time the reaction was
1319 allowed to cool to room temperature. Water (20 mL) was added and the resulting mixture
1320 was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed
1321 with 5% aqueous lithium chloride (3 × 100 mL), washed with saturated aqueous sodium
1322 chloride (300 mL), dried over magnesium sulfate, filtered and concentrated to dryness.
1323 The residue obtained was purified via flash SiO₂ chromatography (34 g silica gel,
1324 gradient of hexanes to 25% ethyl acetate/75% hexanes) to give 5-([1,1'-biphenyl]-3-yl)-1-
1325 (2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-1*H*-

1326 imidazole(**56**)(48 mg, 10%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.61-7.54 (m,
1327 4H), 7.50-7.43 (m, 3H), 7.39-7.31 (m, 2H), 7.04 (s, 1H), 4.78 (s, 2H), 4.24 (s, 2H), 3.58
1328 (q, *J* = 7.0 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 3H), 0.94 (s, 6H), 0.78 (s, 9H); ¹³C NMR (101
1329 MHz, CDCl₃) δ 147.71, 141.85, 140.60, 134.38, 132.21, 129.22, 128.87, 127.68, 127.65,
1330 127.56, 127.15, 126.43, 74.42, 65.93, 65.81, 55.08, 28.62, 25.96, 18.02, 15.15, -2.04.
1331

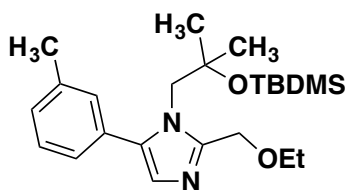


1333 **1-(2-((tert-butyldimethylsilyloxy)-2-methylpropyl)-2-(ethoxymethyl)-5-(*o*-tolyl)-1H-**
1334 **imidazole (57)**

1335 A mixture of 1-{2-[(tert-butyldimethylsilyloxy)-2-methylpropyl]-2-(ethoxymethyl) 1H-
1336 imidazole (469 mg, 1.50 mmol), 1-bromo-2-methylbenzene
1337 (513 mg, 3.00 mmol), and potassium carbonate (690mg, 5.00mmol) in N,N-
1338 dimethylacetamide (10 mL) was degassed and backfilled with nitrogen gas (4×).
1339 Palladium (II) acetate (76 mg, 0.34 mmol) was added and the mixture was degassed and
1340 backfilled with nitrogen gas (4×) again. The mixture was heated at 80 °C for 12 hours,
1341 and after this time the reaction was allowed to cool to room temperature. Water (20 mL)
1342 was added and the resulting mixture was extracted with ethyl acetate (3 × 100 mL). The
1343 combined organic layers were washed with 5% aqueous lithium chloride (3 × 100 mL),
1344 washed with saturated aqueous sodium chloride (300 mL), dried over magnesium sulfate,
1345 filtered and concentrated to dryness. The residue obtained was purified via flash SiO₂
1346 chromatography (34 g silica gel, gradient of hexanes to 25% ethyl acetate/75% hexanes)

1347 to give 1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-5-(*o*-tolyl)-
1348 1H-imidazole(**57**)(186 mg, 31%) as a brown oil. ¹H NMR (400 MHz, CDCl₃) δ 7.29 –
1349 7.17 (m, 4H), 6.94 (s, 1H), 4.79 (s, 2H), 4.01 (s, 2H), 3.54 (q, J = 7.0 Hz, 2H), 2.23 (s,
1350 3H), 1.22 (t, J = 7.0 Hz, 3H), 0.93 (s, 6H), 0.79 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ
1351 147.08, 137.58, 132.83, 131.24, 130.77, 130.53, 128.43, 127.79, 125.86, 74.35, 65.96,
1352 65.66, 55.02, 28.48, 26.08, 20.18, 18.17, 15.28, -1.89.

1353

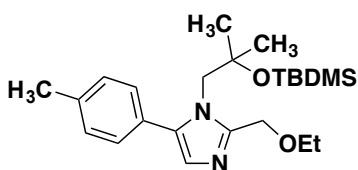


1354

1355 **1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-5-(*m*-tolyl)-1H-**
1356 **imidazole (**58**)**

1357 A mixture of 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl) 1H-
1358 imidazole (469 mg, 1.50 mmol), 1-bromo-3-methylbenzene
1359 (514 mg, 3.00 mmol), and potassium carbonate (552mg, 4.00mmol) in N,N-
1360 dimethylacetamide (10 mL) was degassed and backfilled with nitrogen gas (4×).
1361 Palladium (II) acetate (38mg, 0.17mmol) was added and the mixture was degassed and
1362 backfilled with nitrogen gas (4×) again. The mixture was heated at 80 °C for 12 hours,
1363 and after this time the reaction was allowed to cool to room temperature. Water (20 mL)
1364 was added and the resulting mixture was extracted with ethyl acetate (3 × 100 mL). The
1365 combined organic layers were washed with 5% aqueous lithium chloride (3 × 100 mL),
1366 washed with saturated aqueous sodium chloride (300 mL), dried over magnesium sulfate,
1367 filtered and concentrated to dryness. The residue obtained was purified via flash SiO₂

1368 chromatography (34 g silica gel, gradient of hexanes to 25% ethyl acetate/75% hexanes)
1369 to give 1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-5-(*m*-
1370 tolyl)-1*H*-imidazole(**58**)(138 mg, 23%) as an orange oil. ¹H NMR (400 MHz,
1371 Chloroform-*d*) δ 7.18 – 7.10 (m, 4H), 6.96 (s, 1H), 4.76 (s, 2H), 4.20 (s, 2H), 3.55 (q, *J* =
1372 7.0 Hz, 2H), 2.38 (s, 3H), 1.22 (t, *J* = 7.0 Hz, 4H), 0.90 (d, *J* = 7.6 Hz, 6H), 0.78 (s, 9H), -
1373 0.03(s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 147.41, 138.46, 134.60, 131.53, 129.50,
1374 128.64, 128.39, 127.24, 125.88, 76.71, 74.41, 65.85, 65.74, 54.93, 28.55, 25.94, 21.44,
1375 18.02, 15.13, -2.06.

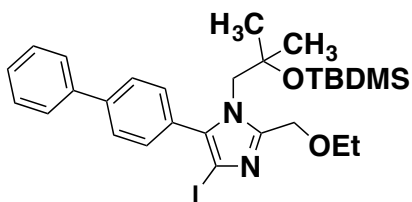


1376

1377 **1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-5-(*p*-tolyl)-1*H*-**
1378 **imidazole (59)**

1379 A mixture of 1-{2-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropyl}-2-(ethoxymethyl) 1*H*-
1380 imidazole (312 mg, 1.00 mmol), 1-bromo-4-methylbenzene (513 mg, 3.00 mmol), and
1381 potassium carbonate (552mg, 4.00mmol) in *N,N*-dimethylacetamide (10 mL) was
1382 degassed and backfilled with nitrogen gas (4 ×). Palladium (II) acetate (38mg,
1383 0.17mmol) was added and the mixture was degassed and backfilled with nitrogen gas (4×)
1384 again. The mixture was heated at 80 °C for 12 hours, and after this time the reaction was
1385 allowed to cool to room temperature. Water (20 mL) was added and the resulting mixture
1386 was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed
1387 with 5% aqueous lithium chloride (3 × 100 mL), washed with saturated aqueous sodium
1388 chloride (300 mL), dried over magnesium sulfate, filtered and concentrated to dryness.

1389 The residue obtained was purified via flash SiO₂ chromatography (34 g silica gel,
1390 gradient of hexanes to 25% ethyl acetate/75% hexanes) to give 1-(2-((*tert*-
1391 butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-5-(*p*-tolyl)-1*H*-
1392 imidazole(**59**)(20 mg, 5%) as an orange oil. ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.19 (m,
1393 4H), 6.97 (s, 1H), 4.79 (s, 2H), 4.22 (s, 2H), 3.58 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 1.25
1394 (t, *J* = 7.0 Hz, 3H), 0.94 (s, 6H), 0.83-0.77 (m, 9H); ¹³C NMR (101 MHz, CDCl₃) δ
1395 147.28, 137.48, 134.47, 129.46, 128.80, 128.67, 127.03, 74.40, 65.83, 65.73, 54.91,
1396 28.56, 25.95, 21.22, 18.02, 15.13, -2.05.



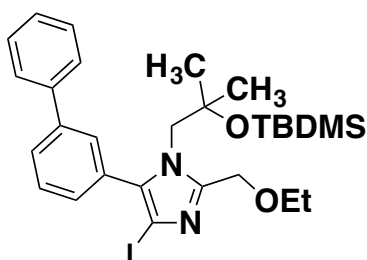
1397

1398 **5-([1,1'-biphenyl]-4-yl)-1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-**
1399 **(ethoxymethyl)-4-iodo-1*H*-imidazole (**60**)**

1400 To a solution of 5-([1,1'-biphenyl]-4-yl)-1-(2-((*tert*-butyldimethylsilyl)oxy)-2-
1401 methylpropyl)-2-(ethoxymethyl)-1*H*-imidazole(**58**)(56mg, 0.12 mmol) in *N,N*-
1402 dimethylformamide (5 mL) at 60 °C was added a solution of *N*-iodosuccinimide (30 mg,
1403 0.13 mmol) in *N,N*-dimethylformamide (1 mL) and the solution was allowed to stir 60 °C
1404 for 12 hours. After this time, water (10 mL) was added, solid sodium thiosulfate
1405 pentahydrate was added until no further color change was observed, and the resulting
1406 mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were
1407 washed with 5% aqueous lithium chloride (3 × 30 mL), washed with saturated aqueous
1408 sodium chloride (30 mL), dried over magnesium sulfate, filtered and concentrated to
1409 dryness. The residue obtained was purified via flash SiO₂ chromatography (10 g silica gel,

1410 gradient of hexanes to 20% ethyl acetate/80% hexanes) to give 5-([1,1'-biphenyl]-4-yl)-1-
1411 (2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-4-iodo-1*H*-
1412 imidazole(**60**) (32 mg, 45%) as a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.67 (dd, *J* =
1413 15.5, 7.8 Hz, 4H), 7.51-7.34 (m, 5H), 4.75 (s, 2H), 4.19 (s, 2H), 3.58 (q, *J* = 7.0 Hz, 2H),
1414 0.93 (s, 6H), 0.79 (s, 9H), -0.01 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 149.23, 141.09,
1415 140.17, 135.72, 133.22, 130.99, 129.51, 128.88, 127.71, 127.26, 127.06, 74.25, 65.96,
1416 65.63, 55.77, 28.59, 25.97, 17.91, 15.13, -2.01.

1417

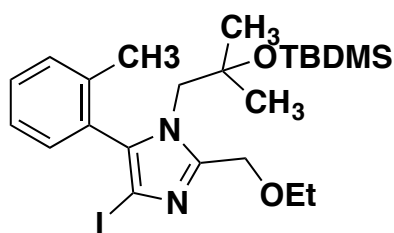


1418

1419 **5-([1,1'-biphenyl]-3-yl)-1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-**
1420 **(ethoxymethyl)-4-iodo-1*H*-imidazole (**61**)**

1421 To a solution of 5-([1,1'-biphenyl]-3-yl)-1-(2-((*tert*-butyldimethylsilyl)oxy)-2-
1422 methylpropyl)-2-(ethoxymethyl)-1*H*-imidazole(**59**)(48mg, 0.10 mmol) in *N,N*-
1423 dimethylformamide (5 mL) at 60 °C was added a solution of *N*-iodosuccinimide (28 mg,
1424 0.12 mmol) in *N,N*-dimethylformamide (1 mL) and the solution was allowed to stir 60 °C
1425 for 12 hours. After this time, water (10 mL) was added, solid sodium thiosulfate
1426 pentahydrate was added until no further color change was observed, and the resulting
1427 mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were
1428 washed with 5% aqueous lithium chloride (3 × 30 mL), washed with saturated aqueous
1429 sodium chloride (30 mL), dried over magnesium sulfate, filtered and concentrated to

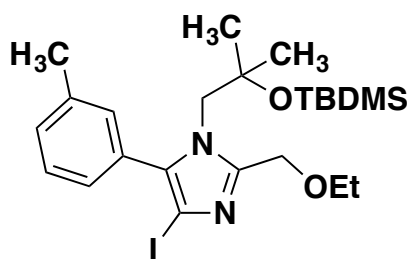
1430 dryness. The residue obtained was purified via flash SiO₂ chromatography (10 g silica gel,
 1431 gradient of hexanes to 20% ethyl acetate/80% hexanes) to give 5-([1,1'-biphenyl]-3-yl)-1-
 1432 (2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-4-iodo-1*H*-
 1433 imidazole(**61**) (13 mg, 21%) as a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.67-7.58 (m,
 1434 4H), 7.50 (dt, *J* = 19.6, 7.7 Hz, 3H), 7.41-7.30 (m, 2H), 4.75 (s, 2H), 4.19 (s, 2H), 3.58 (q,
 1435 *J* = 7.0 Hz, 2H), 1.25 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 6H), 0.78 (s, 9H), -0.02 (s, 6H); ¹³C
 1436 NMR (101 MHz, CDCl₃) δ 149.20, 141.63, 140.42, 135.96, 131.09, 129.47, 129.27,
 1437 129.11, 127.69, 127.17, 84.76, 74.26, 66.00, 65.63, 55.83, 28.59, 25.96, 18.03, 15.13, -
 1438 2.02.
 1439



1440
 1441 **1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-4-iodo-5-(*o*-**
 1442 **tolyl)-1*H*-imidazole (**62**)**

1443 To a solution of 1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-5-
 1444 (*o*-tolyl)-1*H*-imidazole(**62**)(186mg, 0.46 mmol) in *N,N*-dimethylformamide (5 mL) at
 1445 60 °C was added a solution of *N*-iodosuccinimide (125 mg, 0.56 mmol) in *N,N*-
 1446 dimethylformamide (1 mL) and the solution was allowed to stir 60 °C for 12 hours. After
 1447 this time, water (10 mL) was added, solid sodium thiosulfate pentahydrate was added
 1448 until no further color change was observed, and the resulting mixture was extracted with
 1449 ethyl acetate (3 x 10 mL). The combined organic layers were washed with 5% aqueous
 1450 lithium chloride (3 x 30 mL), washed with saturated aqueous sodium chloride (30 mL),

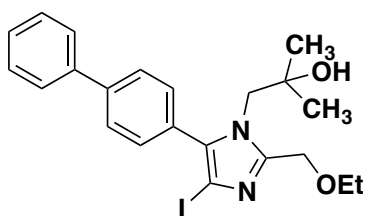
1451 dried over magnesium sulfate, filtered and concentrated to dryness. The residue obtained
1452 was purified via flash SiO₂ chromatography (10 g silica gel, gradient of hexanes to 16.7%
1453 ethyl acetate/83.3% hexanes) to give 1-(2-((*tert*-butyldimethylsilyl)oxy)-2-
1454 methylpropyl)-2-(ethoxymethyl)-4-iodo-5-(*o*-tolyl)-1*H*-imidazole(**62**)(200 mg, 82%) as a
1455 yellow oil; ¹H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.27 (m, 3H), 7.25 – 7.14 (m,
1456 1H), 4.85 – 4.67 (m, 2H), 4.11 (d, *J* = 14.5 Hz, 1H), 3.78 (d, *J* = 14.5 Hz, 1H), 3.54 (dq, *J* = 9.5, 7.0, 4.1 Hz, 2H), 2.17 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.96 (s, 3H), 0.93 (s, 3H),
1457 0.79 (s, 9H), 0.00(s, 6H).



1460 **1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-4-iodo-5-(*m*-**
1461 **tolyl)-1*H*-imidazole (**63**)**

1462 To a solution of 1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-5-
1463 (*m*-tolyl)-1*H*-imidazole(**63**)(127mg, 0.32 mmol) in *N,N*-dimethylformamide (5 mL) at
1464 60 °C was added a solution of *N*-iodosuccinimide (127 mg, 0.56 mmol) in *N,N*-
1465 dimethylformamide (1 mL) and the solution was allowed to stir 60 °C for 12 hours. After
1466 this time, water (10 mL) was added, solid sodium thiosulfate pentahydrate was added
1467 until no further color change was observed, and the resulting mixture was extracted with
1468 ethyl acetate (3 × 10 mL). The combined organic layers were washed with 5% aqueous
1469 lithium chloride (3 × 30 mL), washed with saturated aqueous sodium chloride (30 mL),
1470 dried over magnesium sulfate, filtered and concentrated to dryness. The residue obtained

1471 was purified via flash SiO₂ chromatography (10 g silica gel, gradient of hexanes to 20%
 1472 ethyl acetate/80% hexanes) to give 1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-
 1473 2-(ethoxymethyl)-4-iodo-5-(*m*-tolyl)-1*H*-imidazole(**63**)(90 mg, 71%) as colorless oil; ¹H
 1474 NMR (400 MHz, Chloroform-*d*) δ 7.32 (t, *J* = 7.8 Hz, 1H), 7.24 – 7.12 (m, 3H), 4.73 (s,
 1475 2H), 4.12 (d, *J* = 14.3 Hz, 2H), 3.55 (q, *J* = 7.0 Hz, 2H), 2.40 (s, 3H), 1.23 (dt, *J* = 12.1,
 1476 7.2 Hz, 3H), 0.89 (s, 6H), 0.78 (s, 9H), -0.02 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ
 1477 148.93, 138.32, 136.16, 131.11, 130.42, 129.24, 128.52, 127.82, 84.25, 74.23, 65.92,
 1478 65.57, 55.67, 28.55, 25.96, 21.43, 18.03, 15.12, -2.03.

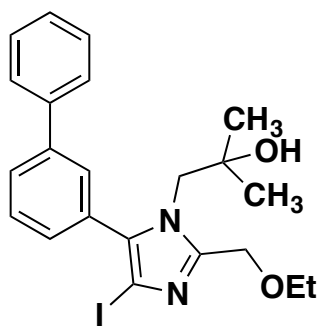


1479
 1480 **1-(5-([1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-iodo-1*H*-imidazol-1-yl)-2-**
 1481 **methylpropan-2-ol (3a)**

1482 To a solution of 5-([1,1'-biphenyl]-4-yl)-1-(2-((*tert*-butyldimethylsilyl)oxy)-2-
 1483 methylpropyl)-2-(ethoxymethyl)-4-iodo-1*H*-imidazole(**65**) (0.027 g, 0.05 mmol) in
 1484 tetrahydrofuran (5 mL) was added tetrabutylammonium fluoride (0.14 mL, 0.14 mmol, 1
 1485 M solution in tetrahydrofuran) and the solution was allowed to stir at room temperature
 1486 for 12hours. After this time, saturated aqueous ammonium chloride (10 mL) was added
 1487 and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic
 1488 layers were washed with saturated aqueous sodium chloride (10 mL), dried over
 1489 magnesium sulfate, filtered and concentrated to dryness. The residue obtained was
 1490 purified via flash SiO₂ chromatography (10 g silica gel, gradient of dichloromethane to 4%
 1491 methanol/96% dichloromethane) to give 1-(5-([1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-

1492 iodo-1*H*-imidazol-1-yl)-2-methylpropan-2-ol(**3a**) (0.021 g, 99%) as a yellow oil; ¹H
1493 NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 7.3 Hz, 2H), 7.47 (d, *J* =
1494 15.1 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 3H), 4.68 (s, 2H), 4.17 (s, 2H), 3.68 (q, *J* = 7.0 Hz, 2H),
1495 3.61 (s, 1H), 1.26 (d, *J* = 7.0 Hz, 3H), 0.93 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ
1496 147.61, 141.54, 140.02, 136.64, 131.26, 128.91, 128.82, 127.82, 127.36, 127.08, 84.98,
1497 70.45, 66.31, 64.61, 55.59, 27.74, 14.90. MS (ESI⁺), calcd C₂₂H₂₅IN₂O₂ (M+H) =
1498 477.1039, found = 477.1046.

1499



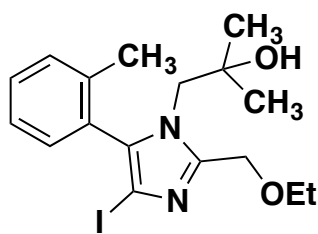
1500

1501 **1-(5-([1,1'-biphenyl]-3-yl)-2-(ethoxymethyl)-4-iodo-1*H*-imidazol-1-yl)-2-**
1502 **methylpropan-2-ol (**3b**)**

1503 To a solution of 5-([1,1'-biphenyl]-3-yl)-1-(2-((*tert*-butyldimethylsilyl)oxy)-2-
1504 methylpropyl)-2-(ethoxymethyl)-4-iodo-1*H*-imidazole(**66**)(0.013 g, 0.02 mmol) in
1505 tetrahydrofuran (5 mL) was added tetrabutylammonium fluoride (0.066 mL, 0.066 mmol,
1506 1 M solution in tetrahydrofuran) and the solution was allowed to stir at room temperature
1507 for 12 hours. After this time, saturated aqueous ammonium chloride (10 mL) was added
1508 and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic
1509 layers were washed with saturated aqueous sodium chloride (10 mL), dried over
1510 magnesium sulfate, filtered and concentrated to dryness. The residue obtained was
1511 purified via flash SiO₂ chromatography (10 g silica gel, gradient of dichloromethane to 4%

1512 methanol/96% dichloromethane) to give 1-(5-([1,1'-biphenyl]-3-yl)-2-(ethoxymethyl)-4-
1513 iodo-1*H*-imidazol-1-yl)-2-methylpropan-2-ol(**3b**)(0.010 g, 95%) as a yellow oil; ¹H NMR
1514 (400 MHz, CDCl₃) δ 7.71-7.54 (m, 5H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 1H),
1515 7.31 (d, *J* = 7.6 Hz, 1H), 4.71 (s, 2H), 4.20 (s, 2H), 3.71 (q, *J* = 7.0 Hz, 2H), 3.61 (s, 1H),
1516 1.29 (s, 3H), 0.95 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 147.58, 141.72, 140.23, 136.90,
1517 130.44, 129.71, 129.51, 129.22, 128.95, 127.79, 127.63, 127.15, 85.30, 70.45, 66.33,
1518 64.56, 55.63, 27.74, 14.89. MS (ESI⁺), calcd C₂₂H₂₅IN₂O₂ (M+H) = 477.1039, found =
1519 477.1046.

1520



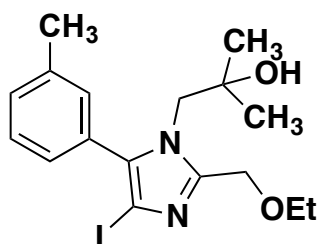
1521

1522 **1-(2-(ethoxymethyl)-4-iodo-5-(*o*-tolyl)-1*H*-imidazol-1-yl)-2-methylpropan-2-ol (3c)**

1523 To a solution of 1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-4-
1524 iodo-5-(*o*-tolyl)-1*H*-imidazole(69) (0.10 g, 0.19 mmol) in tetrahydrofuran (5 mL) was
1525 added tetrabutylammonium fluoride (0.28 mL, 0.28 mmol, 1 M solution in
1526 tetrahydrofuran) and the solution was allowed to stir at room temperature for 12 hours.
1527 After this time, saturated aqueous ammonium chloride (10 mL) was added and the
1528 mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were
1529 washed with saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate,
1530 filtered and concentrated to dryness. The residue obtained was purified via flash SiO₂
1531 chromatography (10 g silica gel, gradient of dichloromethane to 4% methanol/96%
1532 dichloromethane) to give 1-(2-(ethoxymethyl)-4-iodo-5-(*o*-tolyl)-1*H*-imidazol-1-yl)-2-

1533 methylpropan-2-ol (**3c**)(0.021 g, 99%) as a yellow solid; ¹H NMR (400 MHz,
1534 Chloroform-*d*) δ 7.39 – 7.27 (m, 3H), 7.16 (dd, *J* = 7.6, 1.4 Hz, 1H), 4.70 – 4.62 (m, 2H),
1535 4.07 (d, *J* = 14.9 Hz, 1H), 3.88 (s, 1H), 3.76 – 3.58 (m, 3H), 2.12 (s, 3H), 1.23 (t, *J* = 7.0
1536 Hz, 3H), 0.94 (d, *J* = 1.6 Hz, 6H). MS (ESI⁺), calcd C₁₇H₂₄IN₂O₂ (M+H) = 415.0882,
1537 found = 415.0889.

1538

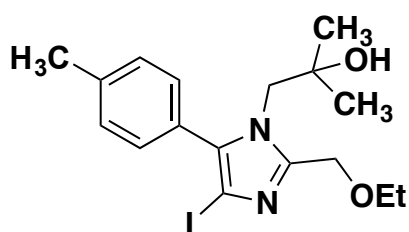


1539

1540 **1-(2-(ethoxymethyl)-4-iodo-5-(*m*-tolyl)-1*H*-imidazol-1-yl)-2-methylpropan-2-ol (3d)**

1541 To a solution of 1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-4-
1542 iodo-5-(*m*-tolyl)-1*H*-imidazole(70)(0.090 g, 0.17 mmol) in tetrahydrofuran (5 mL) was
1543 added tetrabutylammonium fluoride (0.60mL, 0.60 mmol, 1 M solution in
1544 tetrahydrofuran) and the solution was allowed to stir at room temperature for 12hours.
1545 After this time, saturated aqueous ammonium chloride (10 mL) was added and the
1546 mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were
1547 washed with saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate,
1548 filtered and concentrated to dryness. The residue obtained was purified via flash SiO₂
1549 chromatography (10 g silica gel, gradient of dichloromethane to 4% methanol/96%
1550 dichloromethane) to give 1-(2-(ethoxymethyl)-4-iodo-5-(*m*-tolyl)-1*H*-imidazol-1-yl)-2-
1551 methylpropan-2-ol(**3d**) (0.050 g, 71%) as a colorless oil; ¹H NMR (400 MHz,
1552 Chloroform-*d*) δ 7.38 (t, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 7.2 Hz,
1553 2H), 4.68 (s, 2H), 4.14 (s, 2H), 3.69 (q, *J* = 7.0 Hz, 2H), 3.64 (s, 1H), 2.44 (s, 3H), 1.27

1554 (d, $J = 7.1$ Hz, 3H), 0.93 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 147.29, 138.48, 137.11,
1555 131.42, 129.82, 129.73, 128.63, 128.00, 84.67, 70.39, 66.24, 64.56, 55.59, 27.67, 21.43,
1556 14.87. MS (ESI^+), calcd $\text{C}_{17}\text{H}_{24}\text{IN}_2\text{O}_2$ ($\text{M}+\text{H}$) = 415.0882, found = 415.0889.
1557



1558
1559 **1-(2-(ethoxymethyl)-4-iodo-5-(*p*-tolyl)-1*H*-imidazol-1-yl)-2-methylpropan-2-ol (3e)**
1560 To a solution of 1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-5-
1561 (*p*-tolyl)-1*H*-imidazole(**59**)(56mg, 0.12 mmol) in *N,N*-dimethylformamide (5 mL) at
1562 60 °C was added a solution of *N*-iodosuccinimide (30 mg, 0.13 mmol) in *N,N*-
1563 dimethylformamide (1 mL) and the solution was allowed to stir 60 °C for 12 hours. After
1564 this time, water (10 mL) was added, solid sodium thiosulfate pentahydrate was added
1565 until no further color change was observed, and the resulting mixture was extracted with
1566 ethyl acetate (3 × 10 mL). The combined organic layers were washed with 5% aqueous
1567 lithium chloride (3 × 30 mL), washed with saturated aqueous sodium chloride (30 mL),
1568 dried over magnesium sulfate, filtered and concentrated to dryness to obtain the crude
1569 product 1-(2-((*tert*-butyldimethylsilyl)oxy)-2-methylpropyl)-2-(ethoxymethyl)-4-iodo-5-
1570 (*p*-tolyl)-1*H*-imidazole(**64**) without further purification. Then tetrahydrofuran (5ml) and
1571 tetrabutylammonium fluoride (0.23 mL, 0.23 mmol, 1 M solution in tetrahydrofuran)
1572 were added separately and the solution was allowed to stir at room temperature for 17
1573 hours. After this time, saturated aqueous ammonium chloride (10 mL) was added and the
1574 mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were

1575 washed with saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate,
1576 filtered and concentrated to dryness. The residue obtained was purified via flash SiO₂
1577 chromatography (10 g silica gel, gradient of hexanes to 25% ethyl acetate/75% hexanes)
1578 to give 1-(2-(ethoxymethyl)-4-iodo-5-(*p*-tolyl)-1*H*-imidazol-1-yl)-2-methylpropan-2-
1579 ol(**3e**) (15 mg, 72%) as a yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 7.31 (s, 2H), 7.22
1580 (d, *J* = 8.1 Hz, 2H), 4.69 (s, 2H), 4.14 (s, 2H), 3.69 (q, *J* = 7.0 Hz, 2H), 2.44 (s, 3H), 1.26
1581 (t, *J* = 7.0 Hz, 3H), 0.93 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 147.22, 138.97, 137.04,
1582 130.76, 129.53, 126.87, 84.33, 70.38, 66.25, 64.54, 55.56, 27.66, 21.42, 14.88. MS (ESI⁺),
1583 calcd C₁₇H₂₄IN₂O₂ (M+H) = 415.0882, found =415.0889.