An Efficient and Convenient Synthesis of 4-Vinylimidazoles Using a Novel Horner–Wadsworth–Emmons (HWE) Reagent: Synthetic Studies Toward Novel Histamine H_3-Ligands

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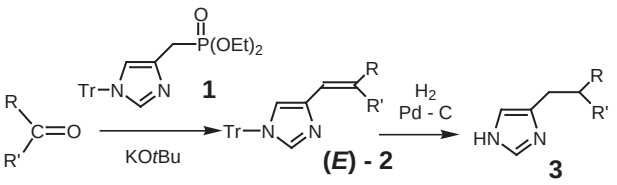
Abstract: A novel Horner–Wadsworth–Emmons (HWE)-type reagent **1** reacted readily with various aldehydes and ketones to produce (*E*)-vinylimidazoles **2** in good yields. The synthetic utility of **1** was demonstrated by the efficient preparation of four histamine H_3 ligands **3** by simple hydrogenation of **2**.

Key words: Horner–Wadsworth–Emmons reaction, vinylimidazole, hydrogenation, H_3 ligands , immepip

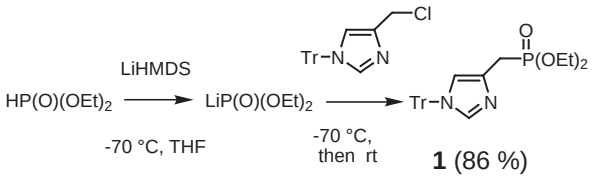


Scheme 1

Imidazoles are important as heterocyclic components of many drugs and biologically active molecules.[1,2] The C-4 substituted imidazole is a common and essential structural feature of the ligands for the histamine H_3 (H_3) receptor.[3] Further, it was shown that the current H_3 ligands have affinity for the novel H_4 (H_4) receptor,[4] which was identified by cloning and pharmacological characterization in 2000. However, only a limited synthetic method for the H_3 ligands has been employed, and many new H_3 ligands have been synthesized using readily available scaffolds like urocainic acid and histamine.[3] In continuation of our ongoing projects involving synthetic studies on novel H_3 and H_4 ligands,[5] we required a reliable and effective procedure for C-4 substituted imidazoles.

Griffith et al.[6] reported an improved synthesis of vinylimidazoles[7] via Horner–Wadsworth–Emmons (HWE) reaction of *N*-tritylimidazole-4-carboxaldehyde. However, to our knowledge, an HWE reagent incorporating a functional imidazole group has not been reported to date.[8] Herein, we report an efficient and convenient synthesis of vinyl imidazoles **2** using a novel HWE reagent **1** (Scheme 1), which reacts not only with a variety of aldehydes, but also ketones in the presence of KOBu-*t* to produce (*E*)-vinylimidazoles **2**. To demonstrate the utility of the novel HWE reagent **1**, an efficient synthesis of four current H_3 ligands was carried out by subsequent hydrogenation of **2**.

Michaelis–Becker reaction[9] of 4-(chloromethyl)-1-tritylimidazole[10] with lithium diethyl phosphonate, prepared in situ by treatment of diethyl phosphite with LiHMDS, generated diethyl (1-tritylimidazol-4-yl)methylphosphonate (**1**) in 86% yield, as air-stable needles (Scheme 2). This substitution gave a higher yield than the Arbuzov reaction[9] (<10%), which required higher reaction temperature (120 °C) and longer reaction time (12 h) in the case of 4-(chloromethyl)-1-tritylimidazole and triethyl phosphite.



Scheme 2

When we first attempted the HWE olefination of cyclohexanecarboxaldehyde using deprotonation of **1** with LiHMDS, *erthro*- (42%) and *threo*-diastereomers (8%) of β-hydroxyphosphonate **4** could be captured, accompanied with the desired vinylimidazole (*E*)-**2a** (34%) (Scheme 3), although direct observation of the intermediate (oxyanion of **4**) in the HWE reaction has not been generally possible.[8] Further, reaction of *threo*-**4** with NaH afforded the (*E*)-olefin **2a** (86%),[11] but that of *erythro*-**4** caused only a *retro*-HWE reaction, with recovery of phosphonate **1**. This result was consistent with the observation of Bottin-Strzalko et al.[12] that the *erythro* intermediate did not give the (*Z*)-olefin.

After investigation of the reaction under various conditions, phosphonate **1** was found to react readily with aldehydes, in the presence of *t*BuOK, to produce C-4 vinylimidazoles **2**,[13] which can be easily isolated by column chromatography owing to the readily removable trityl group. The scope of the olefination using **1** was

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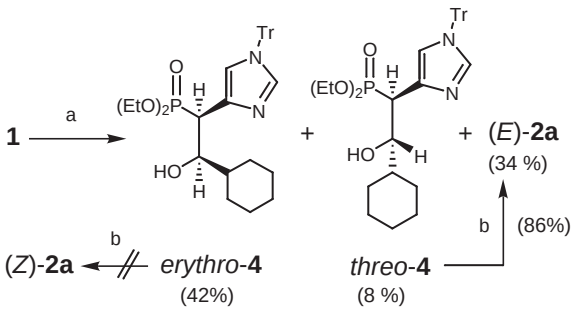


(a) (i) LiHMDS (1.0 eq), -70 °C, 1h; (ii) cyclohexanecarbaldehyde (1.0 equiv), -70 °C to rt, over 1h; (b) NaH, DMF, 50 °C

Scheme 3

examined as shown in Table 1. For all substrates, the reactions afforded selectively the *E*-double bond. Thus, phosphonate **1** reacted with aliphatic aldehydes (Table 1, entries 1–5), aromatic and heteroaromatic aldehydes (Table 1, entries 6–8) to give substituted (*E*)-vinylimidazoles in excellent yields. In the case of **2f** and **2h**, the vinyl and aromatic proton signals were overlapped in ^{1}H NMR, but their *E*-geometry was clearly determined by the vinyl proton signals shifted downfield of their deprotected vinylimidazoles, 4-[2-(4-butylphenyl)]vinyl-1*H*-imidazole hydrochloride (**5f**·HCl) and 4-(2-thiophen-2-yl)vinyl-1*H*-imidazole hydrochloride (**5h**·HCl) obtained by hydrolysis [e.g. **5f**·HCl: δ = 7.03 (d, 1 H, J = 16.7 Hz), 7.24 (d, 1 H, J = 16.7 Hz)]. Further, cinnamaldehyde afforded a dienylimidazole **2i** in good yield (Table 1, entry 9), while cyclohexanone afforded the corresponding **2j** in moderate yield (Table 1, entry 10).

Table 1 Synthesis of **2** Using **1**

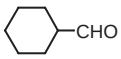
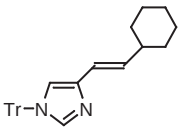
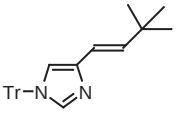
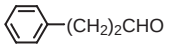
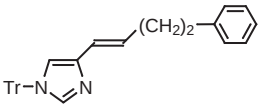
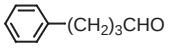
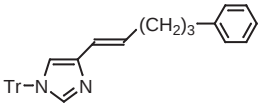
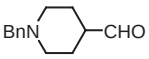
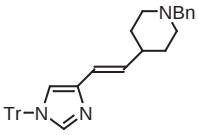
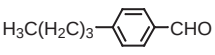
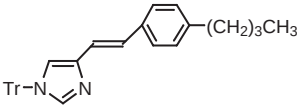
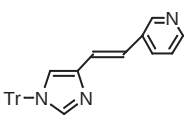
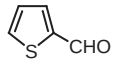
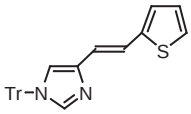
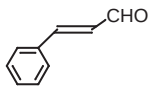
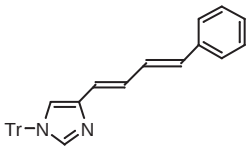
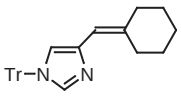
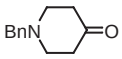
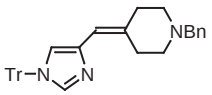
Entry	Substrate	Product	Yield (%)
1[a]		 **2a**	72[b]
2[c]		 **2b**	88
3[a]		 **2c**	56
4[d]		 **2d**	58[e]
5[e]		 **2e**	74
6[e]		 **2f**	99
7[c]		 **2g**	87

Table 1 Synthesis of **2** Using **1** (continued)

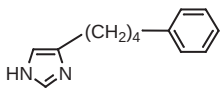
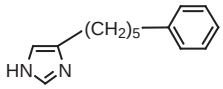
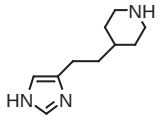
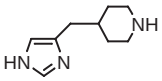
Entry	Substrate	Product	Yield (%)
8[c]		 **2h**	85
9[e]		 **2i**	68
10[c]		 **2j**	58
11[e]		 **2k**	99

[a] Reaction conditions: reflux, 3 h.
[b] The yield was based on **1** [**1** (1.0 equiv), aldehyde (1.2 equiv) and *t*BuOK (1.0 equiv)].
[c] Reaction conditions: reflux, 1 h.
[d] Reaction conditions: r.t., 14 h.
[e] Reaction conditions: reflux, 2 h.

De Esch et al.[14] reported a study on the influence of lipophilic moieties attached to a 4-1*H*-imidazole ring on the histamine H_3 receptor activity using H_3 antagonists VUF 5514 (pA_2 = 7.5) and VUF 5515 (pA_2 = 7.8). These compounds have been synthesized by reaction of the oxazoline intermediate with ammonia under heating in a stainless steel bomb. Compounds **2c** and **2d** thus obtained could be easily converted into VUF 5514 and VUF 5515 by their hydrogenation (10% Pd/C at 3.0 Kg/cm^2), respectively (Table 2, entries 1 and 2). Vinylimidazole **2e** similarly afforded a potent and selective H_3 antagonist VUF 4929[15] (pA_2 = 8.4) in a patent application (Table 2, entry 3). This two-step operation was further applied to an efficient synthesis of immepip (pD_2 = 8.0) which has been extensively used as an H_3 agonist. Immepip was first reported by Vollinga et al.[16], the synthesis of which was achieved by starting from 4-pyridine carboxaldehyde in 20% overall yield, via several steps involving hydrogenation at 50 atmosphere over Pd/C. The present synthetic approach readily provided immepip via **2k** from commercially available 1-benzyl-4-piperidone in nearly quantitative yield (Table 1, entry 11 and Table 2, entry 4).

The preparation of C-4 substituted imidazoles using phosphonate **1** is experimentally straightforward and particularly suitable for the study of novel histamine ligands. Considering the privileged position of imidazole compounds in medicinal chemistry, we believe that the reagent **1** will become a useful tool in the synthesis of bioactive molecules.

Table 2 Conversion of **2** into H_3 Ligands

Entry	Substrate	Product	Yield (%)
1	**2c**	 VUF 5514	90
2	**2d**	 VUF 5515	92
3	**2e**[a]	 VUF 4929	quant
4	**2k**[a]	 immepip	quant[b]

[a] Hydrochlodide of **2** was subjected to hydogenation.
[b] Isolated as dihydrochloride.

The melting points were determined on a hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were taken with tetramethylsilane as internal reference. Reactions with air- and moisture-sensitive compounds were carried out under argon. Unless otherwise noted, all extracts were dried over Na_2SO_4 or $MgSO_4$, and the solvent was removed in a rotary evaporator under reduced pressure. Chromatography was performed on silica gel. THF was distilled from sodium-benzophenone.

Diethyl (1-Tritylimidazol-4-yl)methylphosphonate (1)
Lithium hexamethyldisilazide (1 M in THF, 31.2 mL, 31.2 mmol) was added dropwise over 1 h to a solution of diethyl phosphite (4.30 g, 31.2 mmol) in anhyd THF (10 mL) at –70 °C under argon. A solution of 4-(chloromethyl)-1-tritylimidazole[10] (9.30 g, 26.0 mmol) in THF (80 mL) was then added dropwise to the resulting mixture over 0.5 h. After the reaction mixture was stirred for 15 min at the same temperature, it was allowed to reach r.t. and stirred for 3 h at this temperature. The mixture was diluted with sat. aq NH_4Cl (150 mL), and the THF was removed under reduced pressure. The resulting suspension was extracted with EtOAc (4 × 100 mL), and the organic phase was dried and evaporated. The resulting crude solid mass was purified by column chromatography [MeOH–EtOAc (1:20)] to give **1** (10.30 g, 86%) as a white powder. This was recrystallized from EtOAc–hexane to give white needles; mp 141–144 °C.

^{1}H NMR ($CDCl_3$): δ = 1.24 (t, 6 H, *J* = 8.0 Hz), 3.17 (d, 2 H, *J* = 21.6 Hz), 4.02 (quint, 4 H, *J* = 6.0 Hz), 6.81 (s, 1 H), 7.10–7.40 (m, 16 H).

^{31}P NMR ($CDCl_3$): δ = 27.0 (s).

MS (SIMS): *m*/*z* = 460 (M^+).

HRMS: *m*/*z* calcd for $C_{27}H_{29}N_2O_3P$ (M^+) 460.1914; found 460.1898.

Anal Calcd for $C_{27}H_{29}N_2O_3P$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.03; H, 7.32; N, 6.41.

Reaction of 1 with Cyclohexanecarboxaldehyde in the Presence of LiHMDS
LiHMDS (1 M in THF) (0.5 mL, 0.5 mmol) was added dropwise over 10 min to a solution of **1** (230 mg, 0.5 mmol) in THF (4 mL) at –70 °C with stirring, and the resulting yellow solution was stirred for 10 min. Cyclohexanecarboxaldehyde (56 mg, 0.5 mmol) in THF (4 mL) was then added dropwise over 5 min to the solution. After the reaction mixture had been stirred at –70 °C for 1 h, it was allowed to reach r.t. (25 °C) over 1 h. The resulting mixture was quenched with H_2O, and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc–hexane (1:1, 30 mL), and the organic layer was washed with H_2O (3 × 20 mL), dried, and evaporated to give a crude oil. Chromatography on silica gel using 20% EtOAc in hexane to EtOAc as eluent gave (*E*)-**2a** (70 mg, 34%), *erythro*-**4** (121 mg, 42%), *threo*-**4** (23 mg, 8%), and **1** (21 mg, 9%) in that order.

(*E*)-4-(2-Cyclohexylvinyl)-1-trityl-1*H*-imidazole (2a)
Needles; mp 197–200 °C (hexane–benzene).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.1–1.21 (m, 2 H), 1.21–1.35 (m, 2 H), 1.6–1.7 (br, 2 H), 1.7–1.82 (br, 4 H), 2.08 (br m, 1 H), 6.18 (d, 1 H, *J* = 16.0 Hz), 6.32 (dd, 1 H, *J* = 16.0, 6.9 Hz), 6.67 (s, 1 H), 7.1–7.2 (br s, 6 H), 7.3–7.4 (m, 10 H).

^{13}C NMR (D_2O): δ = 26.1, 26.2, 32.9, 40.8, 75.2, 118.1, 118.9, 128.0, 128.3, 129.7, 135.3, 138.9, 139.7, 142.4.

MS (EI, 70 eV): *m*/*z* = 418 (M^+).

HRMS: *m*/*z* calcd for $C_{30}H_{30}N_2$ (M^+) 418.2407; found 418.2404.

Anal Calcd for $C_{30}H_{30}N_2$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.03; H, 7.32; N, 6.41.

[2-Cyclohexyl-2-hydroxy-1-(1-trityl-1*H*-imidazol-4-yl)]diethyl Phosphonate (*erythro*-4)
Oil.

^{31}P NMR ($CDCl_3$–H_3PO_4): δ = 28.50.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00–1.30 (m, 1 H), 1.20 (t, 3 H, *J* = 7.2 Hz), 1.23 (t, 3 H, *J* = 7.2 Hz), 1.62–1.80 (br m, 10 H), 3.42 (dd, 1 H, J_{H-P} = 24.0, J_{H-H} = 1.9 Hz), 3.87 [td, 1 H, J_{H-P} = $J_{H-H(cyclohexyl)}$ = 9.6 Hz, 1.9 Hz], 3.90–4.12 (m, 4 H), 6.83 (dd, 1 H, *J* = 6.0, 3.0 Hz), 7.10–7.38 (m, 15 H), 7.41 (s, 1 H).

MS (EI, 70 eV): *m*/*z* = 573 (M^+ + 1).

HRMS: *m*/*z* calcd for $C_{34}H_{42}N_2O_4P$ (M^+ + 1), 573.2880; found, 573.2886.

***threo*-4**
Oil.

^{31}P NMR ($CDCl_3$–H_3PO_4): δ = 28.80.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, 3 H, *J* = 7.2 Hz), 1.23 (t, 3 H, *J* = 7.2 Hz), 1.40 (m, 1 H), 1.55–1.82 (br m , 10 H), 3.44 (dd, 1 H, J_{H-P} = 21.3, J_{H-H} = 8.0 Hz), 3.95 (m, 1 H), 4.00–4.16 (m, 4 H), 6.75 (dd, 1 H, *J* = 6.0, 3.0 Hz), 7.10–7.37 (m, 15 H), 7.41 (s, 1 H).

MS (SIMS): *m*/*z* = 573 (M^+ + 1).

HRMS: *m*/*z* calcd for $C_{34}H_{42}N_2O_4P$ (M^+ + 1) 573.2880; found, 573.2879.

Preparation of (*E*)-2a from *threo*-4
NaH (60% dispersion in oil, 0.5 mg, 0.013 mmol) was added in one portion to a stirred solution of *threo*-**4** (7 mg, 0.013 mmol) in anhyd DMF (0.5 mL). The reaction mixture was stirred at 50 °C for 1 h till formation of a white precipitate and diluted with EtOAc (20 mL). The organic layer was washed with H_2O (3 × 5 mL), dried, and evaporated to give a crude oil, which was subsequently purified by column chromatogrphy to give (*E*)-**2a** (4.4 mg, 86%).

Vinylimidazoles 2; General Procedure
*t*BuOK (67 mg, 0.6 mmol) was added to a mixture of phosphonate **1** (276 mg, 0.6 mmol) and the appropriate aldehyde (0.5 mmol) in THF (5 mL). The mixture was refluxed for 1–3 h under argon (TLC monitoring), and concentrated. After the addition of $CHCl_3$ (20 mL) and brine (20 mL), the organic layer was separated, and the aqueous layer was further extracted with $CHCl_3$ (2 × 20 mL). The combined organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (Table 1).

2a
Yield: 72%.

2b
Small needles; yield: 88%; mp 211–215 °C (EtOAc–hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (s, 9 H), 6.16 (d, 1 H, *J* = 16.2 Hz), 6.42 (d, 1 H, *J* = 16.2 Hz), 6.67 (s, 1 H), 7.10–7.40 (m, 16 H).

MS (EI, 70 eV): *m*/z = 392 (M^+).

HRMS: *m*/*z* calcd for $C_{28}H_{28}N_2$ (M^+), 392.2251; found, 392.2247.

Anal Calcd for $C_{28}H_{28}N_2$: C, 85.67; H, 7.19; N, 7.14. Found: C, 85.20; H, 7.14; N, 7.08.

2c
Viscous oil; yield: 56%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48 (q, 2 H, *J* = 8.4 Hz), 2.77 (t, 2 H, *J* = 8.4 Hz), 6.26 (d, 1 H, *J* = 15.6 Hz), 6.27–6.48 (dt, 1 H, *J* = 15.6, 8.4 Hz), 6.69 (s, 1 H), 7.00–7.60 (m, 15 H).

MS (EI, 70 eV): *m*/*z* = 440 (M^+).

HRMS: *m*/*z* calcd for $C_{32}H_{28}N_2$ (M^+), 440.2251; found, 440.2254.

2d
Viscous oil; yield: 58%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77 (quint, 2 H, *J* = 7.4 Hz), 2.20 (q, 2 H, *J* = 7.4 Hz), 2.66 (t, 2 H, *J* = 7.4 Hz), 6.23 (d, 1 H, *J* = 15.8 Hz), 6.36 (dt, 1 H, *J* = 15.8, 7.0 Hz), 6.66 (s, 1 H), 7.05–7.45 (m, 21 H).

MS (EI, 70eV): *m*/*z* = 454 (M^+).

HRMS: *m*/*z* calcd for $C_{33}H_{30}N_2$ (M^+), 454.2407; found, 454.2415.

2e
Viscous oil; yield: 74%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (qd, 2 H, *J* = 15.0, 4.4 Hz), 1.66–1.78 (dm, 2 H, *J* = 15.0 Hz), 1.92–2.23 (m, 3 H), 2.88–2.94 (dm, 2 H, *J* = 15.0 Hz), 3.49 (s, 2 H), 6.19 (d, 1 H, *J* = 15.5 Hz), 6.32 (dd, 1 H, *J* = 15.5, 6.7 Hz), 6.68 (s, 1 H), 7.05–7.40 (m, 21 H).

MS (EI, 70 eV): *m*/*z* = 509 (M^+).

HRMS: *m*/*z* calcd for $C_{36}H_{35}N_3$ (M^+), 509.2829; found, 509.2827.

2f
Prisms; yield: 99%; mp 157–159 °C (EtOAc–hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, *J* = 8.4 Hz), 1.35 (sext, 2 H, *J* = 8.4 Hz), 1.59 (quint, 2 H, *J* = 8.4 Hz), 2.58 (t, 2 H, *J* = 8.4 Hz), 6.85 (s, 1 H), 6.89 (d, 1 H, *J* = 16.4 Hz), 7.10–7.40 (m, 20 H), 7.45 (s, 1 H).

^{13}C NMR (CD_3OD): δ = 13.9, 22.4, 33.5, 35.4, 75.4, 119.3, 119.6, 126.1, 127.1, 128.1, 128.6, 129.8, 135.1, 139.3, 139.5, 141.9, 142.3.

MS (EI, 70 eV): *m*/*z* = 468 (M^+).

HRMS: *m*/*z* calcd for $C_{34}H_{32}N_2$ (M^+), 468.2564; found, 468.2563.

Anal Calcd for $C_{34}H_{32}N_2$: C, 87.14; H, 6.88; N, 5.98. Found: C, 87.04; H, 6.91; N, 5.98.

4-[2-(4-Butylphenyl)]vinyl-1*H*-imidazole Hydrochloride (5f·HCl)
To determine the (*E*)-geometry of **2f**, it was converted into the unsubstituted imidazole, **5f**·HCl as follows. A solution of **2f** (194 mg, 0.415 mmol) in aq 2 N HCl (6 mL)–EtOH (4 mL) was refluxed for 1 h and then diluted with H_2O (10 mL). After neutralization by addition of $NaHCO_3$, the mixture was extracted with $CHCl_3$ (5 × 10 mL). The extract was dried and evaporated to give a residue, which was subsequently chromatographed using MeOH–$CHCl_3$ (1:9) as eluent to give **5f** (74 mg, 80%) as an oil.

^{1}H NMR (500 MHz, CD_3OD): δ = 0.95 (t, 3 H, *J* = 8.4 Hz), 1.38 (sext, 2 H, *J* = 8.4 Hz), 1.60 (quint, 2 H, *J* = 8.4 Hz), 2.62 (t, 2 H, *J* = 8.4 Hz), 7.1 (br s, 4 H), 7.14 (d, 2 H, *J* = 7.9 Hz), 7.38 (d, 2 H, *J* = 7.9 Hz).

MS (SIMS): *m*/*z* = 227 (M^+ + 1).

HRMS: *m*/*z* calcd for $C_{15}H_{19}N_2$ (M^+ + 1), 227.1547; found, 227.1546.

5f·HCl
Viscous oil.

^{1}H NMR (500 MHz, CD_3OD): δ = 0.91 (t, 3 H, *J* = 8.4 Hz), 1.33 (sext, 2 H, *J* = 8.4 Hz), 1.58 (quint, 2 H, *J* = 8.4 Hz), 2.60 (t, 2 H, *J* = 8.4 Hz), 7.03 (d, 1 H, *J* = 16.7 Hz), 7.24 (d, 1 H, *J* = 16.7 Hz), 7.21 (d, 2 H, *J* = 7.6 Hz), 7.46 (d, 2 H, *J* = 7.6 Hz), 7.62 (s, 1 H), 8.92 (s, 1 H).

^{13}C NMR (CD_3OD): δ = 14.4, 23.3, 34.7, 36.4, 112.5, 117.0, 127.9, 130.0, 134.2, 134.4, 135.3.

2g
Viscous oil; yield: 87%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.91 (s, 1 H), 7.00 (d, 1 H, *J* = 17.0 Hz), 7.04–7.40 (m, 17 H), 7.47 (s, 1 H), 7.73 (d, 1 H, *J* = 8.1 Hz), 8.43 (br s, 1 H), 8.69 (br s, 1 H).

MS (SIMS): *m*/*z* = 414 (M^+ + 1).

HRMS: *m*/*z* calcd for $C_{29}H_{24}N_3$ (M^++1), 414.1969; found, 414.1979.

2h
White powder; yield: 85%; mp 204–207 °C (EtOAc–hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.75 (d, 1 H, *J* = 16.5 Hz), 6.82 (s, 1 H), 6.93–7.00 (m, 2 H), 7.10 (d, 1 H, *J* = 5.1 Hz), 7.12–7.20 (m, 6 H), 7.3–7.4 (br s, 10 H), 7.41 (s, 1 H).

MS (SIMS): *m*/*z* = 418 (M^+).

HRMS: *m*/*z* calcd for $C_{28}H_{22}N_2S_1$ (M^+), 418.1499; found, 418.1503.

Anal Calcd for $C_{28}H_{22}N_2S$: C, 80.35; H, 5.30; N, 6.69. Found: C, 80.05; H, 5.25; N, 6.63.

5h·HCl
A solution of **2h** (131 mg, 0.313 mmol) in aq 2 N HCl (4 mL)–EtOH (5 mL) was refluxed for 1 h to give **5h**·HCl (63 mg, 95%) as white powder using the same procedure as for the preparation of **5f**·HCl.

^{1}H NMR (300 MHz, CD_3OD): δ = 6.80 (d, 1 H, *J* = 16.4 Hz), 7.00 (dd, 1 H, *J* = 5.0, 3.6 Hz), 7.15 (d, 1 H, *J* = 3.6 Hz), 7.35 (d, 1 H, *J* = 16.4 Hz), 7.36 (d, 1 H, *J* = 5.0 Hz), 7.50 (s, 1 H), 8.68 (S, 1 H).

2i
Needles; yield: 68%; mp 225–228 °C (EtOAc–hexane).

^{1}H NMR (300 MHz, CD_3OD): δ = 6.50 (d, 1 H, *J* = 15.3 Hz), 6.68 (d, 1 H, *J* = 15.3 Hz), 6.81 (s, 1 H), 6.88 (dd, 1 H, *J* = 15.3, 11.0 Hz), 7.05 (dd, 1 H, *J* = 15.3, 11.0 Hz), 7.15–7.20 (br s, 5 H), 7.26–7.44 (br s, 16 H).

Anal Calcd for $C_{32}H_{26}N_2$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.21; H, 5.97; N, 6.31.

2j
White powder; yield: 58%; mp 222–223 °C (EtOAc–hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (m, 6 H), 2.23 (m, 2 H), 2.64 (m, 2 H), 5.98 (s, 1 H), 6.65 (s, 1 H), 7.10–7.38 (m, 15 H), 7.40 (s, 1 H).

MS (EI, 70 eV): *m*/*z* = 404 (M^+).

HRMS: *m*/*z* calcd for $C_{29}H_{28}N_2$ (M^+), 404.2251; found, 404.2248.

Anal Calcd for $C_{29}H_{28}N_2$: C, 86.10; H, 6.98; N, 6.92. Found: C, 86.21; H, 6.97; N, 6.90.

4-(4-Phenylbutyl)-1*H*-imidazole (VUF5514)[14]
A solution of **2c** (252 mg, 0.57 mmol) in MeOH–EtOAc (1:3, 10 mL) was hydrogenated with 10% Pd/C (150 mg) as catalyst at a initial pressure of 3.0 kg/cm^2 for 15 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated to give a crude oil, which was subsequently purified by column chromatography using MeOH–CH_2Cl_2 (1:9) as eluent to give VUF5514 (103 mg, 90%) as a viscous oil.

^{1}H NMR (300 MHz, CD_3OD): δ = 1.70 (m, 4 H), 2.26 (m, 4 H), 4.40–5.80 (br s, 1 H), 7.78 (s, 1 H), 7.10–7.20 (m, 5 H), 7.56 (s, 1 H).

MS (SIMS): *m*/*z* = 201 (M^+ + 1).

HRMS: *m*/*z* calcd for $C_{13}H_{17}N_2$ (M^+ + 1), 201.1391; found, 201.1396.

4-(4-Phenylpentyl)-1*H*-imidazole (VUF5515)[14]

This compound was synthesized from **2d** (132 mg, 0.29 mmol) according to the synthetic procedure for VUF5514 and was obtained as a colorless oil in 92% yield.

^{1}H NMR (300 MHz, CD_3OD): δ = 1.30–1.50 (m, 2 H), 1.60–1.80 (m, 4 H), 2.61 (t, 2 H, *J* = 7.6 Hz), 2.64 (t, 2 H, *J* = 7.6 Hz), 7.08–7.36 (m, 6 H), 8.45 (s, 1 H).

MS (SIMS): *m*/*z* : 215 (M^+ + 1).

HRMS: *m*/*z* : calcd for $C_{14}H_{19}N_2$ (M^+ + 1), 215.1547; found, 201.1551.

Preparation of Immepip [4-(1*H*-imidazol-4-yl)methylpiperidine] via 2k

2k

Phosphonate **1** (276 mg, 0.6 mmol) and KOBu-*t* (67 mg, 0.6 mmol) were added to a solution of 1-benzyl-4-piperidone (95 mg, 0.5 mmol) in THF (6 mL). After the reaction mixture was refluxed for 2 h, sat. aq NH_4Cl (1 mL) was added and evaporated. The residue was dissolved with saturated aq NH_4Cl (10 mL) and extracted with $CHCl_3$ (3 × 20 mL), and the $CHCl_3$ layer was dried ($MgSO_4$) and evaporated. The resulting oily residue was purified by column chromatography (EtOAc) to give **2k** (246 mg, 99%) as a colorless viscous oil.

^{1}H NMR (300MHz, $CDCl_3$): δ = 2.30–2.40 (m, 2 H), 2.42–2.60 (m, 4 H), 2.79–2.90 (m, 2 H), 3.52 (s, 2 H), 6.02 (s, 1 H), 6.66 (s, 2 H) 7.08–7.44 (m, 21 H).

MS (EI, 70eV): *m*/*z* = 495 (M^+).

HRMS: *m*/*z*: 495.2681 (calcd for $C_{35}H_{33}N_3$: 495.2673).

Immepip·2HCl

A solution of **2k** (162 mg, 0.327 mmol) in aq 1 N HCl (1.5 mL)–EtOH (5 mL) was stirred at r.t. for 10 min, and evaporated to give a residue (**2k**·2HCl). A solution of the dihydrochloride in MeOH (20 mL) was subsequently hydrogenated with 10% Pd/C (120 mg) as catalyst at an initial pressure of 3.0 kg/cm^2 for 15 h. The catalyst was removed by filtration and the filtrate was concentrated to give a residue, which was subsequently dissolved with H_2O (20 mL). The aqueous solution was washed with benzene (3 × 20 mL) and evaporated to give immepip·2HCl (80 mg, quant) as a white powder; mp 235–239 °C.

^{1}H NMR (500 MHz, CD_3OD): δ = 1.52 (m, 2 H), 1.92 (d, 2 H, *J* = 13.0 Hz), 2.02 (br, 1 H), 2.77 (d, 2 H, *J* = 7.0 Hz), 3.01 (t, 2 H, *J* = 13.0 Hz), 3.41 (d, 2 H, *J* = 13.0 Hz), 7.42 (s, 1 H), 8.85 (s, 1 H).

^{13}C NMR (CD_3OD): δ = 29.4, 31.4, 34.7, 45.0, 118.0, 132.7, 135.0.

MS (EI, 70 eV): *m*/*z* = 165 (M^+).

HRMS: *m*/*z* calcd for $C_9H_{15}N_3$ (M^+) 165.1265; found 165.1263.

The dihydrochloride thus obtained was further confirmed by conversion into immepip·2HBr synthesized by Vollinga et al.[16]

Immepip

To a MeOH solution of the immepip·2HCl was added a small amount of Chromatorex NH-DM 1020. The solvent was evaporated to give a coated silica gel, which was subsequently placed on a column (Chromatorex NH-DM 1020). Chromatography using $CHCl_3$–MeOH–28% NH_4OH (50:2:1) as the eluent gave immepip (48 mg, 89% from **2k**) as a colorless oil.

^{1}H NMR (CD_3OD): δ = 1.10 (qd, 2 H, *J* = 13.0, 5.0 Hz), 1.63 (dm, 3 H, *J* = 13.0 Hz), 2.49 (tm, 4 H, *J* = 13.0 Hz, 4 H), 2.95 (dm, 2 H, *J* = 13.0 Hz), 6.67 (s, 1 H), 7.46 (s, 1 H).

Immepip·2HBr

50% Aq HBr solution (240 mg, 5 equiv) was added to a solution of immepip (48 mg) in EtOH (20 mL). The mixture was stirred at r.t. for 15 min and evaporated to give a residue, which was subsequently washed with acetone (4 × 3 mL) and dried to give immepip·2HBr (95 mg, quant) as white powder; mp 237–239 °C (Lit.[16b] mp 221.1–222.7 °C).

^{1}H NMR (D_2O): δ = 1.46 (qd, 2 H, *J* = 13.0, 5.0 Hz), 1.92 (dm, 2 H, *J* = 13.0 Hz), 1.99 (m, 1 H), 2.75 (d, 2 H, *J* = 7.0 Hz), 2.99 (tm, 2 H, *J* = 13.0 Hz, 2 H), 3.43 (dm, 2 H, *J* = 13.0 Hz), 7.28 (s, 1 H), 8.59 (s, 1 H).

^{13}C NMR (D_2O): δ = 29.2, 31.3, 34.4, 45.3, 117.8, 132.4, 134.5.

Anal Calcd for $C_9H_{15}N_3$·2HBr: C, 33.05; H, 5.24; N, 12.85. Found: C, 32.80; H, 5.24; N, 12.70.

4-(1*H*-Imidazol-4-yl)ethylpiperidine (VUF4929)[15]

Vinylimidazole **2e** (196 mg, 0.385 mmol) was converted into VUF4929 (68 mg, quant, free amine) according to the synthetic procedure of immepip described above.

^{1}H NMR (300 MHz)(CD_3OD): δ = 1.19 (qd, 2 H, *J* = 13.0, 3.5 Hz), 1.36–1.52 (m, 2 H), 1.60 (q, 2 H, *J* = 7.2 Hz), 1.70–1.82 (dm, 2 H, *J* = 13.0 Hz), 2.50–2.70 (m, 4 H), 3.00–3.10 (dm, 2 H, *J* = 13.0 Hz), 6.78 (s, 1 H), 7.59 (s, 1 H).

VUF4929·2HCl

The free amine was stirred with aq 1 N HCl–EtOH at r.t. for 15 min and evaporated to give VUF4929·2HCl as a white powder; mp 216–220 °C.

^{1}H NMR (500 MHz, CD_3OD): δ = 1.47 (qd, 2 H, *J* = 13.0, 3.5 Hz), 1.65–1.75 (m, 3 H), 1.97–2.04 (dm, 2 H, *J* = 13.0 Hz), 2.80 (t, 2 H, *J* = 7.2 Hz), 3.00 (t, 2 H, *J* = 13.0 Hz), 3.37–3.43 (dm, 2 H, *J* = 13.0 Hz), 7.36 (s, 1 H), 8.81 (s, 1 H).

^{13}C NMR (CD_3OD): δ = 22.4, 29.7, 34.2, 35.6, 45.2, 116.8, 134.7, 135.3.

MS (EI, 70eV): *m*/*z* = 179 (M^+).

HRMS: *m*/*z* calcd for $C_{10}H_{17}N_3$ (M^+), 179.1422; found, 179.1424.

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