Monocyclic, Substituted Imidazoles as Glycosidase Inhibitors

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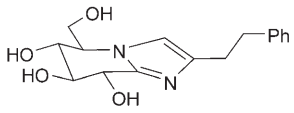
Dedicated to the Memory of *Jacques van Boom*

A range of 4-monosubstituted and 2,4-disubstituted 1*H*-imidazoles and 1*H*-imidazole-1-ethanols (R–C(4): CH_2CH_2Ph, $CHOHCH_2Ph$, Ph, or Me; R–C(2): CH_2OH, $CHOHCH_2OH$, CN, or CH_2NHAc) were prepared and tested as inhibitors of α- and β-glucosidases and of a β-galactosidase. A new access to 4-(2-phenylethyl)-1*H*-imidazoles starting from 4-phenylbutan-1-ol was elaborated. The strongest inhibitors are the 2-substituted 4-(2-phenylethyl)-1*H*-imidazoles **24a** and **26a** (R–C(2): CH_2OH and $CHOHCH_2OH$) and the 2-phenylethanol **34**. They inhibit the β-galactosidase from bovine liver and the β-glucosidase from *Caldocellum saccharolyticum* with inhibition constants in the micromolar range, but do not inhibit the α-glucosidase from brewer's yeast.

Introduction. – Tetrahydropyrido-azoles, particularly tetrahydropyridoimidazoles, are strong, mostly competitive, or mixed-type inhibitors of β-D-glycopyranosidases with inhibition constants in the micro- to low nanomolar range [1]. The *C(2)*-substituent significantly affects the inhibitory activity, as shown by comparing the inhibition by **1**, possessing a 2-(2-phenylethyl) substituent and so far the best inhibitor ($K_i = 0.1$ nM) of the β-glucosidase from *Caldocellum saccharolyticum* (family 1) to the inhibition by the related unsubstituted tetrahydropyridoimidazole **2** ($K_i = 20$ nM), or the aminomethyl derivative **3** ($IC_{50} = 150$ nM) [2]. These imidazoles are also strong inhibitors of the β-glucosidases from sweet almonds ($K_i = 1.2$ (**1**) and 100 nM (**2**); $IC_{50} = 1600$ nM (**3**)).



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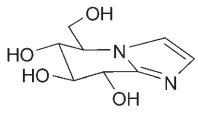

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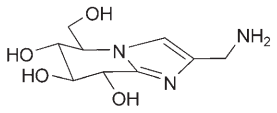

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Surprisingly, the much simpler 4-phenyl-1*H*-imidazole is also a strong inhibitor of sweet almond β-glucosidases ($K_i = 800$ nM [3]). This raises the question about the effect of the substituents of the imidazole ring that potentially mimic the aglycon, and of the polar substituents of the tetrahydropyridine ring corresponding to the substituents of the glycon moiety of the substrate. To shed some light on the relative importance of these substituents of tetrahydropyridoimidazoles, we intended to prepare substituted monocyclic imidazoles possessing some of the substituents that enhanced the inhibition by tetrahydropyridoimidazoles and further substituted

imidazoles that also possess part of the hydroxy or acetamido groups of the substrate glycon moiety, and to evaluate their inhibitory properties[1]).

The desired 2,4-disubstituted and 1,2,4-trisubstituted 1*H*-imidazoles can be prepared by condensation reactions or by alkylation of imidazoles. *N*-Alkylation followed by *C*-alkylation should lead to 1,4-dialkylated 1*H*-imidazoles, whereas alkylation of *N*-protected 1*H*-imidazoles preferentially affords 1,5-dialkylated 1*H*-imidazoles [6]. Moreover, the isomerisation of 1,5-disubstituted 1*H*-imidazoles into the 1,4-regioisomers was recently described [7].

Results and Discussion. – *Synthesis.* 4-(2-Phenylethyl)-1*H*-imidazole (**6**) [8–10] was prepared in four steps and in an overall yield of 4.1% from diethyl 2-benzylmalonate [8]. We developed an alternative procedure. *Swern* oxidation [11][12] of 3-phenylbutan-1-ol to the corresponding aldehyde **4** was followed by a mild bromination with *Amberlyst 26* (Br_3^- form) [13] to the bromoaldehyde **5** [14] (*Scheme 1*). Condensation of **5** with formamidine acetate [15] provided **6** in an overall yield of 23%. *N*-Alkylation of **6** with (2-iodoethoxy)benzene [16] gave a *ca.* 2:1 mixture of the 4- and 5-(2-phenylethyl)-substituted products **7** and **8**, respectively, which were separated by flash chromatography to afford 45% of **7** and 21% of **8**. Debenzylation of **7** with BBr_3 proceeded more rapidly and in higher yields (61%) than hydrogenolysis.

Similarly, alkylation of 4-methyl-1*H*-imidazole (**10**) with ethylene carbonate and $BF_3 \cdot OEt_2$ in DMSO [17][18] gave 40% of a 4:1 mixture of the 4- and 5-methylated 1*H*-imidazoles **11a** and **11b**, respectively, which were silylated to **12a** and **12b** (6:1 mixture, 49%; *Scheme 1*). Formylation of **12a**/**12b** 6:1 with BuLi and DMF in Et_2O gave **13a** and **13b** (7:1 mixture, 61%), which were separated by flash chromatography on silica gel *H*. The main aldehyde **13a** was reduced to the desired methanol **14** (85%), which was deprotected with CF_3CO_2H in MeOH to the diol **15** (76%). Bu_4NF (TBAF) $\cdot 3\ H_2O$ proved inconvenient for the desilylation, as it possesses a similar polarity as the product **15**.

The Ph group of 4-phenyl-1*H*-imidazole (**16**) [19] should protect N(3) against alkylation. Indeed, the reaction of **16** with ^{t}BuOK and ^{t}BuMe$_2$SiO(CH$_2$)$_2$Br [20] gave selectively the desired 4-phenylated 1*H*-imidazole **17** (49%) that was formylated to **18**, reduced to the methanol **19**, and desilylated with TBAF $\cdot 3\ H_2O$ to the diol **20** (56% overall yield).

The structure of 4- and 5-substituted 1*H*-imidazoles is readily assigned, since in 1-monosubstituted 1*H*-imidazoles the *d* of C(5) resonates 8–10 ppm upfield to the *d* of C(4) [21]. Thus, a *d* at 115.0–117.4 ppm and a large $\Delta\delta$ (17–22 ppm) reveals the 1,4-disubstitution in **7**, **9**, **11a**–**13a**, **14**, **15**, **17**, and **19** (see *Table 1* in the *Exper. Part*). In contradistinction, the downfield shift of the *d* at 125.4–126.7 ppm and a small $\Delta\delta$ (≤ 5 ppm) between this *d* and the *s* for C(5) evidences the 1,5-substitution in **8**, **11b**, and **12b**. The CHO group of **13a**, **13b**, and **18** leads to a strong downfield shift of the C(5) signal ($\Delta\delta = 8-10$ ppm), but to a distinctly weaker shift of the C(4) signal ($\Delta\delta \leq 4$ ppm). Together with ^5J(5,CHO) = 0.9 Hz of **13a** and **18** and ^5J(4,CHO) = 0 Hz of

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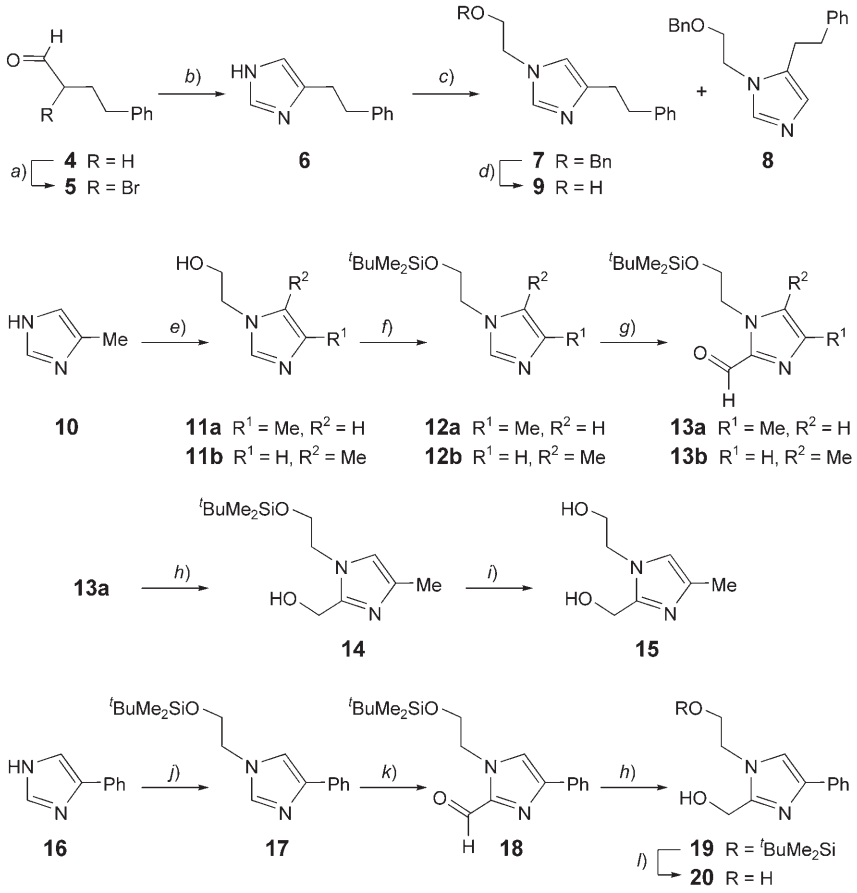
[1]) For the inhibition of *N*-acetyl-β-glucosaminidases by tetrahydropyridoazoles, see [4][5].

Scheme 1

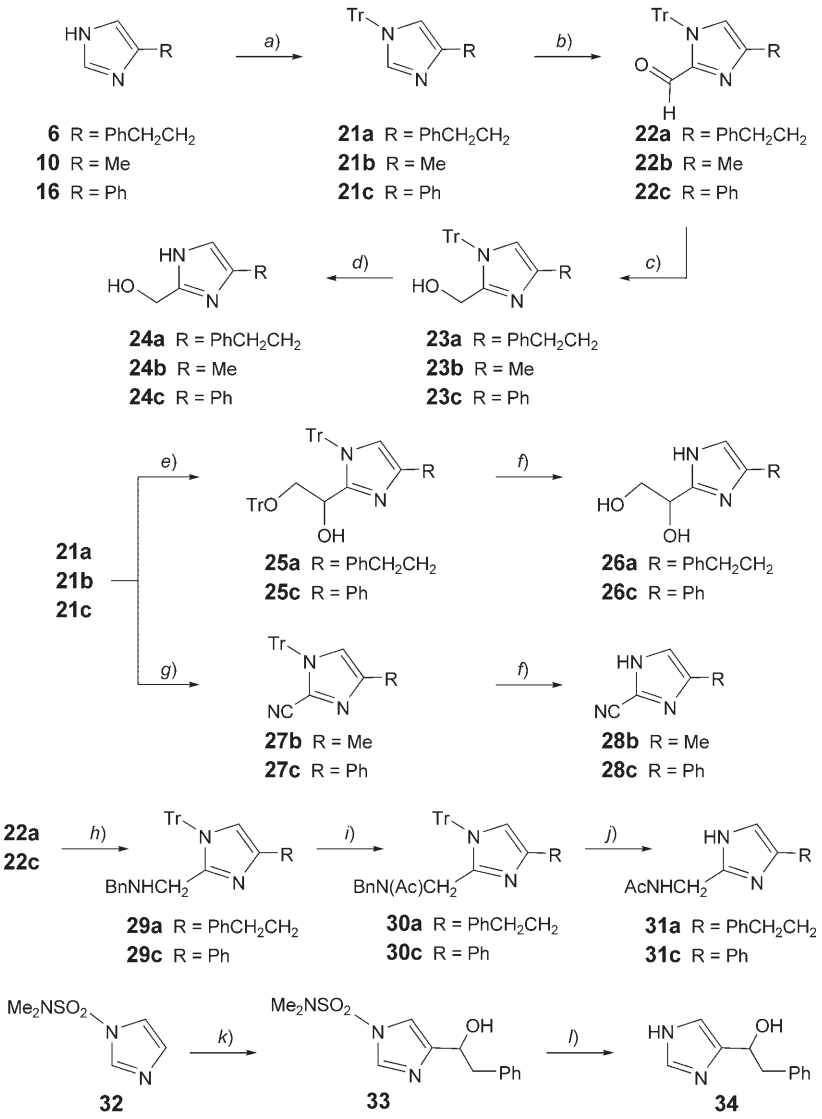


a) *Amberlyst 26* (Br_3^- form), CH_2Cl_2; 72%. *a*) Formamidine acetate, liq. NH_3; 39% (23% from 4-phenylbutan-1-ol). *c*) ^{t}BuOK, ^{t}BuOH, $BnOCH_2CH_2I$, DMF; 45% of **7**, 21% of **8**. *d*) BCl_3, CH_2Cl_2; 61%. *e*) Ethylene carbonate, $BF_3 \cdot Et_2O$, DMSO; 40% of **11a**/**11b** 4:1. *f*) ^{t}BuMe$_2$SiCl, Et_3N, 4-(dimethylamino)pyridine (DMAP), DMF; 49% of **12a**/**12b** 6:1. *g*) BuLi, DMF, Et_2O; 61% of **13a**/**13b** 7:1. *h*) $NaBH_4$, MeOH; 85% of **14**; 93% of **19**. *i*) CF_3CO_2H, MeOH; 76%. *j*) ^{t}BuOK, ^{t}BuOH, ^{t}BuMe$_2$SiOCH$_2$CH$_2$I, DMF; 49%. *k*) BuLi, DMF, THF; 61%. *l*) $Bu_4NF \cdot 3\ H_2O$, THF; 99%.

13b, this evidences a preferred s-*trans* orientation of the CHO group (as depicted in *Scheme 1*).

To access the 4-substituted 1*H*-imidazole-2-methanols, N(1) of **6**, **10**, and **16** was tritylated leading, in 88–98% yield, exclusively to the 4-substituted 1*H*-imidazoles **21a**, **21b** [22], and **21c** [23] [24], respectively (*Scheme 2*). Formylation of **21a**, **21b**, and **21c** was similar to the one of **15**, providing **22a**, **22b**, and **22c** [25] (66–75%) that were reduced to the methanols **23a**, **23b**, and **23c** (66–75%), respectively. Detritylation with AcOH in MeOH gave the disubstituted, *N*-unprotected imidazoles **24a** (91%), **24b** [26][27] (83%), and **24c** (54%), respectively.

Scheme 2



a) Trityl chloride (TrCl = triphenylmethyl chloride), Et_3N, DMF; 96% of **21a**, 88% of **21b**, 98% of **21c**. *b*) BuLi, DMF, THF; 66% of **22a**, 71% of **22b**, 75% of **22c**. *c*) $NaBH_4$, MeOH; 92% of **23a**, 93% of **23b**, 77% of **23c**. *d*) AcOH, MeOH; 91% of **24a**, 83% of **24b**, 54% of **24c**. *e*) BuLi, THF, then $TrOCH_2CHO$; 42% of **25a**, 72% of **25c**. *f*) AcOH/MeOH 1:2; 70% of **26a**, 52% of **26c**, 81% of **28b**, 61% of **28c**. *g*) BuLi, THF, then TsCN; 55% of **27b**, 64% of **27c**. *h*) $BnNH_2$, $MgSO_4$, CH_2Cl_2; $NaBH_4$, MeOH; 92% of **29a**, 80% of **29c**. *i*) Ac_2O, DMAP, THF; 85% of **30a**, 79% of **30c**. *j*) Na, NH_3/THF; 87% of **31a**, 37% of **31c**. *k*) BuLi, Et_3SiCl, THF; *s*-BuLi, BnCHO, THF; 2N HCl, 25°; 57%. *l*) 2N HCl, reflux; 94%.

Deprotonation of **21a** and **21c** with BuLi [28–30] and *in situ* reaction of the resulting 1*H*-imidazol-2-ides with $TrOCH_2CHO$ [28] led to the ditritylated glycols **25a** (42%) and **25c** (72%) which were deprotected to the 1*H*-imidazole-2-glycols **26a** (70%) and **26c** (52%), respectively (*Scheme 2*). Similarly, treatment of the 1*H*-imidazol-2-ides derived from **21b** and **21c** with TsCN gave the 1*H*-imidazole-2-carbonitriles **27b** (55% besides 38% of **21b**) and **27c** (64% besides 30% of **21c**), respectively, which were detritylated to **28b** (81%) and **28c** (61%). None of these carbonitriles reacted with $LiAlH_4$, and the desired 2-(acetamidomethyl)-1*H*-imidazoles **31a** and **31c** were synthesized from the aldehydes **22a** and **22c**. Treatment of **22a** and **22c** with $BnNH_2$ gave the corresponding methanimines, which were directly reduced with $NaBH_4$ in MeOH to the benzylamines **29a** and **29c** (85 and 79%, respectively). Acetylation of **29a** and **29c** to **30a** and **30c**, respectively, was followed by treatment with Na in liquid NH_3 which removed both the Bn and Tr groups to give the acetamides **31a** and **31c** (74 and 29% overall yield), respectively.

Another access to 4-(2-phenylethyl)-1*H*-imidazoles was investigated by starting with the sulfono-1*H*-imidazolide **32** [31] that was transformed in three steps [32], *viz.* silylation at C(2), alkylation at C(4), and desilylation, into the (1-hydroxy-2-phenylethyl)-1*H*-imidazole **33** (57%). Attempts to 2-phenylethylate **32** with 2-phenylethyl bromide failed; elimination to styrene was the main process. Hydrogenolytic dehydroxylation of **33** with H_2/Pd and other deoxygenation methods failed. Treating **33** with boiling 2N HCl cleaved the sulfonamide leading in 94% yield to the *N*-unsubstituted 2-phenylethanol **34**.

The ^{13}C-NMR spectra of the tritylamines **21**–**23** (each **a**–**c**), **25c**, **27b**, **27c**, **29**–**30** (each **a** and **c**), and of the sulfonamide **33** show the expected upfield shift for the *d* of C(5) at 114–120 ppm (weaker upfield shift for the aldehydes **22** (122.9–124.4 ppm) and nitriles **27a** and **27c** (120.5–122 ppm)) and a large $\Delta\delta$ between this *d* and the C(4) *s* of 16–23 ppm (smaller for the aldehydes **22** (10–17 ppm) and nitriles **27a** and **27c** (12–16 ppm); see *Table 2* in the *Exper. Part*). The CN substituent has a similar, but weaker influence upon the chemical shift of C(5) than the CHO group. The equilibrium between 1*H*- and 3*H*-imidazoles is evidenced by broadening of the signals for C(4) and C(5) and by a smaller $\Delta\delta$ for these signals that may go as far as coalescence [21]. The position of the equilibrium and the energy barrier between the isomers appear to strongly depend upon the imidazole substituents, as evidenced by comparing the NMR spectra of the phenylethanol **34** (coalescence of the C(4) and C(5) signals) and of the related 2-phenylethyl derivative **6** that shows some line broadening and a strong preference for the 4-substituted tautomer ($\Delta\delta$(C(4)/C(5)) = 19.4 ppm; *Table 1* in the *Exper. Part*). A similar preference of the 4-substituted tautomer is observed for the disubstituted 1*H*-imidazoles **24a**–**24c**, **26a**, **26c**, **28b**, **28c**, **31a**, and **31c** which show similar chemical shifts for C(4) and C(5) as their tritylated precursors ($\Delta\delta < 2.5$ ppm; 4 ppm for C(4) of **24b**).

Enzyme Inhibition. The 4-substituted *N*-unprotected 1*H*-imidazoles **6**, **10**, **16**, 4-benzyl-1*H*-imidazole [32], **24a**, **24b**, **24c**, **26a**, **26c**, **28b**, **28c**, **31a**, **31c**, and **34** as well as the 4-substituted 1*H*-imidazole-1-ethanols **9**, **11b**, **15**, and **20** were tested as inhibitors of the β-glucosidase from *Caldocellum saccharolyticum,* the β-galactosidase from bovine liver, and the α-glucosidase from brewer's yeast. IC_{50} Values lower than 5 mM against the β-glucosidase are listed in the *Figure* that also lists the K_i values of the best inhibitors against the β-glucosidase and the β-galactosidase.

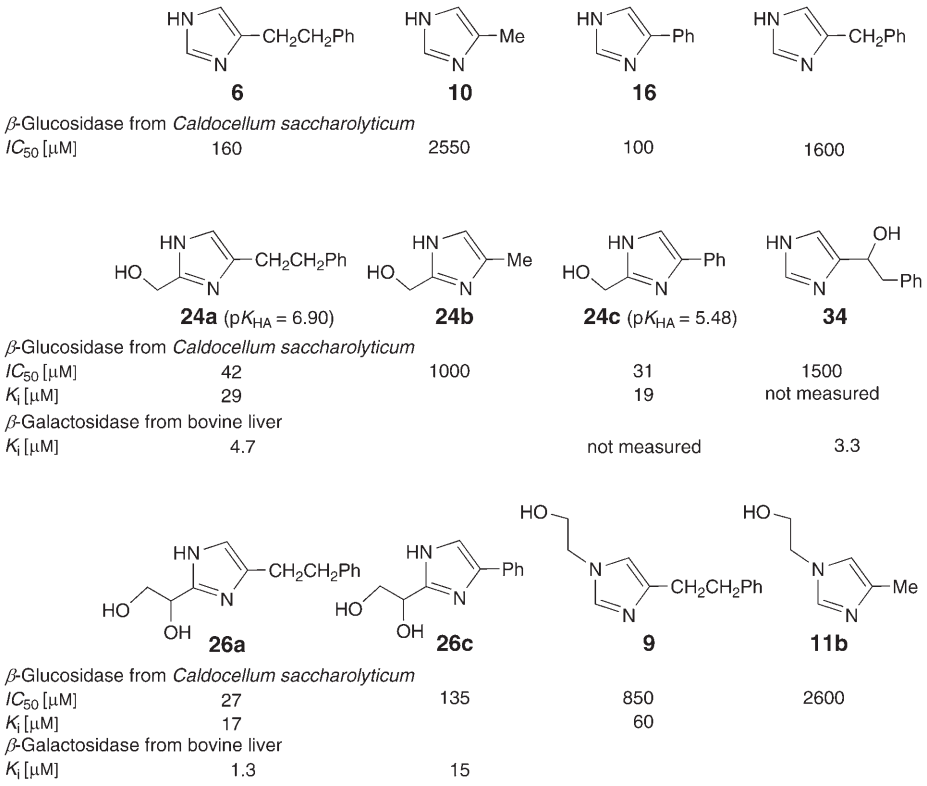


Figure. IC_{50} *and* K_i *values of 4-substituted* N*-unprotected 1*H*-imidazoles and of 4-substituted 1*H*-imidazole-1-ethanols*

Among the monosubstituted 1*H*-imidazoles, only the 2-phenylethyl and the phenyl derivatives **6** and **16**, respectively, showed a strong inhibition of the β-glucosidase from *Caldocellum saccharolyticum* ($IC_{50} = 160$ and 100 μM, resp.) that is, however, weaker than that of **16** against sweet almond β-glucosidases ($K_i = 800$ nM [3]). 4-Benzyl-1*H*-imidazole showed a 1.6 time stronger inhibition than the corresponding methylimidazole **10**, evidencing some effect of π-π stacking between the phenyl ring of the inhibitor and aromatic amino acid residues of the glucosidase. The 2-hydroxymethyl group in **24a**, **24b**, and **24c** increased the inhibition by a factor of 2.5–3.8. The 1*H*-imidazole-1-ethanols **9** and **11b** are weaker inhibitors than **6** and **10**, respectively; the $HOCH_2CH_2$ group hardly mimics the $HOCH_2$ substituent of the tetrahydropyridoimidazoles. A strong decrease of the inhibitory power is observed upon *N*-hydroxyethylation of **24c** ($IC_{50} = 31$ μM); the resulting **20** is only a very weak inhibitor. The assumption that AcNH substituents enhance the inhibitory power of 1*H*-imidazoles was not confirmed; **31a** and **31c** did not show any inhibition. Also the nitriles **28b** and **28c** were inactive. The strongest inhibitor was **26a** ($IC_{50} = 27$ μM) possessing a 1,2-dihydroxyethyl substituent. This 2-phenylethyl derivative is a five times better inhibitor than the corresponding phenyl analogue **26c**.

The 2-phenylethyl derivatives **24a** and **26a**, and the phenyl derivative **26c** are 6 to 13 times stronger inhibitors of the β-galactosidase from bovine liver than of the β-glucosidase from *C. saccharolyticum* (see *Fig.*). Noteworthy is the good inhibition of the β-galactosidase by the 2-phenylethanol **34** ($K_i = 3.3$ μM). The inhibitors **26a**, **26c**, and **34** are racemates; a rather strong inhibition is expected for one of their enantiomers. All compounds were inactive up to a concentration of 5 mM against the α-glucosidase from brewer's yeast.

The results confirm the importance of the precise interaction of all inhibitor substituents with a specific glycosidase, as realised for both the imidazole and the tetrahydropyridine ring substituents of many of the tetrahydropyridoimidazole-derived inhibitors. Considering, however, that a fair number of the strongest inhibitors of this type possessing a *C(2)*-substituent show a mixed-type or non-competitive inhibition [2][33][34], it is to be expected that their inhibition may be improved further by modifying the nature (and perhaps also the orientation) of the tetrahydropyridine ring substituents.

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Experimental Part

General. See [33]. Inhibition experiments were performed according to [33][35].

*4-(2-Phenylethyl)-1*H*-imidazole* (**6**) [8–10]. Formamidine acetate (2.85 g, 27 mmol) and **5** [14] (6.16 g, 27 mmol) were placed in a steel autoclave. NH_3 (100 g) was condensed into the vessel. After heating to 75° for 4 h, NH_3 was allowed to evaporate. The oily residue was transferred with MeOH into a 50-ml flask. After evaporation, the residue was suspended in $CHCl_3$ and the precipitate was filtered off. Evaporation of the filtrate, FC (700 g, $CHCl_3$/MeOH 9:1), and *Kugelrohr* distillation (190°/0.2 Torr) gave **6** (1.81 g, 39%). White solid. R_f ($CHCl_3$/MeOH 9:1) 0.26. M.p. 81–82° (AcOEt; [8]: 81°, [9]: 83–84°). IR and ^{1}H-NMR: see [10]. ^{13}C-NMR (50 MHz, $CDCl_3$): see *Table 1*; additionally, 139.32 (*s*); 126.08 (4*d*); 123.70 (*d*); 33.42 (*t*, C(2′)); 26.31 (*t*, C(1′)).

*1-[2-(Benzyloxy)ethyl]-4-(2-phenylethyl)-1*H*-imidazole* (**7**) *and 1-[2-(Benzyloxy)ethyl]-5-(2-phenylethyl)-1*H*-imidazole* (**8**). A suspension of **6** (344.5 mg, 2 mmol) and ^{t}BuOK (280 mg, 2.5 mmol) in ^{t}BuOH (15 ml) was heated to 80° for 45 min. After evaporation of ^{t}BuOH, the residue was suspended in DMF (4 ml), treated with a soln. of (2-iodoethoxy)benzene [16] (524 mg, 2 mmol) in DMF (6 ml), and heated to 70° for 30 min. After removal of DMF by *Kugelrohr* distillation *i.v.*, a soln. of the residue in $CHCl_3$ (40 ml) was washed twice with brine, dried ($MgSO_4$), and evaporated. FC (AcOEt/MeOH 97:3) gave **7** (272 mg, 45%) and **8** (128 mg, 21%).

Data of **7**: Colourless oil. R_f ($CHCl_3$/MeOH 9:1) 0.52. IR ($CHCl_3$): 2946*s*, 2863*s*, 1949*w*, 1877*w*, 1810*w*, 1672*m*, 1603*m*, 1498*s*, 1454*s*, 1355*m*, 1309*m*, 1165*m*, 1112*s*, 1029*m*, 994*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 1*; additionally, 7.37–7.15 (*m*, 10 arom. H); 4.47 (*s*, PhCH_2O); 4.00 (*t*, J = 5.3, BnOCH_2); 3.65 (*t*, J = 5.3, CH_2N) 3.03–2.86 (*m,* CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 1*; additionally, 142.56, 142.53 (2*s*); 128.75 (4*d*); 128.54 (2*d*); 127.89 (2*d*); 128.13, 126.04 (2*d*); 73.46 (*t*, PhCH_2O); 69,53 (*t*, BnOCH_2); 47.15 (*t*, CH_2N); 35.96 (*t*, PhCH_2CH_2); 30.49 (*t,* PhCH_2CH_2).

Data of **8**: Colourless oil. R_f ($CHCl_3$/MeOH 9:1): 0.42. IR ($CHCl_3$): 2950*s*, 2865*s*, 1949*w*, 1877*w*, 1813*w*, 1722*w*, 1604*m*, 1561*w*, 1496*s*, 1454*s*, 1355*m*, 1265*m*, 1111*s*, 1076*m*, 1029*m*, 922*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 1*; additionally, 7.35–7.14 (*m*, 10 arom. H); 4.45 (*s*, PhCH_2O); 3.92 (*t*, J = 5.3, BnOCH_2); 3.60 (*t*, J = 5.3, CH_2N) 2.96–2.78 (*m,* CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 1*; additionally, 141.33, 137.79 (2*s*); 128.76 (4*d*); 128.63 (2*d*); 127.86 (2*d*); 128.12, 126.35 (2*d*); 73.46 (*t*, PhCH_2O); 69,25 (*t*, BnOCH_2); 44.60 (*t*, CH_2N); 34.97 (*t,* PhCH_2CH_2), 26.13 (*t,* PhCH_2CH_2).

*4-(2-Phenylethyl)-1*H*-imidazole-1-ethanol* (**9**). A soln. of **7** (92 mg, 0.3 mmol) in CH_2Cl_2 (3 ml) was cooled to −78°, treated with 1M BCl_3 in CH_2Cl_2 (1.2 ml, 1.2 mmol), allowed to warm to 0° within 1 h, cooled to −78°, treated with H_2O (1 ml), warmed to r.t., diluted with CH_2Cl_2 (10 ml), and washed with aq. Na_2CO_3 soln. After extracting the aq. layers with CH_2Cl_2, the combined org. layers were dried ($MgSO_4$) and evaporated. FC ($CHCl_3$/MeOH 9:1) gave **9** (39 mg, 61%). White solid. R_f ($CHCl_3$/MeOH 9:1) 0.34. M.p. 122–123°

Table 1. *Selected ^1H- and ^{13}C-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the 1*H*-Imidazoles* **6**–**9**, **11**–**15**, *and* **17**–**20** *in $CDCl_3$*

	6[a])	**7**	**8**	**9**	**11a**	**11b**	**12a**	**12b**
H–C(2)	7.57	7.45	7.50	7.42	7.21	7.28	7.32	7.38
H–C(4)	–	–	6.84	–	–	6.56	–	6.70
H–C(5)	6.78	6.63	–	6.57	6.59	–	6.59	–
^4J(2,4)	–	–	0.9	–	–	1.2	–	1.2
^4J(2,5)	1.5	0.9	–	0.9	1.2	–	1.2	–
C(2)	132.14	137.02	137.68	136.80	136.27	137.02	136.81	137.58
C(4)	134.30	137.68	126.53	[b])	137.17	125.41	138.24	126.74
C(5)	115.10	115.88	131.50	115.74	115.59	127.16	115.97	127.17
	13a	**13b**	**14**	**15**[c])	**17**	**18**	**19**	**20**[c])
H–C(2)	–	–	–	–	7.54	–	–	–
H–C(4)	–	6.95	–	–	–	–	–	–
H–C(5)	6.95[d])	–	6.60	6.82	7.25	7.52[d])	7.14	7.50
^4J(5,Me)	0.6	0.6[e])	0.9	0.9	–	–	–	–
^4J(2,5)	–	–	–	–	1.2	–	–	–
C(2)	142.00	143.33	147.61	147.63	137.34	143.26	147.69	
C(4)	140.44	130.48	135.85	136.30	134.04	132.60	133.53	
C(5)	125.72	136.68	117.42	118.73	114.93	123.84	116.42	

[a]) ^{1}H-NMR Data from [10]. [b]) Hidden by the noise. [c]) In CD_3OD. [d]) ^5J(5,CHO) = 0.9 Hz. [e]) ^4J(4,Me).

(cyclohexane/toluene). IR ($CHCl_3$): 3608*w*, 3148*m* (br.), 2939*s*, 2860*s*, 1945*w*, 1868*w*, 1810*w*, 1603*m*, 1559*m*, 1499*s*, 1454*s*, 1438*m*, 1375*m*, 1355*m*, 1309*m*, 1164*s*, 1076*s*, 1050*m*, 999*m*, 866*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 1*; additionally, 7.28–7.15 (*m*, 5 arom. H); 4.28 (br. *s*, OH); 3.94, 3.83 (2*t*, *J* = 5.1, $HOCH_2CH_2N$); 2.95–2.86, 2.84–2.75 (2*m*, CH_2CH_2). ^{13}C-NMR (50 MHz, $CDCl_3$): see *Table 1*; additionally, 128.68 (2*d*); 128.52 (2*d*); 126.11 (*d*); 61.85 (*t*, CH_2OH); 49.93 (*t*, CH_2N); 35.66 (*t*, Ph*C*H_2CH_2); 30.06 (*t*, $PhCH_2CH_2$). Anal. calc. for $C_{13}H_{16}N_2O$ (216.28): C 72.19, H 7.46, N 12.95; found: C 72.06, H 7.33, N 12.85.

*2-(4-Methyl-1*H*-imidazol-1-yl)ethanol* (**11a**) *and 2-(5-Methyl-1*H*-imidazol-1-yl)ethanol* (**11b**). A soln. of **10** (4.11 g, 50 mmol), ethylene carbonate (9.0 g, 102 mmol), $BF_3 \cdot OEt_2$ (0.63 ml, 5 mmol) in DMSO (5 ml) was heated to 100° for 12 h. *Kugelrohr* distillation (160–200°/0.5–0.35 mm Hg) and FC (200 g, AcOEt/MeOH/conc. NH_4OH 92:5:3) of the distillate (2.95 g) gave **11a**/**11b** 4:1 (2.497 g, 40%). Brownish oil. R_f ($CHCl_3$/MeOH 9:1) 0.06. ^{1}H-NMR (300 MHz, $CDCl_3$, **11a**/**11b** 4:1): see *Table 1*; additionally, 5.20 (br. *s*, OH); 3.90 (*t*, *J* = 5.4, CH_2O); 3.79 (*t*, *J* = 5.4, CH_2N); 2.15 (*d*, *J* = 0.8, 0.6 H), 2.06 (*d*, *J* = 0.8, 2.4 H) (Me). ^{13}C-NMR (75 MHz, $CDCl_3$, **11a**/**11b** 4:1): see *Table 1*; additionally for **11a**: 61.23 (*t*, CH_2OH); 49.91 (*t*, CH_2N); 13.26 (*q*, Me); additionally for **11b**: 60.77 (*t*, CH_2OH); 47.34 (*t*, CH_2N); 9.31 (*q*, Me).

*1-{2-[(*tert*-Butyl)dimethylsilyloxy]ethyl}-4-methyl-1*H*-imidazole* (**12a**) *and 1-{2-[(*tert*-Butyl)dimethylsilyloxy]ethyl}-5-methyl-1*H*-imidazole* (**12b**). A soln. of **11a**/**11b** 4:1 (579 mg, 4.59 mmol), ^{t}BuMe$_2$SiCl (1.53 g, 10.18 mmol), and 4-(dimethylamino)pyridine (10 mg, 0.08 mmol) in DMF (5 ml) was treated with Et_3N (1.5 ml, 11 mmol), stirred for 7 h at 23°, and evaporated. A suspension of the residue in $CHCl_3$ was washed with aq. $NaHCO_3$ soln. (20 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. FC (80 g, AcOEt/MeOH 15:1) gave **12a**/**12b** 6:1 (537 mg, 49%). Colourless oil. R_f (AcOEt/MeOH 9:1): 0.38. ^{1}H-NMR (300 MHz, $CDCl_3$, **12a**/**12b** 6:1): see *Table 1*; additionally, 3.89 (*t*, *J* = 5.3, CH_2O); 3.75 (*t*, *J* = 5.3, CH_2N); 2.16 (*s*, 2.57 H), 2.15 (*s*, 0.43 H) (Me). ^{13}C-NMR (75 MHz, $CDCl_3$, **12a**/**12b** 6:1): see *Table 1*; additionally for **12a**: 63.02 (*t*, CH_2O); 49.54 (*t*, CH_2N); 25.92 (*q*, *Me*$_3$C); 18.34 (*s*, Me$_3$*C*); 13.81 (*q*, Me); –5.53 (*q*, Me_2Si); additionally for **12b**: 62.80 (*t*, CH_2O); 46.98 (*t*, CH_2N); 25.92 (*q*, *Me*$_3$C); 18.34 (*s*, Me$_3$*C*); 9.46 (*q*, Me); –5.58 (*q*, Me_2Si).

*1-{2-[(*tert*-Butyl)dimethylsilyloxy]ethyl}-4-methyl-1*H*-imidazole-2-carbaldehyde* (**13a**) *and 1-{2-[(*tert*-Butyl)dimethylsilyloxy]ethyl}-5-methyl-1*H*-imidazole-2-carbaldehyde* (**13b**). A soln. of **12a**/**12b** 6:1 (827 mg, 2.23 mmol) in Et_2O (10 ml) was cooled to –15°, treated with 1.6M BuLi in hexane (1.6 ml, 2.5 mmol), warmed to 23, stirred for 1 h, cooled to –10°, treated with DMF (0.52 ml, 6.69 mmol), warmed to 23°, stirred for 2 h, diluted with Et_2O (20 ml), and washed with H_2O. The combined org. layers were dried ($MgSO_4$) and

evaporated. FC (50 g, hexane/AcOEt 3:1) gave **13a**/**13b** 7:1 (563 mg, 61%). The isomers were separated by FC on silica gel H.

Data of **13a**: R_f (hexane/AcOEt 3:1) 0.19. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 1*; additionally, 9.69 (*d*, *J* = 0.9, CHO); 4.42 (*t*, *J* = 5.1, CH_2O); 3.82 (*t*, *J* = 5.1, CH_2N); 2.55 (*d*, *J* = 0.6, Me); 0.80 (*s*, Me_3C); −0.12 (*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 1*; additionally, 181.66 (*d*, CHO); 62.35 (*t*, CH_2O); 49.86 (*t*, CH_2N); 25.70 (*q*, *Me*$_3$C); 18.12 (*s*, Me$_3$*C*); 13.50 (*q*, Me); −5.77 (*q*, Me_2Si).

Data of **13b**: R_f (hexane/AcOEt 3:1) 0.17. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 1*; additionally, 9.68 (*s*, CHO); 4.37 (*t*, *J* = 5.1, CH_2O); 3.87 (*t*, *J* = 5.1, CH_2N); 2.30 (*d*, *J* = 0.6, Me); 0.76 (*s*, Me_3C); −0.15 (*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 1*; additionally, 181.10 (*d*, CHO); 62.82 (*t*, CH_2O); 47.05 (*t*, CH_2N); 25.83 (*q*, *Me*$_3$C); 18.25 (*s*, Me$_3$*C*); 10.06 (*q*, Me); −5.67 (*q*, Me_2Si).

*1-{2-[(*tert*-Butyl)dimethylsilyloxy]ethyl}-4-methyl-1*H*-imidazole-2-methanol* (**14**). A soln. of **13a** (0.221 g, 0.82 mmol) in MeOH (10 ml) was treated with $NaBH_4$ (0.10 g, 2.6 mmol), stirred for 1 h, and filtered. Evaporation of the filtrate and FC (30 g, AcOEt/MeOH 9:1) gave **14** (0.190 g, 85%). White solid. R_f (AcOEt/MeOH 9:1) 0.19. M.p. 100–103° (hexane). IR ($CHCl_3$): 3530–2900*m*, 2955*s*, 2930*s*, 2858*s*, 1575*w*, 1498*m*, 1472*s*, 1438*m*, 1389*m*, 1361*m*, 1302*m*, 1258*s*, 1171*m*, 1111*s*, 1066*m*, 1032*m*, 1007*m*, 925*s*, 838*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 1*; additionally, 4.58 (*s*, C*H*$_2$OH); 4.05 (*t*, *J* = 5.3, CH_2OSi); 3.85 (*t*, *J* = 5.3, CH_2N); 2.12 (*d*, *J* = 0.9, Me); 0.84 (*s*, Me_3C); −0.06 (*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 1*; additionally, 63.20 (*t*, CH_2OSi); 55.57 (*t*, CH_2OH); 48.27 (*t*, CH_2N); 25.83 (*q*, *Me*$_3$C); 18.25 (*s*, Me$_3$*C*); 13.01 (*q*, Me); −5.72 (*q*, Me_2Si). Anal. calc. for $C_{13}H_{26}N_2O_2Si$ (270.45): C 57.74, H 9.69, N 10.36; found: C 57.70, H 9.51, N 10.47.

*2-(Hydroxymethyl)-4-methyl-1*H*-imidazole-1-ethanol* (**15**). A soln. of **14** (229 mg, 0.85 mmol) in MeOH (5 ml) was treated with TFA (5 ml), heated to reflux for 30 min, and evaporated. FC (40 g, AcOEt/MeOH/conc. NH_4OH 90:7:3) gave **15** (101 mg, 76%). Colourless oil. R_f ($CHCl_3$/MeOH 4:1): 0.29. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 1*; additionally, 4.59 (*s*, HOC*H*$_2$–C(2)); 4.09 (*t*, *J* = 5.3, C*H*$_2$OH); 3.79 (*t*, *J* = 5.3, CH_2N); 2.13 (*d*, *J* = 0.9, Me). ^{13}C-NMR (75 MHz, CD_3OD): see *Table 1*; additionally, 62.47 (*t*, CH_2OH); 56.48 (*t*, $HOCH_2$–C(2)); 49.24 (*t*, CH_2N); 12.93 (*q*, Me).

*1-{2-[(*tert*-Butyl)dimethylsilyloxy]ethyl}-4-phenyl-1*H*-imidazole* (**17**). A soln. of **16** [19] (1.01 g, 7 mmol) and ^{t}BuOK (0.90 g, 8 mmol) in ^{t}BuOH (10 g) was heated to 80° for 45 min and evaporated. The residue was dissolved in DMF (15 ml) and treated with a soln. of ^{t}BuMe$_2$SiO(CH$_2$)$_2$Br [20] (1.68 g, 7 mmol) in DMF (5 ml) and heated to 70° for 1 h. After removal of DMF in a *Kugelrohr* apparatus, the residual semi-solid was partitioned between $CHCl_3$ and H_2O. After extraction of the aq. layer with $CHCl_3$, the combined $CHCl_3$ layers were dried ($MgSO_4$) and evaporated. FC (200 g, hexane/AcOEt 1:1) gave **17** (1.031 g, 49%). Colourless oil. R_f (hexane/AcOEt 1:1) 0.29. ^{1}H-NMR (200 MHz, $CDCl_3$): see *Table 1*; additionally, 7.80–7.75 (*m*, 2 arom. H); 7.41–7.33 (*m*, 2 arom. H); 7.26–7.19 (*m*, 1 arom. H); 4.05 (*t*, *J* = 5.0, CH_2O); 3.87 (*t*, *J* = 5.0, CH_2N); 0.88 (*s*, Me_3C); −0.01 (*s*, Me_2Si). ^{13}C-NMR (50 MHz, $CDCl_3$): see *Table 1*; additionally, 141.60 (*s*); 128.17 (2*d*); 126.20 (*d*); 124.33 (2*d*); 62.41 (*t*, CH_2O); 49.30 (*t*, CH_2N); 25.36 (*q*, *Me*$_3$C); 17.74 (*s*, Me$_3$*C*); −6.10 (*q*, Me_2Si).

*1-{2-[(*tert*-Butyl)dimethylsilyloxy]ethyl}-4-phenyl-1*H*-imidazole-2-carbaldehyde* (**18**). A soln. of **17** (1.031 g, 3.41 mmol) in THF (30 ml) was cooled to −10°, treated with 1.6M BuLi in hexane (2.5 ml, 4 mmol), warmed to 23°, stirred for 1 h, cooled to −5°, treated with DMF (0.52 ml, 6.69 mmol), warmed to 23°, and stirred for 2 h. After evaporation, a soln. of the oily residue in AcOEt (20 ml) was washed with brine, and the aq. layers were extracted with AcOEt. The combined org. layers were dried ($MgSO_4$) and evaporated. FC (90 g, hexane/AcOEt 3:1) gave **18** (693 mg, 61%). Colourless oil. R_f (hexane/AcOEt 3:1) 0.34. IR ($CHCl_3$): 2956*m*, 2930*m*, 2858*m*, 1681*s*, 1607*w*, 1546*w*, 1472*s*, 1449*s*, 1423*m*, 1400*w*, 1359*w*, 1275*m*, 1259*m*, 1112*s*, 1006*w*, 950*w*, 933*m*, 838*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 1*; additionally, 9.86 (*d*, *J* = 0.9, CHO); 7.81–7.78 (*m*, 2 arom. H); 7.45–7.39 (*m*, 2 arom. H); 7.34–7.28 (*m*, 1 arom. H); 4.55 (*t*, *J* = 5.0, CH_2O); 3.92 (*t*, *J* = 5.0, CH_2N); 0.83 (*s*, Me_3C); −0.08 (*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 1*; additionally, 181.96 (*s*, CHO); 142.50 (*s*); 128.50 (2*d*); 127.49 (*d*); 124.79 (2*d*); 61.88 (*t*, CH_2O); 49.81 (*t*, CH_2N); 25.28 (*q*, *Me*$_3$C); 17.66 (*s*, Me$_3$*C*); −6.25 (*q*, Me_2Si).

*1-{2-[(*tert*-Butyl)dimethylsilyloxy]ethyl}-4-phenyl-1*H*-imidazole-2-methanol* (**19**). A soln. of **18** (0.693 g, 1.95 mmol) in MeOH (20 ml) was treated with $NaBH_4$ (0.22 g, 5.84 mmol) and stirred for 2 h. Evaporation and FC (60 g, AcOEt/hexane 1:1) gave **19** (0.605 g, 93%). White solid. R_f (AcOEt) 0.38. M.p. 89–90° (hexane). IR ($CHCl_3$): 3596*w*, 3161*m* (br.), 2955*s*, 2931*s*, 2858*s*, 1608*w*, 1507*m*, 1463*s*, 1432*m*, 1389*m*, 1361*m*, 1258*s*, 1112*s*, 1068*m*, 1027*m*, 928*s*, 838*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 1*; additionally, 7.69–7.64 (*m*, 2 arom. H); 7.40–7.32 (*m*, 2 arom. H); 7.26–7.17 (*m*, 1 arom. H); 5.30 (br. *s*, *H*OCH$_2$); 4.75 (*s*, HOC*H*$_2$); 4.04 (*t*, *J* = 5.0, CH_2O); 3.83 (*t*, *J* = 5.0, CH_2N); 0.84 (*s*, Me_3C); −0.08 (*s*, Me_2Si). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 1*; additionally, 139.09 (*s*); 128.20 (2*d*); 126.20 (*d*); 124.26 (2*d*); 62.45 (*t*, CH_2OSi); 55.81 (*t*, $HOCH_2$); 48.00 (*t*,

Table 2. *Selected ^1H- and ^{13}C-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of the 1*H*-Imidazoles* **21**–**31**, **33**, *and* **34** *in* $CDCl_3$

	21a	**22a**	**23a**	**24a**[a])	**21b**[b])	**22b**	**23b**	**24b**[c])
H–C(2)	[c])	–	–	–	7.40	–	–	–
H–C(5)	6.40	6.50	6.30	6.75	6.56	6.72	6.43	6.72
^4J(2,5)	0.8	–	–	–	1.0	–	–	–
^4J(5,Me)	–	–	–	–	0.85	0.6	0.6	1.3
C(2)	138.49	144.09	149.54	148.82	137.83	144.81	149.43	147.47
C(4)	141.06	141.01	138.28	137.14	136.79	139.23	134.36	130.40
C(5)	118.52	123.74	118.31	117.88	117.71	124.40	118.08	116.45
	21c	**22c**	**23c**	**24c**[a])	**25a**	**26a**[a])	**25c**	**26c**[a])
H–C(2)	7.51	–	–	–	–	–	–	–
H–C(5)	7.14	[d])	7.10	7.33	6.22	6.72	7.03	7.32
^4J(2,5)	1.2	–	–	–	–	–	–	–
C(2)	139.52	145.64	150.05	149.54		149.23	149.71	150.79
C(4)	134.44	132.95	133.70	133.95		136.96	134.00	134.50
C(5)	117.61	122.87	117.55	116.45		117.69	117.15	116.78

	27b	**28b**[a])	**27c**	**28c**[a])	**29a**	**30a** ((*E*)/(*Z*) 3 : 2)	**31a**[a])
H–C(5)	6.81	6.99	[d])	7.64	6.30	6.40/6.35	6.60
^4J(5,Me)	0.6	0.6	–	–	–	–	–
C(2)	122.70	119.33	123.88	129.44	148.14	143.60/144.59	145.91
C(4)	138.73	137.07	132.22	130.81	140.44	138.18/137.68	138.24
C(5)	122.02	124.75	120.50	120.56	118.02	119.69/118.96	118.50
	29c	**30c** ((*E*)/(*Z*) 3 : 2)	**31c**[a])	**33**	**34**[a])		
H–C(2)	–	–	–	7.82	7.23		
H–C(5)	7.06	[d])	7.32	7.00	6.67		
^4J(2,5)	–	–	–	1.2	0		
^4J(5,Me)	–	–	–	–			
C(2)	148.69	145.27/146.28	146.91	136.80	136.19		
C(4)	133.84	134.26/134.75	134.10	137.90	[e])		
C(5)	116.76	118.68/118.26	116.88	113.98	[e])		

[a]) In CD_3OD. [b]) ^{1}H-NMR Data from [22]. [c]) ^{1}H-NMR in CD_3OD, ^{13}C-NMR in $CDCl_3$ (with 1 equiv. of AcOH). [d]) Hidden by the Ph signals at 7.45–7.00 ppm. [e]) Hidden due to coalescence.

CH_2N); 25.33 (*q*, *Me*$_3$C); 17.77 (*q*, Me$_3$*C*); −6.16 (*q*, Me_2Si). Anal. calc. for $C_{18}H_{28}N_2O_2Si$ (332.52): C 65.02, H 8.49, N 8.42; found: C 65.28, H 8.37, N 8.65.

*2-(Hydroxymethyl)-4-phenyl-1*H*-imidazole-1-ethanol* (**20**). A soln. of **19** (0.200 g, 0.622 mmol) in THF (5 ml) was treated with $Bu_4NF \cdot 3\,H_2O$ (0.216 g, 0.684 mmol) and stirred for 1 h at 23°. Evaporatation and FC (45 g, $CHCl_3$/MeOH 9 : 1) gave **20** (0.131 g, 99%). White solid. R_f ($CHCl_3$/MeOH 9 : 1) 0.13. M.p. 140–141° (AcOEt). IR (KBr): 3301*s*, 3069*s*, 2906*s*, 1604*m*, 1503*m*, 1487*s*, 1462*s*, 1427*s*, 1375*s*, 1354*s*, 1200*s*, 1095*s*, 1063*m*, 1024*s*, 976*s*, 877*m*, 801*s*. ^{1}H-NMR (200 MHz, CD_3OD): see *Table 1*; additionally, 7.73–7.68 (*m*, 2 arom. H); 7.39–7.30 (*m*, 2 arom. H) 7.26–7.17 (*m*, 1 arom. H); 4.73 (*s*, HOCH_2–C(2)); 4.23 (*t*, J = 5.2, CH_2O); 3.89 (*t*, J = 5.2, CH_2N). Anal. calc. for $C_{12}H_{14}N_2O_2$ (218.25): C 66.04, H 6.47, N 12.84; found: C 65.95, H 6.35, N 12.82.

*4-(2-Phenylethyl)-1-(triphenylmethyl)-1*H*-imidazole* (**21a**). A soln. of **6** (861 mg, 5 mmol) and chloro(triphenyl)methane (TrCl; 1.67 g, 16 mmol) in dry DMF (5 ml) was treated with Et_3N (0.85 ml, 6 mmol) and stirred overnight. The mixture was partitioned between $CHCl_3$ and H_2O and the aq. layer extracted with $CHCl_3$. The combined $CHCl_3$ layers were washed with brine, dried ($MgSO_4$), and evaporated. FC (70 g, AcOEt) of the oily residue gave **21a** (1.999 g, 96%). White solid. R_f (AcOEt/MeOH 9 : 1) 0.67. M.p. 158–159° (EtOH). IR ($CHCl_3$): 3088*m*, 2948*s*, 2859*w*, 1959*w*, 1815*w*, 1602*m*, 1560*w*, 1494*s*, 1446*s*, 1325*m*, 1156*m*, 1130*s*, 1088*m*, 1037*m*,

1002*m*, 907*m*, 870*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): see *Table 2*; additionally, 7.36–7.07 (*m*, 21 arom. H); 3.01–2.81 (*m,* CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 142.86 (3*s*); 142.29 (*s*); 130.04 (6*d*); 128.86 (3*d*); 128.41 (2*d*); 128.21 (6*d*); 128.15 (2*d*); 125.90 (*d*); 75.17 (*s*, Ph_3C); 35.66 (*t*, C(2′)); 30.34 (*t*, C(1′)). Anal. calc. for $C_{30}H_{26}N_2$ (414.55): C 86.92, H 6.32, N 6.76; found: C 86.91, H 6.50, N 6.78.

*4-(2-Phenylethyl)-1-(triphenylmethyl)-1*H-*imidazole-2-carbaldehyde* (**22a**). A soln. of **21a** (1.244 g, 3 mmol) in THF (65 ml) was cooled under Ar to 0°, treated with 1.6M BuLi in hexane (2.25 ml, 3.6 mmol), warmed to r.t., stirred for 1 h, cooled to 0°, treated with DMF (0.7 ml, 9 mmol) in one portion, warmed to r.t., stirred for 2 h, and evaporated. A soln. of the residue in AcOEt (50 ml) was washed with aq. NH_4Cl soln. and brine, dried ($MgSO_4$), and evaporated. FC (70 g, hexane/AcOEt 4:1) of the yellow oil gave **22a** (0.874 g, 66%). White solid. R_f (hexane/AcOEt 3:1) 0.16. M.p. 164–166° (EtOH). IR ($CHCl_3$): 3156*w*, 2851*w*, 1960*w*, 1814*w*, 1699*s*, 1682*s*, 1602*w*, 1540*m*, 1493*s*, 1447*s*, 1400*m*, 1332*m*, 1164*m*, 1154*m*, 1123*w*, 1087*w*, 1034*w*, 1002*w*, 941*w*, 906*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): see *Table 2*; additionally, 9.14 (*s*, CHO); 7.34–7.04 (*m*, 20 arom. H); 3.05–2.86 (*m,* CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 178.09 (*d*, CHO); 141.87 (*s*); 141.01 (4*s*); 129.07 (6*d*); 128.18 (2*d*); 127.84 (2*d*); 127.74 (3*d*); 127.64 (6*d*); 125.49 (*d*); 76.18 (*s*, Ph_3C); 35.07 (*t*, C(2′)); 29.80 (*t*, C(1′)). Anal. calc. for $C_{31}H_{26}N_2O$ (442.56): C 84.13, H 5.92, N 6.33; found: C 83.98, H 6.18, N 6.35.

*4-(2-Phenylethyl)-1-(triphenylmethyl)-1*H-*imidazole-2-methanol* (**23a**). A soln. of **22a** (631 mg, 1.42 mmol) in THF/MeOH 1:1 (20 ml) was treated with $NaBH_4$ (160 mg, 4.3 mmol), stirred for 2 h, and evaporated. FC (AcOEt/MeOH 96:4) gave **23a** (584 mg, 92%). White solid. R_f (AcOEt/hexane 1:1) 0.14. M.p. 179–180° (MeOH). IR ($CHCl_3$): 3573*w*, 3422*w* (br.), 3165*w*, 3064*m*, 2946*m*, 2860*m*, 1960*w*, 1909*w*, 1816*w*, 1602*m*, 1567*w*, 1494*s*, 1447*s*, 1370*s*, 1281*m*, 1162*m*, 1087*m*, 1036*s*, 1002*m,* 907*m*, 890*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.35–7.07 (*m*, 20 arom. H); 4.12 (br. *s*, OH); 3.70 (*s*, CH_2O); 2.93–2.75 (*m,* CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 142.52 (3*s*); 142.29 (*s*); 130.04 (6*d*); 128.88 (2*d*); 128.34 (9*d*); 128.25 (2*d*); 125.93 (*d*); 74.92 (*s*, Ph_3C); 58.83 (*t*, CH_2OH); 35.73 (*t*, C(2′)); 30.18 (*t*, C(1′)). Anal. calc. for $C_{31}H_{28}N_2O$ (444.58): C 83.75, H 6.35, N 6.30; found: C 83.88, H 6.32, N 6.27.

*4-(2-Phenylethyl)-1*H-*imidazole-2-methanol* (**24a**). A soln. of **23a** (532 mg, 1.20 mmol) in MeOH (20 ml) was treated with glacial AcOH (1 ml), heated to reflux for 4 h, and evaporated. The residue was treated with H_2O (100 ml) and extracted with $CHCl_3$ (3 × 50 ml). The combined $CHCl_3$ layers were extracted with 5% aq. AcOH (3×). The combined aq. layers were evaporated and dried *i.v.* Crystallisation from AcOEt gave **24a** (221 mg, 91%). R_f (AcOEt/MeOH 9:1) 0.17. M.p. 139–140° (AcOEt). IR (KBr): 1581*m*, 1495*m*, 1468*s*, 1442*s*, 1387*w*, 1345*w*, 1306*w*, 1218*m*, 1122*w*, 1073*m*, 1048*s*, 1011*m*, 861*m*. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 2*; additionally, 7.27–7.07 (*m*, 5 arom. H); 4.63 (*s*, CH_2O); 2.95–2.83 (*m,* CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 142.81 (*s*); 129.73 (2*d*); 129.70 (2*d*); 127.40 (*d*); 57.65 (*t*, CH_2O); 35.73 (*t*, C(2′)); 30.18 (*t*, C(1′)). Anal. calc. for $C_{12}H_{14}N_2O$ (202.26): C 71.26, H 6.98, N 13.85; found: C 71.21, H 7.14, N 13.61.

*4-Methyl-1-(triphenylmethyl)-1*H-*imidazole* (**21b**) [22]. ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 142.24 (3*s*); 129.42 (6*d*); 127.55 (9*d*); 74.57 (*s*, Ph_3C); 13.49 (*q*, Me).

*4-Methyl-1-(triphenylmethyl)-1*H-*imidazole-2-carbaldehyde* (**22b**). A soln. of **21b** (684 mg, 2 mmol) in THF (25 ml) was cooled under Ar to −5°, treated with 1.6M BuLi in hexane (1.5 ml, 2.4 mmol), stirred for 1.5 h at r.t., cooled to 0°, treated with DMF (0.46 ml, 6 mmol) in one portion, and stirred for 1 h at r.t. After addition of H_2O (25 ml) and extraction with AcOEt (3 × 75 ml), the combined org. layers were washed with brine, dried ($MgSO_4$), and evaporated. FC (100 g, hexane/AcOEt 3:1) gave **22b** (502 mg, 71%). Pale yellow solid. R_f (hexane/AcOEt 3:1) 0.21. M.p. 190–191° (AcOEt). IR ($CHCl_3$): 3064*m*, 2841*w*, 1960*w*, 1816*w*, 1699*s*, 1682*s*, 1599*w*, 1545*m*, 1493*m*, 1446*s*, 1429*s*, 1402*m*, 1378*m*, 1340*m*, 1274*m*, 1154*m*, 1124*w*, 1088*w*, 1035*w*, 1016*w*, 1002*w*, 906*m*, 895*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 9.12 (*s*, CHO); 7.34–7.30 (*m*, 9 arom. H); 7.14–7.11 (*m*, 6 arom. H); 2.27 (*d*, J = 0.6, Me). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 178.74 (*d*, CHO); 142.58 (3*s*); 129.80 (6*d*); 128.33 (6*d*); 128.42 (3*d*); 76.82 (*s*, Ph_3C); 13.82 (*q*, Me). Anal. calc. for $C_{24}H_{20}N_2O$ (352.43): C 81.79, H 5.72, N 7.95; found: C 81.77, H 5.89, N 8.03.

*4-Methyl-1-(triphenylmethyl)-1*H-*imidazole-2-methanol* (**23b**). A soln. of **22b** (1.418 g, 4 mmol) in MeOH (30 ml) was heated to 45°, treated with $NaBH_4$ (0.49 g, 13 mmol) in three portions within 10 min and stirred for 2 h. The white solid was filtered off, washed with $CHCl_3$, and the combined filtrate and washings were evaporated. FC (AcOEt/MeOH 95:5) gave **23b** (1.330 g, 93%). White solid. R_f (AcOEt/MeOH 9:1) 0.57. M.p. 232–234° (AcOEt, dec.). IR ($CHCl_3$): *ca.* 3600*w*, 3360*w* (br.), 3167*m*, 3065*m*, 3007*s*, 2924*m*, 2862*m*, 1960*w*, 1909*w*, 1818*w*, 1733*w*, 1597*m*, 1574*m*, 1493*s*, 1448*s*, 1370*s*, 1283*m*, 1155*m*, 1087*m*, 1039*s*, 1017*m*, 1002*m,* 907*m*, 890*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.35–7.30 (*m*, 9 arom. H); 7.14–7.10 (*m*, 6 arom. H); 4.18 (br. *s*, OH); 3.64 (*s*, CH_2O); 2.12 (br. *s*, Me). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 142.26 (3*s*); 129.88 (6*d*); 128.12 (6*d*); 128.02 (3*s*); 74.74 (*s*, Ph_3C); 58.76 (*t*, $HOCH_2$); 13.46 (*q,* Me). Anal. calc. for $C_{24}H_{22}N_2O$ (354.45): C 81.33, H 6.26, N 7.90; found: C 81.09, H 6.49, N 7.89.

*4-Methyl-1*H-*imidazole-2-methanol* (**24b**) [26][27]. A suspension of **23b** (1.318 g, 3.72 mmol) in MeOH (40 ml) was treated with glacial AcOH (2 ml) and heated to reflux for 5 h. MeOH was evaporated. The oily residue was partitioned between benzene and H_2O, and the H_2O layer was extracted twice with benzene. Evaporation of the H_2O layer and FC (30 g; $CHCl_3$/MeOH 9:1 → 2:1) gave **24b** (0.414 g, 83%). White solid. R_f ($CHCl_3$/MeOH 9:1) 0.15. M.p. 127–128° (AcOEt/MeOH; [26]: 129°). IR (KBr): 3500–2500*s*, 1598*m*, 1505*m*, 1464*s*, 1390*m*, 1350*w*, 1288*w*, 1233*m*, 1146*m*, 1038*s*, 1026*s*, 988*s*, 858*m*, 795*s*. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 2*; additionally, 4.58 (*s*, C*H*$_2$OH); 2.20 (*d*, *J* = 1.3, Me). ^{1}H-NMR ((D_6)DMSO): see [27]. ^{13}C-NMR (75 MHz; 1 equiv. of AcOH/$CDCl_3$): see *Table 2*; additionally, 55.37 (*t*, CH_2OH); 10.46 (*q*, Me). Anal. calc. for $C_5H_8N_2O$ (112.13): C 53.56, H 7.19, N 24.98; found: C 53.57, H 7.13, N 24.91.

*4-Phenyl-1-(triphenylmethyl)-1*H-*imidazole* (**21c**) [23][24]. Prepared according to [25]. R_f (hexane/AcOEt 1:1) 0.59. M.p. 190–192° (EtOH; [23]: 188–189°, [24]: 190–191°). IR ($CHCl_3$): 3064*m*, 2965*m*, 1960*w*, 1816*w*, 1732*w*, 1606*m*, 1484*s*, 1445*s*, 1306*w*, 1168*s*, 1147*m*, 1087*w*, 1068*s*, 1038*m*, 1002*w*, 943*m*, 908*m*, 869*m*, 834*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.77–7.72 (*m*, 2 arom. H); 7.39–7.32 (*m*, 11 arom. H); 7.27–7.18 (*m*, 7 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 142.68 (3*s*); 141.17 (*s*); 130.12 (6*d*); 128.81 (3*d*); 128.39 (8*d*); 127.05 (*d*); 125.07 (2*d*); 75.68 (*s*, Ph_3C).

*4-Phenyl-1-(triphenylmethyl)-1*H-*imidazole-2-carbaldehyde* (**22c**) [25]. Prepared according to [25]. White solid. R_f (hexane/AcOEt 3:1) 0.31. M.p. 184° (EtOH; [25]: 187°). IR ($CHCl_3$): 3158*w*, 3064*w*, 2899*w*, 2844*w*, 1960*w*, 1815*w*, 1699*s*, 1605*w*, 1492*s*, 1461*s*, 1446*s*, 1426*m*, 1395*m*, 1354*m*, 1274*m*, 1167*w*, 1153*m*, 1103*m*, 1087*w*, 1035*w*, 950*m*, 904*w*, 892*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 9.22 (*s*, CHO); 7.77–7.74 (*m*, 2 arom. H); 7.37–7.15 (*m*, 19 arom. H). ^{1}H-NMR ((D_6)DMSO): see [25]. ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 179.08 (*d*, CHO); 142.35 (3*s*); 142.03 (*s*); 129.88 (6*d*); 128.94 (2*d*); 128.62 (3*d*); 128.47 (6*d*); 128.10 (*d*); 125.48 (2*d*); 77.34 (*s*, Ph_3C).

*4-Phenyl-1-(triphenylmethyl)-1*H-*imidazole-2-methanol* (**23c**). A soln. of **22c** (561 mg, 1.35 mmol) in MeOH (10 ml) was treated with $NaBH_4$ (0.18 g, 4.7 mmol), stirred for 2 h, and evaporated. FC (AcOEt/hexane 1:1) gave **23c** (433 mg, 77%). White solid. R_f (hexane/AcOEt 1:1) 0.47. M.p. 195–196° (EtOH). IR ($CHCl_3$): 3454*w* (br.), 3163*w*, 3064*m*, 2873*w*, 1960*w*, 1817*w*, 1732*w*, 1607*m*, 1493*s*, 1446*s*, 1365*s*, 1316*m*, 1167*s*, 1087*m*, 1043*s*, 1002*m*, 952*m*, 908*m*, 885*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): see *Table 2*; additionally, 7.72–7.69 (*m*, 2 arom. H); 7.39–7.31 (*m*, 11 arom. H); 7.24–7.16 (*m*, 7 arom. H); 3.67 (*d*, *J* = 4.1, C*H*$_2$OH); 3.21 (br. *s*, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 141.80 (3*s*); 137.94 (*s*); 129.91 (6*d*); 128.55 (2*d*); 128.28 (9*d*); 126.77 (*d*); 124.60 (2*d*); 75.23 (*s*, Ph_3C) 59.18 (*t*, CH_2O). Anal. calc. for $C_{29}H_{22}N_2O$ (416.52): C 83.63, H 5.81, N 6.73; found: C 83.47, H 5.99, N 6.86.

*4-Phenyl-1*H-*imidazole-2-methanol* (**24c**). A soln. of **23c** (430 mg, 1.03 mmol) in MeOH (20 ml) was treated with glacial AcOH (1 ml), heated to reflux for 4 h, and evaporated. The residue was dissolved in H_2O (100 ml) and evaporated. The solid was crystallized from AcOEt/MeOH to give **24c** (97 mg, 54%). White solid. R_f (AcOEt/MeOH 9:1) 0.39. M.p. 199–200° (AcOEt/MeOH). IR (KBr): 3200–2300*s*, 1605*w*, 1534*w*, 1480*w*, 1458*m*, 1397*w*, 1227*m*, 1142*m*, 1092*m*, 1040*s*, 1006*m*, 835*m*. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 2*; additionally, 7.69–7.65 (*m*, 2 arom. H); 7.38–7.32 (*m*, 2 arom. H); 7.24–7.19 (*m*, 1 arom. H); 4.66 (*s*, CH_2O). ^{13}C-NMR (75 MHz, CD_3OD): see *Table 2*; additionally, 139.09 (*s*); 129.32 (2*d*); 127.44 (*d*); 125.41 (2*d*); 57.98 (*t*, CH_2OH). Anal. calc. for $C_{10}H_{10}N_2O$ (174.20): C 68.95, H 5.79, N 16.08; found: C 68.92, H 6.01, N 15.88.

*2-[4-(2-Phenylethyl)-1-(triphenylmethyl)-1*H-*imidazol-2-yl]-2-(triphenylmethoxy)ethanol* (**25a**). A soln. of **21a** (622 mg, 1.5 mmol) in THF (20 ml) was cooled to −40°, treated with 1.6M BuLi in hexane (1.4 ml, 2.2 mmol), stirred for 2 h at −40° and for 45 min at r.t., cooled to −40°, treated dropwise within 5 min with a soln. of (trityloxy)acetaldehyde [28] (1.1 g 3.7 mmol) in THF (4 ml), stirred for 30 min at −40° and for 2 h at r.t., and evaporated. The resulting foam was partitioned between AcOEt (50 ml) and aq. NH_4Cl soln. (50 ml), and the aq. layer was extracted with AcOEt (2 × 30 ml). The combined org. layers were washed with brine, dried ($MgSO_4$), and evaporated. FC (130 g, hexane/AcOEt 3:1) of the yellow foam gave **25a** (448 mg, 42%). White solid. R_f (hexane/AcOEt 3:1) 0.17. M.p. 96–99° (hexane/cyclohexane). IR ($CHCl_3$): 3573*w*, 3063*m*, 2929*m*, 1959*w*, 1817*w*, 1697*w*, 1597*w*, 1493*s*, 1448*s*, 1373*w*, 1283*m*, 1154*m*, 1075*s*, 1034*m*, 1002*m*, 992*m*, 908*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): see *Table 2*; additionally, 7.37–7.05 (*m*, 35 arom. H); 4.28 (*ddd*, *J* = 7.9, 6.6, 3.3, CH–C(2)); 3.20 (*dd*, *J* = 9.5, 7.9, TrOC*H*); 2.96–2.72 (*m*, CH_2CH_2); 2.39 (*dd*, *J* = 9.3, 3.5, TrOC*H*′); 2.13 (*d*, *J* = 6.9, OH).

*1-[4-(2-Phenylethyl)-1*H-*imidazol-2-yl]ethane-1,2-diol* (**26a**). A suspension of **25a** (172 mg, 0.24 mmol) in MeOH/AcOH 2:1 (12 ml) was heated to reflux for 10 h, evaporated, and co-evaporated with toluene (3 times). The oily residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ layer was extracted with H_2O (3×). The combined aq. layers were evaporated. Reversed-phase (RP) FC (20 g of *LiChroprep*; MeOH) of the oily residue (53 mg) gave **26a** (39 mg, 70%). R_f (RP silica gel; MeOH) 0.23. M.p. 129–130° ($CHCl_3$). IR (KBr): 3200*s*, 2923*s*, 1603*m*, 1573*m*, 1496*m*, 1455*s*, 1426*m*, 1323*m*, 1282*m*, 1105*s*, 1068*m*, 1033*s*, 896*m*, 800*m*. ^{1}H-NMR

(300 MHz, CD_3OD): see *Table 2*; additionally, 7.27–7.12 (*m*, 5 arom. H); 4.79 (*dd*, *J* = 6.2, 4.7, CH–C(2)); 3.81 (*dd*, *J* = 11.2, 4.7), 3.73 (*dd*, *J* = 11.2, 6.5) (CH_2OH); 2.95–2.83 (*m,* CH_2CH_2). ^{13}C-NMR (75 MHz, CD_3OD): see *Table 2*; additionally, 142.68 (*s*); 129.49 (2*d*); 129.45 (2*d*); 127.12 (*d*); 69.80 (*d*, CH–C(2)); 66.45 (*t*, CH_2OH); 36.65 (*t*, $PhCH_2$); 29.32 (*t*, CH_2–C(4)). Anal. calc. for $C_{13}H_{16}N_2O_2$ (232.28): C 67.22, H 6.94, N 12.06; found: C 67.05, H 7.05, N 11.92.

*1-[4-Phenyl-1-(triphenylmethyl)-1*H*-imidazol-2-yl]-2-(triphenylmethoxy)ethanol* (**25c**). A soln. of **21c** (580 mg, 1.5 mmol) in THF (20 ml) was cooled to −40°, treated with 1.6M BuLi in hexane (1.1 ml, 1.76 mmol), stirred for 2 h at −40° and 1 h at r.t., cooled to −40°, treated dropwise within 5 min with a soln. of (trityloxy)acetaldehyde (1.05 g, 3.5 mmol) in THF (5 ml), stirred for 30 min at −40° and 2 h at r.t., and evaporated. The foamy residue was partitioned between AcOEt (50 ml) and aq. NH_4Cl soln. (50 ml), and the aq. layer was extracted with AcOEt (2 × 30 ml). The combined org. layers were washed with brine, dried ($MgSO_4$), and evaporated. FC (100 g, hexane/AcOEt 3:1) gave **25c** (743 mg, 72%). Colourless foam. R_f (hexane/AcOEt 3:1) 0.36. IR ($CHCl_3$): 3568*w*, 3062*m*, 1959*w*, 1908*w*, 1818*w*, 1756*w*, 1597*m*, 1492*s*, 1448*s*, 1321*m*, 1154*m*, 1086*s*, 1034*m*, 1002*m*, 949*m*, 901*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.73–7.68 (*m*, 2 arom. H); 7.37–7.17 (*m*, 33 arom. H); 4.31 (*ddd*, *J* = 7.5, 6.9, 3.5, CH–C(2)); 3.07 (*dd*, *J* = 9.3, 7.5, TrOC*H*); 2.53 (*dd*, *J* = 9.3, 3.5, TrOC*H*′); 2.27 (*d*, *J* = 6.9, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 143.91 (3*s*); 142.30 (3*s*); 138.63 (*s*); 129.81 (6*d*); 129.02 (6*d*); 128.44 (3*d*); 128.13 (8*d*); 127.66 (6*d*); 126.84 (3*d*); 126.66 (*d*); 124.82 (2*d*); 86.47 (*s*, Ph_3CO); 75.23 (*s*, Ph_3CN); 66.96 (*d,* CH–C(2)); 65.79 (*t,* $TrOCH_2$).

*1-(4-Phenyl-1*H*-imidazol-2-yl)ethane-1,2-diol* (**26c**). A suspension of **25c** (509 mg, 0.74 mmol) in MeOH/AcOH 2:1 (15 ml) was heated to reflux for 24 h, evaporated, and co-evaporated with toluene (3 times). Crystallisation of the oily residue from AcOEt gave white crystalline **26c** (53 mg). Evaporation of the mother liquor and FC (30 g, AcOEt/MeOH 95:5) gave additional **26c** (26 mg, 52% total yield). R_f (AcOEt/MeOH 9:1) 0.20. M.p. 161–163° ($CHCl_3$/MeOH). IR (KBr): 3600–2300*s*, 1586*m*, 1535*m*, 1481*s*, 1461*s*, 1375*s*, 1319*s*, 1273*m*, 1244*m*, 1133*s*, 1074*s*, 1032*s*, 976*s*, 920*m*, 833*m*, 794*m*. ^{1}H-NMR (200 MHz, CD_3OD): see *Table 2*; additionally, 7.72–7.65 (*m*, 2 arom. H); 7.39–7.30 (*m*, 2 arom. H); 7.26–7.16 (*m*, 1 arom. H); 4.85 (*dd*, *J* = 6.6, 4.6, CH–C(1)); 3.90 (*dd*, *J* = 11.2, 4.6), 3.78 (*dd*, *J* = 11.2, 6.6) (CH_2OH). ^{13}C-NMR (75 MHz, CD_3OD): see *Table 2*; additionally, 139.53 (*s*); 129.72 (2*d*); 127.83 (*d*); 125.02 (2*d*); 70.31 (*d*, CH–C(2)); 66.74 (*t*, CH_2OH). Anal. calc. for $C_{11}H_{12}N_2O_2$ (204.23): C 64.69, H 5.92, N 13.72; found: C 64.65, H 6.02, N 13.57.

*4-Methyl-1-(triphenylmethyl)-1*H*-imidazole-2-carbonitrile* (**27b**). A soln. of **21b** (1.074 g, 3.32 mmol) in THF (60 ml) was cooled to −10°, treated with 1.6M BuLi in hexane (2.3 ml, 3.65 mmol), stirred for 40 min at 23°, cooled to −10°, treated with a soln. of TsCN (1.26 g, 6.95 mmol) in THF (15 ml), warmed to r.t., stirred 2 h, and evaporated. A soln. of the residue in AcOEt was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. FC (150 g, hexane/AcOEt 3:1) gave **27b** (0.633 g, 55%) and **21b** (0.408 g, 38%).

Data of **27b**: White solid. R_f (hexane/AcOEt 3:1) 0.43. M.p. 172–173° (hexane/AcOEt). IR ($CHCl_3$): 3065*m*, 2933*w*, 2235*s*, 1959*w*, 1909*w*, 1815*w*, 1729*w*, 1598*m*, 1574*m*, 1493*s*, 1446*s*, 1390*s*, 1376*s*, 1272*w*, 1165*s*, 1124*m*, 1087*m*, 1036*w*, 1015*w*, 1002*w*, 908*m*, 881*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.39–7.35 (*m*, 9 arom. H); 7.17–7.14 (*m*, 6 arom. H); 2.22 (*d*, *J* = 0.6, Me). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 141.17 (3*s*); 129.91 (6*d*); 128.58 (3*d*); 128.31 (6*d*); 111.11 (*s*, CN); 76.88 (*s*, Ph_3C); 13.84 (*q,* Me). Anal. calc. for $C_{24}H_{19}N_3$ (349.43): C 82.49, H 5.48, N 12.03; found: C 82.38, H 5.63, N 12.21.

*4-Methyl-1*H*-imidazole-2-carbonitrile* (**28b**). A soln. of **27b** (312 mg, 0.89 mmol) in AcOH/MeOH 1:2 (15 ml) was refluxed for 1.5 h, cooled to r.t., and evaporated. FC (90 g, hexane/AcOEt 1:1) gave **28b** (77 mg, 81%). White solid. R_f (hexane/AcOEt 1:3) 0.41. M.p. 169–170° (cyclohexane/AcOEt). IR (KBr): 3117*m*, 3062*m*, 2934*s*, 2234*s*, 1603*m*, 1471*m*, 1433*s*, 1396*m*, 1229*m*, 1156*m*, 1025*s*, 992*m*, 909*s*, 840*s*, 824*s*. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 2*; additionally, 2.26 (*d*, *J* = 0.9, Me). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 112.54 (*s*, CN); 11.22 (*q,* Me). Anal. calc. for $C_5H_5N_3$ (107.11): C 56.07, H 4.70, N 39.23; found: C 56.30, H 4.98, N 38.95.

*4-Phenyl-1-(triphenylmethyl)-1*H*-imidazole-2-carbonitrile* (**27c**). A soln. of **21c** (773 mg, 2 mmol) in THF (20 ml) was cooled to −10°, treated with 1.6M BuLi in hexane (1.4 ml, 2.2 mmol), warmed to r.t., stirred for 1 h, cooled to −10°, treated with a soln. of TsCN (797 mg, 4.4 mmol) in THF (20 ml) during 15 min (syringe pump), warmed to r.t., stirred for 2 h, and evaporated. The residue was partitioned between AcOEt (20 ml) and H_2O (20 ml), and the aq. layer extracted with AcOEt (25 ml). The combined org. layers were washed with brine, dried ($MgSO_4$), and evaporated. FC (80 g, hexane/AcOEt 9:1) of the orange oil gave **27c** (526 mg, 64%) and **21c** (231 mg, 30%).

Data of **27c**: White solid. R_f (hexane/AcOEt 3:1) 0.46. M.p. 170–173° (hexane/AcOEt). IR ($CHCl_3$): 3065*m*, 2959*s*, 2928*m*, 2236*s*, 1732*m*, 1492*s*, 1484*s*, 1447*s*, 1381*s*, 1346*m*, 1328*m*, 1172*s*, 1095*s*, 1036*m*, 1002*m*, 950*m*, 876*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.76–7.73 (*m*, 2 arom. H); 7.45–7.36 (*m*, 12 arom.

H); 7.33–7.27 (*m*, 1 arom. H); 7.27–7.23 (*m*, 6 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 141.79 (*s*); 140.96 (3*s*); 129.98 (6*d*); 128.81 (3*d*); 128.49 (6*d*); 128.05 (2*d*); 125.15 (3*d*); 111.05 (*s*, CN); 75.23 (*s*, Ph_3C).

*4-Phenyl-1*H-*imidazole-2-carbonitrile* (**28c**). A soln. of **27c** (353 mg, 0.86 mmol) in AcOH/MeOH 1:2 (30 ml) was refluxed for 7 h, cooled to r.t., and evaporated. FC (90 g, hexane/AcOEt 3:1) of the yellow solid residue gave **28c** (89 mg, 61%). White solid. R_f (hexane/AcOEt 3:1) 0.12. M.p. 215–216° (cyclohexane/AcOEt; dec.). IR (KBr): 3116*s*, 2228*s*, 1588*m*, 1567*m*, 1502*m*, 1459*s*, 1426*s*, 1307*m*, 1281*m*, 1172*m*, 1092*m*, 1023*s*, 875*s*. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 2*; additionally, 7.72–7.69 (*m*, 2 arom. H); 7.41–7.34 (*m*, 2 arom. H); 7.32–7.26 (*m*, 1 arom. H). ^{13}C-NMR (75 MHz, CD_3OD): see *Table 2*; additionally, 139.45 (*s*); 129.61 (2*d*); 128.88 (*d*); 125.97 (2*d*); 112.36 (*s*, CN). Anal. calc. for $C_{10}H_7N_3$ (169.19): C 70.99, H 4.17, N 24.84; found: C 70.98, H 4.32, N 24.73.

*2-[(Benzylamino)methyl]-4-(2-phenylethyl)-1-(triphenylmethyl)-1*H-*imidazole* (**29a**). A suspension of **22a** (594 mg, 1.34 mmol) and $MgSO_4$ (240 mg, 2 mmol) in CH_2Cl_2 (15 ml) was treated with $BnNH_2$ (0.18 ml, 1.6 mmol), stirred at 23° overnight, and filtered. Evaporation of the filtrate gave an orange residue, which was dissolved in MeOH (15 ml), treated with $NaBH_4$ (0.25 g, 6.7 mmol), and heated to 50° for 30 min. Evaporation and FC (50 g, hexane/AcOEt 1:3) gave **29a** (661 mg, 92%). Colourless oil. R_f (hexane/AcOEt 1:1) 0.18. IR ($CHCl_3$): 3328*w*, 3064*m*, 2932*m*, 1958*w*, 1817*w*, 1603*w*, 1494*s*, 1448*s*, 1410*m*, 1284*m*, 1162*m*, 1125*m*, 1086*m*, 1030*m*, 907*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): see *Table 2*; additionally, 7.33–7.07 (*m*, 25 arom. H); 3.42 (*s*, PhCH_2N); 3.01 (*s*, CH_2–C(2)); 3.01–2.79 (*m*, CH_2CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 142.90 (3*s*); 142.48 (*s*); 138.52 (*s*); 130.06 (6*d*); 128.86 (2*d*); 128.42 (2*d*); 128.34 (2*d*); 128.28 (2*d*); 128.20 (6*d*); 127.99 (3*d*); 126.81, 125.85 (2*d*); 74.73 (*s*, Ph_3C); 53.50 (*t*, PhCH_2N); 47.99 (*t*, CH_2–C(2)); 35.90 (*t*, C(2′)); 30.45 (*t*, C(1′)).

N-*Benzyl*-N-*{[4-(2-phenylethyl)-1-(triphenylmethyl)-1*H-*imidazol-2-yl]methyl}acetamide* (**30a**). A soln. of **29a** (632 mg, 1.18 mmol) and DMAP (15 mg, 0.12 mmol) in THF (20 ml) was treated with Ac_2O (0.25 ml, 2.65 mmol), stirred at 23° for 3 h, and evaporated. Crystallisation from cyclohexane/hexane gave pure **30a** (577 mg, 85%). R_f (AcOEt/hexane 3:1) 0.35. M.p. 132–133°. IR ($CHCl_3$): 3165*w*, 3087*w*, 2930*w*, 2858*w*, 1641*s*, 1495*s*, 1474*m*, 1447*s*, 1421*m*, 1354*w*, 1281*m*, 1162*m*, 1032*m*, 988*m*, 908*m*, 889*w*. ^{1}H-NMR (500 MHz, $CDCl_3$, 27°, (*E*)/(*Z*) 3:2; assignment based on a HQSC spectrum): see *Table 2*; additionally, 7.31–7.05 (*m*, 23.8 arom. H); 6.86 (*d*, *J* = 8.5, 1.2 arom. H); 4.53 (*s*, 1.2 H), 4.38 (*s*, 0.8 H) (PhCH_2N); 3.60 (*s*, 0.8 H), 3.25 (*s*, 1.2 H) (CH_2–C(2)); 2.95–2.90 (*m*, CH_2CH_2–C(4)); 2.87–2.80 (*m*, CH_2CH_2–C(4)); 2.09 (*s*, 1.2 H), 1.76 (*s*, 1.8 H) (AcN). ^{13}C-NMR (125 MHz, $CDCl_3$, 27°; (*E*)/(*Z*) 3:2; assignment based on a HQSC spectrum): see *Table 2*; additionally, 142.12, 142.04 (*s*, 1 arom. C); 141.96, 141.80 (2*s*, 3 arom. C); 137.68, 136.96 (2*s*, 1 arom. C); 129.91, 129.73 (2*d*, 6 arom. C); 128.79, 128.71, 128.54, 128.08 (4*d*, 4 arom. C); 128.24 (*d*, 2 arom. C); 128.16, 127.94 (2*d*, 6 arom. C); 128.05 (*d*, 3 arom. C); 127.79 (*d*, 1 arom. C); 127.08, 126.98 (2*d*, 1 arom. C); 126.34, 125.62 (2*d*, 2 arom. C); 74.68 (*s*, 0.4 C), 74.37 (*s*, 0.6 C) (Ph_3C); 52.19 (*t*, 0.4 C), 49.16 (*t*, 0.6 C) (PhCH_2N); 47.08 (*t*, 0.6 C), 44.39 (*t*, 0.4 C) (CH_2–C(2)); 35.65, 35.59 (2*t*, CH_2CH$_2$–C(4)); 30.07 (*t*, 0.4 C), 29.93 (*t*, 0.6 C) (CH_2CH_2–C(4)); 21.58 (*q*, 0.4 C), 21.27 (*q*, 0.6 C) (*Me*C=O); C=O signals not registered.

N-*{[4-(2-Phenylethyl)-1*H-*imidazol-2-yl]methyl}acetamide* (**31a**). A soln. of **30a** (454 mg, 0.79 mmol) in THF (4 ml) was cooled to −78°, treated with freshly condensed NH_3 and with Na (145 mg, 6.3 mmol) in small pieces, stirred for 2 h, treated with solid NH_4Cl (400 mg), and allowed to warm to 23°, leading to complete evaporation of NH_3. The residual white suspension was partitioned between $CHCl_3$ (30 ml) and diluted NH_4Cl soln. (30 ml). The aq. layer was extracted with $CHCl_3$ (3 × 10 ml). The combined org. layers were washed with brine, dried ($MgSO_4$), and evaporated. FC (AcOEt/MeOH 3:40 → 1:4) gave **31a** (166 mg, 87%). White solid. R_f (AcOEt/MeOH 9:1) 0.31. M.p. 174–175° (AcOEt/MeOH). IR (KBr): 3273*s*, 3062*m*, 1634*s*, 1604*m*, 1552*s*, 1492*m*, 1458*s*, 1444*s*, 1388*m*, 1371*m*, 1333*m*, 1286*s*, 1219*m*, 1133*s*, 1028*m*. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 2*; additionally, 7.26–7.10 (*m*, 5 arom. H); 4.36 (*s*, CH_2–C(2)); 2.92–2.78 (*m*, CH_2CH_2); 1.98 (*s*, AcN). ^{13}C-NMR (75 MHz, CD_3OD): see *Table 2*; additionally, 173.86 (*s*, C=O); 143.26 (*s*); 129.73 (2*d*); 129.65 (2*d*); 127.27 (*d*); 36.97 (*t*, CH_2N); 35.73 (*t*, C(2′)); 29.92 (*t*, C(1′)); 22.61 (*q*, Me).

*2-[(Benzylamino)methyl]-4-phenyl-1-(triphenylmethyl)-1*H-*imidazole* (**29c**). A suspension of **22c** (819 mg, 2 mmol) and $MgSO_4$ (363 mg, 3 mmol) in CH_2Cl_2 (15 ml) was treated with $BnNH_2$ (0.24 ml, 2.2 mmol), stirred at 23° overnight, and filtered. The filtrate was evaporated. The solid residue was dissolved in MeOH (30 ml), warmed to 55°, treated with $NaBH_4$ (0.38 g, 10 mmol), and cooled to 10°. The precipitate was filtered off and dried affording **29c** (758 mg). Evaporation of the filtrate and FC (hexane/AcOEt 1:1) gave additional **29c** (51 mg, 80% total yield). R_f (hexane/AcOEt 3:1) 0.13. M.p. 120–122° (MeOH). IR ($CHCl_3$): 3326*w*, 3064*m*, 2962*m*, 1959*w*, 1817*w*, 1606*m*, 1493*s*, 1447*s*, 1405*m*, 1323*m*, 1166*m*, 1070*m*, 1028*m*, 988*m*, 950*m*, 909*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): see *Table 2*; additionally, 7.75–7.70 (*m*, 2 arom. H); 7.37–7.29 (*m*, 12 H); 7.24–7.12 (*m*,

12 H); 3.48 (*s*, PhCH_2N); 3.02 (*s*, CH_2–C(2)). ^{13}C-NMR (50 MHz, $CDCl_3$): see *Table 2*; additionally, 141.83 (3*s*); 139.71, 137.74 (2*s*); 129.49 (6*d*); 128.06 (2*d*); 127.84 (2*d*); 127.71 (9*d*); 127.58 (2*d*); 126.25, 126.06 (2*d*); 124.22 (2*d*); 74.66 (*s*, Ph_3C); 52.88 (*t*, PhCH_2N); 47.46 (*t*, CH_2–C(2)).

N-*Benzyl*-N-*{[4-phenyl-1-(triphenylmethyl)-1*H*-imidazol-2-yl]methyl}acetamide* (**30c**). A soln. of **29c** (708 mg, 1.4 mmol) and DMAP (18 mg, 0.15 mmol) in THF (30 ml) was treated with Ac_2O (0.30 ml, 3.2 mmol), stirred at 23° for 4 h, and evaporated. A soln. of the foamy residue in $CHCl_3$ (20 ml) was washed with aq. Na_2CO_3 soln., H_2O, and brine, dried ($MgSO_4$), and evaporated. Crystallization from PrOH gave **30c** (605 mg, 79%). White crystals. R_f (AcOEt/hexane 1:1) 0.52. M.p. 224° (PrOH; dec.). IR ($CHCl_3$): 3161*w*, 3086*w*, 1642*s*, 1608*m*, 1494*s*, 1474*m*, 1447*s*, 1419*m*, 1323*m*, 1301*m*, 1165*m*, 1031*m*, 988*m*, 948*m*, 885*w*. ^{1}H-NMR (300 MHz, $CDCl_3$, 27°; (*E*)/(*Z*) 3:2): see *Table 2*; additionally, 7.76 (*d*, *J* = 7.8, 1.2 arom. H); 7.72 (*d*, *J* = 7.8, 0.8 arom. H); 7.36–7.11 (*m*, 22 arom. H); 7.05–7.02 (*m*, 1.2 arom. H); 6.94–6.91 (*m*, 0.8 arom. H); 4.60 (*s*, 1.2 H), 4.54 (*s*, 0.8 H) (PhCH_2N); 3.58 (*s*, 0.8 H), 3.40 (*s*, 1.2 H) (CH_2–C(2)); 2.14 (*s*, 1.2 H), 1.82 (*s*, 1.8 H) (AcN). ^{13}C-NMR (75 MHz, $CDCl_3$, 27°; (*E*)/(*Z*) 3:2): see *Table 2*; additionally, 172.43 (*s*, 0.6 C), 171.80 (*s*, 0.4 C) (C=O); 142.08 (*s*, 1.2 C), 141.92 (*s*, 1.8 C) (3 arom. C); 138.37 (*s*, 0.6 C), 137.37 (*s*, 0.4 C) (1 arom. C); 138.10 (*s*); 130.33 (3*d*); 130.07 (6*d*); 128.76–128.28 (several *d*); 127.39, 127.19, 126.63 (3*d*, 3 arom. C); 126.91 (*d*, 2 arom. C); 124.93 (*d*, 0.8 C), 124.86 (*d*, 1.2 C) (2 arom. C); 75.26 (*s*, 0.4 C), 75.01 (*s*, 0.6 C) (Ph_3C); 52.62 (*t*, 0.4 C), 49.37 (*t*, 0.6 C) (PhCH_2N); 47.33 (*t*, 0.6 C), 44.45 (*t*, 0.4 C) (CH_2–C(2)); 21.69 (*q*, 0.4 C), 21.33 (*q*, 0.6 C) (*Me*C=O). Anal. calc. for $C_{38}H_{33}N_3O$ (547.70): C 83.33, H 6.07, N 7.67; found: C 83.32, H 6.22, N 7.55.

N-*[(4-Phenyl-1*H*-imidazol-2-yl)methyl]acetamide* (**31c**). A soln. of **30c** (116 mg, 0.21 mmol) in THF (2 ml) was cooled to −78°, treated with freshly condensed NH_3 (15 ml) and with Na (29 mg, 1.2 mmol) in small pieces, stirred for 2 h at −78°, treated with solid NH_4Cl (300 mg), and allowed to warm to 23° leading to complete evaporation of NH_3. The residual white suspension was partitioned between $CHCl_3$ (15 ml) and diluted NH_4Cl soln. (15 ml). After extraction of the aq. layer with $CHCl_3$, the combined org. layers were washed with brine, dried ($MgSO_4$), and evaporated. FC (AcOEt/MeOH 1:19 → 1:4) gave **31c** (17 mg, 37%). White solid. R_f (AcOEt/MeOH 9:1) 0.15. M.p. 190–192°(AcOEt/MeOH; dec.). IR (KBr): 3304*s*, 3116*m*, 3067*m*, 2931*m*, 1633*s*, 1593*m*, 1545*s*, 1516*s*, 1461*s*, 1370*m*, 1344*m*, 1272*m*, 1219*m*, 1162*m*, 1094*m*, 1031*m*, 908*m*, 886*m*. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 2*; additionally, 7.68–7.64 (*m*, 2 arom. H); 7.37–7.30 (*m*, 2 arom. H); 7.22 (*tt*, *J* = 7.0, 1.2, 1 arom. H); 4.45 (*s*, CH_2N); 2.01 (*s*, AcN). ^{13}C-NMR (75 MHz, CD_3OD): see *Table 2*; additionally, 173.45 (*s*, C=O); 139.45 (*s*); 129.58 (2*d*); 127.75 (*d*); 125.65 (2*d*); 37.71 (*t*, CH_2N); 22.36 (*q*, Me).

4-(1-Hydroxy-2-phenylethyl)-N,N-*dimethyl-1*H*-imidazole-1-sulfonamide* (**33**). A soln. of **32** [31] (8.76 g, 0.05 mol) in THF (240 ml) was cooled to −78°, treated with 1.6M BuLi in hexane (38 ml, 0.06 mol), stirred for 0.5 h, treated with Et_3SiCl (15 ml, 0.09 mol), allowed to warm to r.t., stirred for 5 h, and evaporated. A soln. of the brown oil (19.9 g) in THF (175 ml) was cooled to −78°, treated with 1.3M *s*-BuLi in cyclohexane (75 ml, 0.097 mol), stirred for 25 min, treated with phenylacetaldehyde (12 ml, 0.103 mol), stirred for 10 min at −78° and 5 h at 23°, and evaporated. The resulting brown oil was dissolved in 2M HCl (250 ml), stirred for 1.5 h, and extracted with Et_2O (3 × 200 ml). The aq. layer was basified with 40% KOH to pH 12. The precipitate was filtered off, washed with H_2O, and dried. Crystallization of the colourless solid (11.1 g) from EtOH gave **33** (8.45 g, 57%). R_f ($CHCl_3$/MeOH 9:1) 0.40. M.p. 147–148° (EtOH). IR ($CHCl_3$): 3582*w*, 3320*w* (br.), 3134*w*, 3000*w*, 1585*w*, 1560*w*, 1495*m*, 1460*m*, 1420*s*, 1394*s*, 1177*s*, 1158*s*, 1150*s*, 1092*s*, 1055*m*, 971*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): see *Table 2*; additionally, 7.30–7.16 (*m*, 5 arom. H); 4.92 (br. *dd*, *J* = 7.8, 5.3, CH–C(4)); 3.22 (*dd*, *J* = 13.7, 5.3), 3.07 (*dd*, *J* = 13.7, 7.8) (PhCH_2); 2.77 (*s*, Me_2N); 2.60 (br. *s*, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): see *Table 2*; additionally, 146.17 (*s*); 129.80 (2*d*); 128.72 (2*d*); 126.86 (*d*); 69.57 (*d*, CH–C(4)); 43.51 (*t*, $PhCH_2$); 38.20 (*q*, Me_2N). Anal. calc. for $C_{13}H_{17}N_3O_3S$ (295.36): C 52.87, H 5.80, N 14.23; found: C 52.89, H 5.81, N 14.12.

*1-(1*H*-Imidazol-4-yl)-2-phenylethanol* (**34**). A soln. of **33** (1.181 g, 4 mmol) in 2M HCl (30 ml) was heated to reflux for 1 h, cooled to r.t., neutralised with 40% KOH and extracted with AcOEt (1 × 75 ml, 3 × 50 ml). The combined org. layers were washed with brine, dried ($MgSO_4$), and evaporated to afford **34** (0.705 g, 94%). White crystals. R_f ($CHCl_3$/MeOH 9:1) 0.08. M.p. 122–123° ($CHCl_3$). IR (KBr): 3300–2100*s*, 1601*m*, 1577*m*, 1495*s*, 1460*s*, 1332*m*, 1300*s*, 1236*m*, 1221*s*, 1178*m*, 1090*s*, 1066*s*, 1017*s*, 990*m*, 934*s*, 880*s*, 834*s*. ^{1}H-NMR (300 MHz, CD_3OD): see *Table 2*; additionally, 7.23 (*s*, H–C(2)); 7.22–7.11 (*m*, 5 arom. H); 4.89 (*dd*, *J* = 8.1, 5.6, CH–C(4)); 3.11 (*dd*, *J* = 13.7, 5.6), 3.03 (*dd*, *J* = 13.7, 8.1) (PhCH_2). ^{13}C-NMR (75 MHz, CD_3OD): see *Table 2*; additionally, 139.95 (*s*); 130.61 (2*d*); 129.19 (2*d*); 127.23 (*d*); 70.10 (br. *d*, *C*H–C(4)); 44.80 (*t*, PhCH_2). Anal. calc. for $C_{11}H_{12}N_2O$ (188.23): C 70.19, H 6.43, N 14.88; found: C 70.17, H 6.69, N 14.91.

Inhibition Experiments. Inhibition constants (K_i) and IC_{50} values were determined using 0.08M potassium phosphate buffer (pH 6.8), and the appropriate substrate and reaction temp. (4-nitrophenyl α-D-glucopyranoside at 37°, 4-nitrophenyl β-D-glucopyranoside at 55°, and 2-nitrophenyl β-D-galactopyranoside at 37°). The increase of the absorption per min at 400 nm was taken as the velocity for the substrate hydrolysis.

Determination of the inhibitor concentration to half the velocity measured in the absence of the inhibitor gave the appropriate IC_{50} value. K_i values were determined by taking the slopes from the *Lineweaver–Burk* plots and plotting them *vs.* the inhibitor concentrations. After fitting a straight line to the data by linear regression, the negative [*I*]-intercept of this plot gave the appropriate K_i.

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