Synthesis and Structure−Activity Relationships of Conformationally Constrained Histamine H_3 Receptor Agonists

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Immepip, a conformationally constrained analogue of the histamine congener imbutamine, shows high affinity and functional activity on the human H_3 receptor. Using histamine and its homologues as prototypes, other rigid analogues containing either a piperidine or pyrrolidine ring in the side chain were synthesized and tested for their activities at the human H_3 receptor and the closely related H_4 receptor. In the series of piperidine containing analogues, immepip was found to be the most potent H_3 receptor agonist, whereas its propylene analogue **13a** was identified as a high-affinity neutral antagonist for the human H_3 receptor. Moreover, replacement of the piperidine ring of immepip by a pyrrolidine ring led to a pair of enantiomers that show a distinct stereoselectivity at the human H_3 and H_4 receptor.

Introduction

Histamine, an autocoid as well as a neurotransmitter in the brain,[1] is endogenously synthesized from L-histidine by the enzyme L-histidine decarboxylase (HDC). The biogenic amine neurotransmitter is implicated in a wide range of physiological effects through the activation of distinct subtypes of histamine receptors. The histamine receptors, members of G-protein-coupled receptors (GPCRs) families, were initially categorized based on their pharmacological characterization, but are currently classified as H_1, H_2, H_3, and H_4 receptors owing to the diversity of their amino acid sequences.[2,3] The existence of a histamine H_3 receptor was reported for the first time in 1983 by Arrang and colleagues.[4] The receptor was identified as a presynaptic autoreceptor; activation of the H_3 receptor inhibits the synthesis and release of histamine from neurons. Subsequently, it has been found that the H_3 receptor also acts as a heteroreceptor on nonhistaminergic axon terminals controlling the release of several neurotransmitters, e.g., acetylcholine,[5,6] dopamine,[7] noradrenaline,[8] serotonin,[9] in both the central and peripheral nervous systems. Therapeutic applications of histamine H_3 receptor antagonists have been proposed for several diseases and CNS disorders, for example, attention-deficit hyperactivity disorder (ADHD),[10,11] Alzheimer's disease,[12] epilepsy,[13−15] schizophrenia,[15,16] and obesity,[17,18] whereas the therapeutic potential for histamine H_3 receptor agonists for myocardial ischemia, inflammatory, and gastric acid related diseases have also been published.[19−23] In 1999, the cDNA of the human H_3 receptor has been successfully cloned by Lovenberg et al.[24] Tissue distribution analysis indicated that the expression of the receptor is predominantly restricted to the brain.[25]

In 2000, the histamine H_4 receptor, mainly expressed on leukocytes, was identified.[26] The receptor is suggested to be a new therapeutic target for the regulation of immune functions with possible uses in allergy and asthma.[27] An alignment of deduced amino acid sequences of the human histamine H_4 receptor indicates an overall 43% identity homology to the histamine H_3 receptor.[28] Consequently, many imidazole-based histamine H_3 ligands also act at the H_4 receptor.

In a preliminary study from our laboratory, histamine and various homologues showed a high affinity and full agonist potency on the human H_3 receptor. Yet, the high flexibility of the ligand side chain does not seem to result in an optimal interaction between the ligand and the H_3 receptor. A recent study demonstrated that immepip, a conformationally constrained analogue of imbutamine (the butylene analogue of histamine), possesses a much higher affinity and functional activity on the human histamine H_3 receptors than the flexible imbutamine.[29] In this study, other conformationally constrained ligands were designed using histamine and its homologues as prototypes. All ligands were tested for their activities at both the human H_3 and H_4 receptor. The variation of the spacer length between the piperidine and the imidazole ring and/or alteration of nitrogen position in the piperidine ring will provide useful information for structure activity relationships (SAR) and molecular modeling studies of histamine H_3 receptor ligands. Moreover, characterization of these ligands on the

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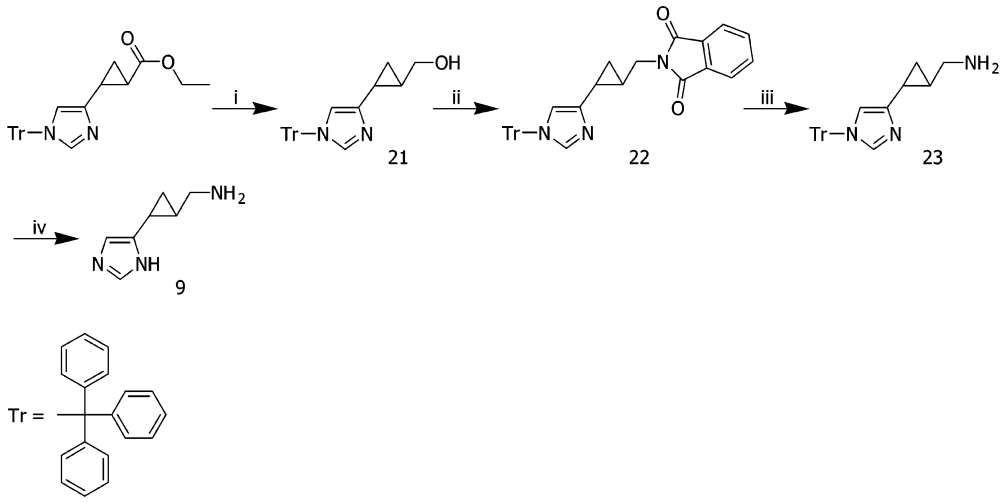
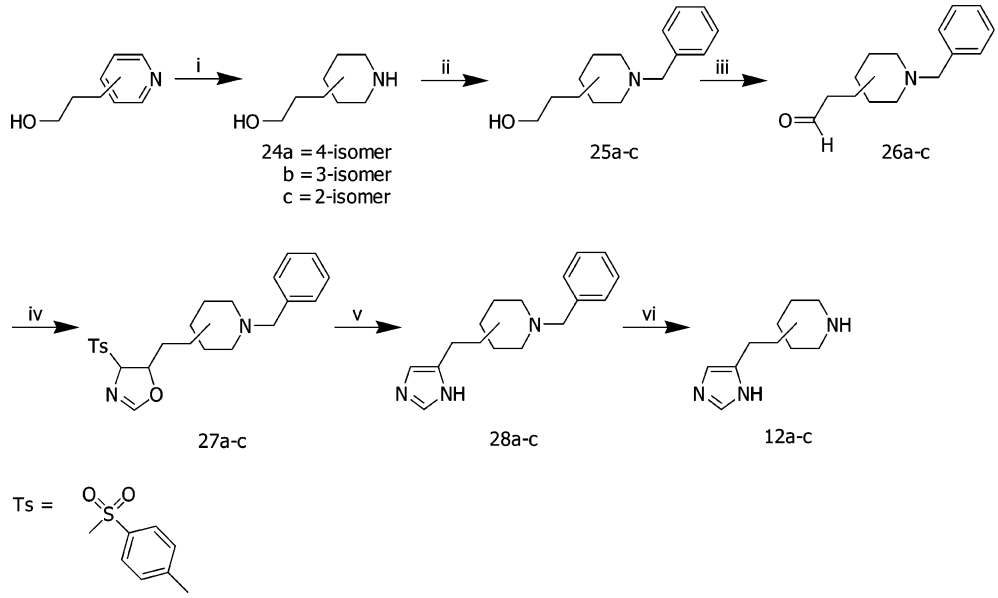
Scheme 1. Synthetic Pathway for **9**[a]



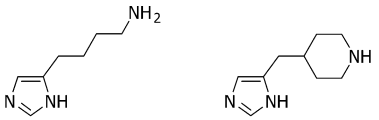
[a] Reagents and conditions: (i) $LiAlH_4$, ether, reflux 3 h; (ii) DEAD, phthalimide, triphenylphosphine, THF, rt, 2 h; (iii) hydrazine, EtOH, reflux, 6 h; (iv) 0.5 M HCl, reflux, 1.5 h.

Scheme 2. Synthetic Pathway for **12a**−**c**[a]



[a] Reagents and conditions: (i) 5% Rh/C, 10% Pd/C, glacial acetic acid, H_2 100 atm, 24 h; (ii) benzyl bromide, K_2CO_3, EtOH, rt, 1 h, reflux, 2 h; (iii) oxalyl chloride, dimethyl sulfoxide, triethylamine, DCM, −78 °C to rt, 5 h; (iv) TosMIC, NaCN, EtOH; (v) sat. NH_3 in EtOH, 90−110 °C, 10−12 atm, 24 h; (vi) 10% Pd/C, ammonium formate, MeOH, reflux, 24 h.

histamine H_4 receptor might provide a key for the development of histamine H_4 receptor ligands.

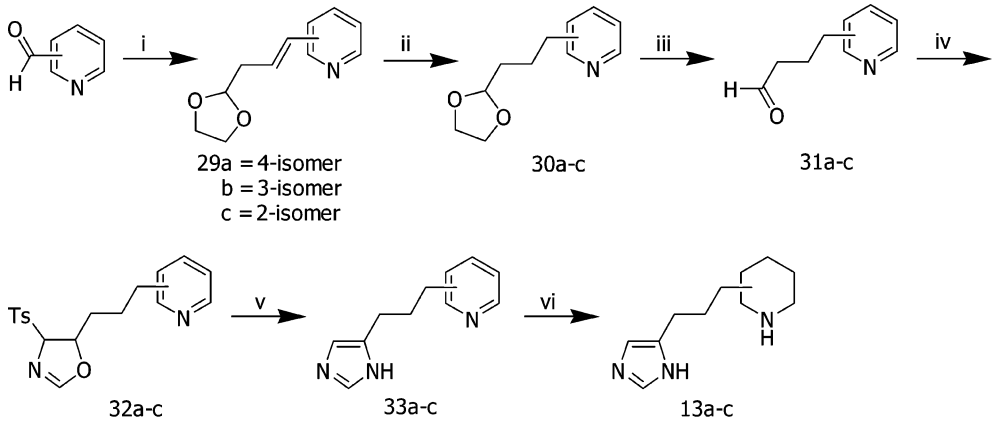


Chemistry

The synthesis of all compounds is outlined in Schemes 1−6. Compound **9** was synthesized (Scheme 1) from a known intermediate, (±)-*trans*-ethyl 2-(1-triphenylmethylimidazol-4-yl)cyclopropanecarboxylate.[30] Reduction of the intermediate using $LiAlH_4$ gave an alcohol (**21**), which was subsequently transformed into amine (**9**) via a Mitsunobu reaction and hydrolysis in a good yield (90%).[31,32]

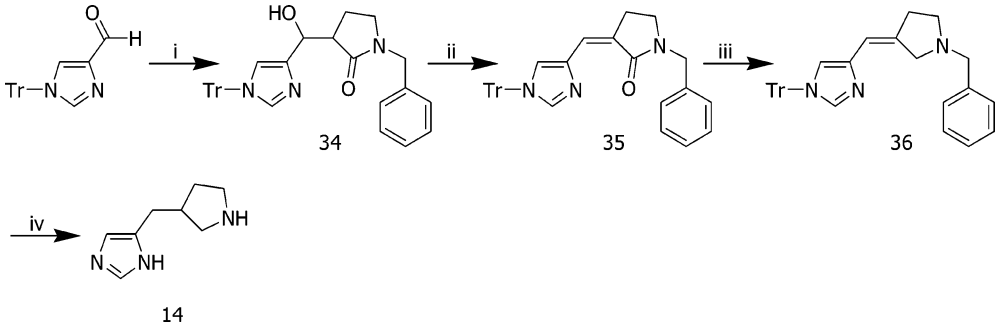
Compounds **12a**−**c** were prepared according to Scheme 2. The key intermediates, 3-piperidinepropanals (**26a**−**c**), were easily obtained from the corresponding pyridinepropanols via catalytic hydrogenation under acidic conditions, using Pd/C and Rh/C as catalysts. Next, the piperidine nitrogen was protected by treatment with benzylbromide[33,34] and the hydroxyl group was subsequently transformed into the corresponding aldehyde via a Swern oxidation.[35] The aldehyde group was readily converted to an imidazole ring using TosMIC chemistry.[36] Some of the intermediate 4-tosyloxazolines (**27a**−**c**) precipitated from the solution and were used after filtration. Otherwise, the mixture was concentrated and used immediately in the next step without further purification. The 4-tosyloxazolines were heated in a saturated solution of ammonia in ethanol to give the imidazole compounds in moderate to good yields. Debenzylation using ammonium formate in the presence

Scheme 3. Synthetic Pathway for **13a**−**c**[a]



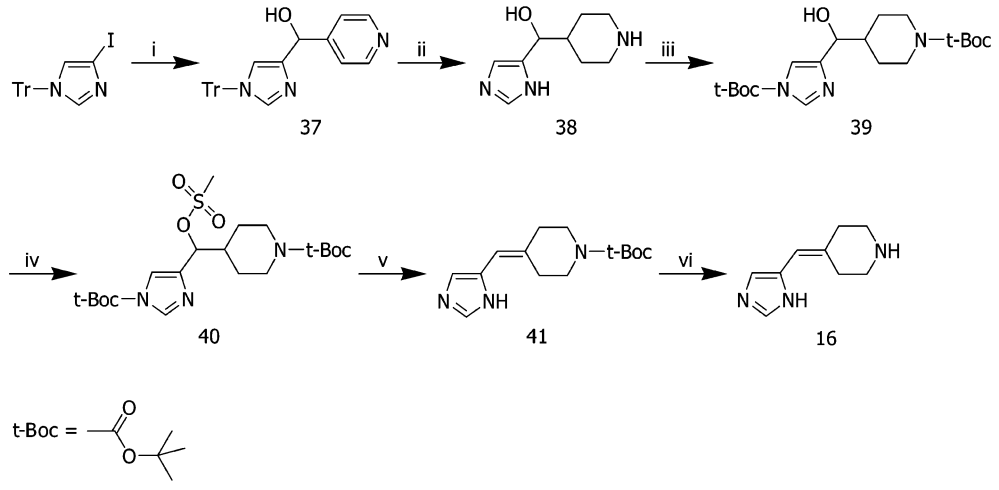
[a] Reagents and conditions: (i) *n*-BuLi, THF, [2-(1,3-dioxolan-2-yl)ethyl]triphenyl phosphonium bromide, −30 °C, 3 h; (ii) H_2, 5% Pd/C, 1 atm, 24 h; (iii) 1 N HCl, rt, 10 min; (iv) TosMIC, NaCN, EtOH, rt, 2 h; (v) sat. NH_3 in EtOH, 90−110 °C, 10−12 atm, 24 h; (vi) HBr, 10% Pd/C, 5% Rh/C, H_2, 100 atm, 48 h.

Scheme 4. Synthetic Pathway for **14**[a]



[a] Reagents and conditions: (i) *N*-benzylpyrrolidone, *n*-BuLi, −60 °C, THF; (ii) (1) $POCl_3$, pyridine, rt, 1 h, (2) DBU, rt, 3 h; (iii) $LiAlH_4$, THF, 0 °C, H_2SO_4; (iv) (1) $Pd(OH)_2$, MeOH, H_2, 50 atm, 72 h, (2) di-*tert*-butyl dicarbonate, triethylamine, MeOH, rt, (3) 2 N HBr.

Scheme 5. Synthetic Pathway for **16**[a]

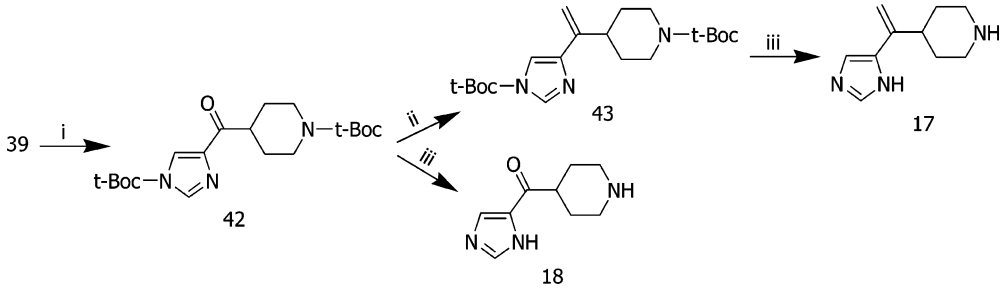


[a] Reagents and conditions: (i) EtMgBr, DCM, 4-pyridinecarboxaldehyde, rt, 16 h; (ii) HBr, 10% Pd/C, 5% Rh/C, 100 atm H_2, 48 h; (iii) di-*tert*-butyl dicarbonate, triethylamine, MeOH, rt; (iv) methanesulfonyl chloride, triethylamine, DCM; (v) $CaCO_3$, DMF, 140 °C; (vi) 1 N HCl.

of 10% Pd/C as a catalyst resulted in the final products (**12a**−**c**) in moderate yields (45−65%).

The synthesis of 3-(1*H*-imidazol-4-yl)propyl-piperidines (**13a**−**c**) followed Scheme 3. The intermediates, *ω*-pyridinebutanals, were synthesized using [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide and pyridinecarboxaldehydes as starting reagents and gave 3-(1,3-dioxolan-2-yl)propen-1-yl pyridines in high yields.[37] Many attempts to hydrolyze the dioxolane ring either in an acidic solution or in the presence of ferric chloride hexahydrate[38] in this step failed. However, after hydrogenation of **29** using Pd/C as catalyst, the resulting 3-(1,3-dioxolan-2-yl)propyl pyridines were easily hydrolyzed under mildly acidic conditions to give the corresponding pyridinebutanals (**31a**−**c**). The aldehyde group was converted to an imidazole ring via the aforemen-

Scheme 6. Synthetic Pathway for **17** and **18**[a]



[a] Reagents and conditions: (i) oxalyl chloride, dimethyl sulfoxide, triethylamine, DCM, −78 °C to rt, 5 h; (ii) methyl triphenylphosphonium bromide, potassium-*tert*-butoxide, toluene; 1 N HCl, rt; (iii) 1 N HCl, rt.

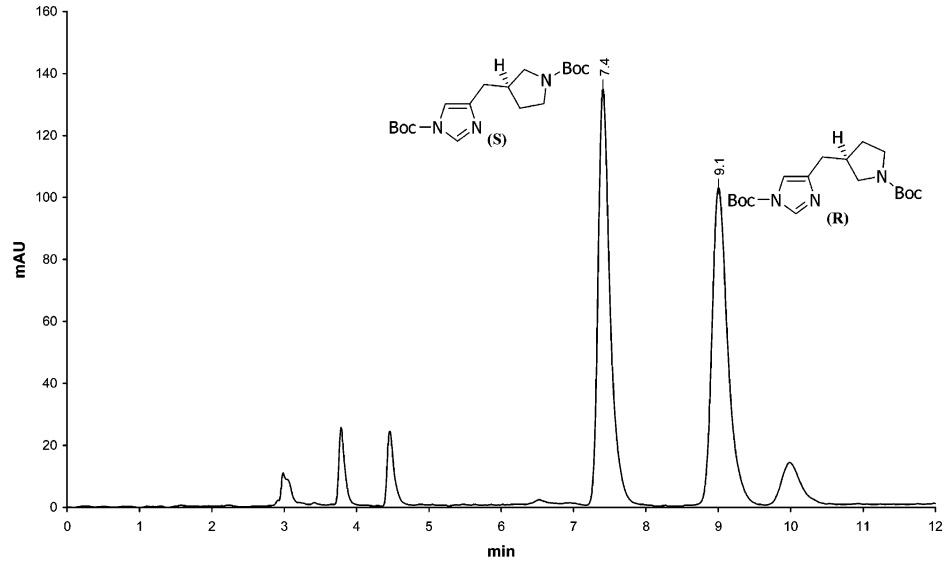


Figure 1. Chromatogram of enantiomers of bis-protected **14**. The enantiomers were separated by preparative liquid chromatography using a Chiralpak AD 100 × 500 mm column and eluted with a solution of 10% EtOH, 90% isohexane, and 0.1% DEA (diethylamine) at a flow rate of 300 mL/min. The collected peaks were controlled by HPLC using a Chiralpak AD-H column and eluted with a solution of 10% EtOH, 90% isohexane, and 0.1% DEA; the retention times of the (*S*)- and (*R*)-enatiomers were 7.4 and 9.1 min, respectively.

tioned TosMIC chemistry. Catalytic hydrogenation of the pyridine rings gave the final products (**13a**−**c**) in moderate yields (40−50%).

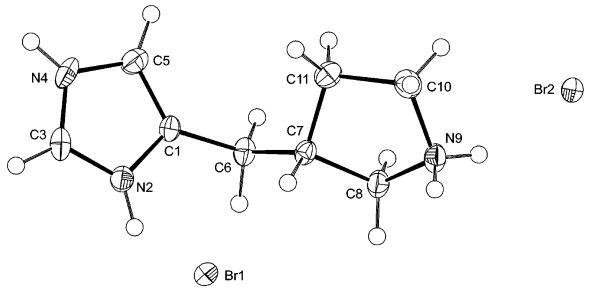
Compound **14** was prepared using 1-(triphenylmethyl)imidazol-4-ylcarboxaldehyde[39] as starting chemical (Scheme 4). The substance was reacted with *N*-benzylpyrrolidinone in the presence of *n*-BuLi to give an intermediate alcohol (**34**).[40] Dehydration of the alcohol using $POCl_3$ and DBU resulted in **35**. Lithium aluminum hydride reduction of the pyrrolidone provided the desired pyrrolidine (**36**). Hydrogenation of **36** using Pd-$(OH)_2$ as catalyst, in a one-pot procedure via simultaneous deprotection, debenzylation, and reduction of the double bond, gave the product **14** in a good yield (90%).

For the synthesis of 4-(1*H*-imidazol-4-ylmethylene)-piperidine (**16**), the intermediate (1*H*-imidazol-4-yl)-piperidin-4-ylmethanol (**38**) was required. Following Scheme 5, treatment of 4-iodo-1-trityl-1*H*-imidazole[41] with 4-pyridinecarboxaldehyde in the presence of ethylmagnesium bromide[42] and subsequently catalytic hydrogenation of the pyridine ring gave the desired intermediate (**38**) in a good yield (85%). Dehydration of the resulting intermediate under acidic conditions, however, did not provide **16**. In contrast, many unidentified products were observed. An alternative route was therefore considered: the compound **38** was first protected by treatment with di-*tert*-butyl dicarbonate to give **39**. The intermediate **39** was mesylated using methanesulfonyl chloride and subsequently heated under reflux in dimethylformamide in the presence of calcium carbonate to give **41**. In this step, deprotection of the imidazole nitrogen occurred, whereas the piperidine nitrogen remained protected. Deprotection of the piperidine nitrogen under mildly acidic conditions resulted in **16** in a good yield (90%).

Compounds **17** and **18** were synthesized according to Scheme 6. The intermediate alcohol (**39**) was transformed to ketone (**42**) via a Swern oxidation reaction. Treatment of **42** with methyl triphenylphosphonium bromide in the presence of potassium *tert*-butoxide gave **43** in a moderate yield (50%). Deprotection of the nitrogen atoms of **42** and **43** under mildly acidic conditions resulted in **18** and **17**, respectively.

Enantiomer Separation. The racemate **14** was protected by treatment with di-*tert*-butyl dicarbonate (using the procedure for **39**). The enantiomers were separated by preparative liquid chromatography using a Chiralpak AD 100 × 500 mm column and eluted with a solution of 10% EtOH, 90% isohexane, and 0.1% DEA (diethylamine) at a flow rate of 300 mL/min. The collected peaks were controlled by HPLC using a Chiralpak AD-H column and eluted with a solution of 10% EtOH, 90% isohexane, and 0.1% DEA, to give (*S*)- and (*R*)-**14** at the retention time of 7.4 and 9.1 min,

A



B

	D-H [Å]	H...Br [Å]	D....Br [Å]	D-H...Br [deg.]
N2-H2...Br1	0.89(2)	2.46(2)	3.2663(17)	152(2)
N4-H4...Br2^{i}	0.87(2)	2.40(3)	3.2511(18)	166(2)
N9-H9A...Br2	0.86(3)	2.51(3)	3.286(2)	151(3)
N9-H9B...Br2^{ii}	0.84(2)	2.52(2)	3.350(2)	164(2)
C3-H3...Br1^{iii}	0.94(2)	2.79(2)	3.692(2)	161.7(19)

Symmetry operations i: x, y, z+1; ii: x+0.5, 1.5-y, 1-z; iii: 1.5-x, 1-y, z+0.5

Figure 2. (A) Displacement ellipsoid plot of (*S*)-VUF4848 (**19**), drawn at the 50% probability level. Selected torsion angles (deg): C5−C1−C6−C7, 93.9(3); N2−C1−C6−C7, 84.5(2); C1−C6−C7−C8, 174.05(17); C1−C6−C7−C11, 70.1(2). (B) A table outlining the hydrogen bonding.

respectively (Figure 1). The compounds **19** and **20** were obtained after deprotection of the nitrogen atoms in 1 N HBr and recrystallization from EtOH/$(Et)_2O$.

Crystal Structure of (*S*)-VUF4848 (19). Single crystals of **19** for structure determination were obtained from EtOH and ether using the vapor phase diffusion technique:[43] $C_8H_{15}Br_2N_3$, Fw = 313.05, colorless needle, 0.36 × 0.15 × 0.09 mm^3, orthorhombic, $P2_12_12_1$ (no. 19), a = 8.2324(1) Å, b = 11.6971(1) Å, c = 12.0629(1) Å, V = 1161.60(2) Å^3, Z = 4, D_x = 1.790 g/cm^3, μ = 6.942 mm^{-1}. A total of 17 802 reflections were measured on a Nonius KappaCCD diffractometer with rotating anode (λ = 0.71073 Å) at a temperature of 150(2) K up to a resolution of $(\sin\theta/\lambda)_{max}$ = 0.65 Å^{-1}; 2662 reflections were unique (R_{int} = 0.046). An absorption correction based on multiple measured reflections was applied (0.30−0.49 transmission). The structure was solved with Patterson methods (DIRDIF-97) and refined with SHELXL-97 against F^2 of all reflections.[44,45] Non-hydrogen atoms were refined freely with anisotropic displacement parameters; hydrogen atoms were refined freely with isotropic displacement parameters (178 refined parameters, no restraints). R-values [$I > 2\sigma(I)$]: R1 = 0.0158, wR2 = 0.0363. R-values (all refln): R1 = 0.0174, wR2 = 0.0369. GoF = 1.045. Flack parameter x = −0.013(8).[46] Residual electron density was between −0.26 and 0.40 e/Å^3. Molecular illustration, structure checking, and calculations were performed with the PLATON package[47] (Figure 2).

Pharmacology

Radioligand Displacement Studies. Homogenates of SK-N-MC cells, stably expressing either the human histamine H_3[24] or the human histamine H_4 receptor,[27] were used for determining ligand affinities for the H_3 and H_4 receptor, respectively. Cell homogenates of H_3-receptor-expressing cells (131 ± 11 fmol/mg of protein) were incubated for 40 min at 25 °C with 0.9−1.1 nM [^{3}H]-N^{α}-methylhistamine (82 Ci/mmol) in 50 mM sodium phosphate buffer (pH 7.4) with or without competing ligands; cell homogenates of H_4-receptor-expressing cells (166 ± 26 fmol/mg of protein) were incubated for 60 min at 37 °C with 9−11 nM [^{3}H]histamine (23.2 Ci/mmol) in 50 mM Tris HCl (pH 7.4), with or without competing ligands.

Incubations were terminated by the addition of 3 mL of ice-cold wash buffer (H_3: 25mM Tris HCl, 145 mM NaCl, pH 7.4 at 4 °C; H_4: 50mM Tris HCl, pH 7.4 at 4 °C), and filtered through 0.3% polyethyleneimine-pretreated Whatman GF/C filters. Filters were subsequently washed twice with wash buffer. Retained radioactivity was determined by liquid scintillation counting. Nonspecific binding was defined with 1 μM thioperamide as competing ligand. Competition isotherms were analyzed with the GraphPad Prism software (GraphPad, Intuitive Software for Science, San Diego, CA). K_i values were determined with the equation $K_i = IC_{50}/(1 + ([ligand]/K_d))$. Protein concentrations were determined spectrophotometrically by a Packard Argus 400 microplate reader using the Bradford reagent,[48] with bovine serum albumin as a standard.

Colorimetric cAMP Assay. SK-N-MC cells stably expressing either the human histamine H_3 [24] or the human histamine H_4 receptor,[27] as well as a cyclic AMP responsive element (CRE)−responsive β-galactosidase reporter-gene were grown overnight in 96-well plates before the assay. To start the assay, the cells were incubated for 6 h with 1 μM forskolin and respective ligands at 37 °C. Thereafter, the medium was aspirated and cells were incubated overnight at 4 °C with 100 μL of assay buffer (100 mM NaH_2PO_4, 100 mM Na_2HPO_4, pH 8, 2 mM $MgSO_4$, 0.1 mM $MnCl_2$, 0.5% Triton, 40 mM β-mercaptoethanol, and 4 mM *o*-nitrophenyl-β-D-galactopyranoside (ONPG). The absorbance at 405 nm was determined by using a Victor^2 plate reader (Perkin-Elmer).

Results and Discussion

Characterization of histamine and its homologues (**1**−**5**) on the human histamine H_3 receptor showed that all longer homologues of histamine (**3**−**5**) display affinities as high as histamine, except compound **2**, which exhibits a lower affinity (pK_i = 7.31). Compared to histamine, impentamine exhibits a 4-fold increase in the functional activity (pEC_{50} = 8.63), whereas the shorter and longer homologues are somewhat less effective. The optimum chain length between the imidazole ring and the side chain nitrogen in the series is five methylene units. Although the longer homologue (**5**) still shows moderate affinity and functional activity on the histamine H_3 receptor, its intrinsic activity is decreased (α = 0.61).

As previously reported, (*R*)-α-methylhistamine (**6**) possesses an affinity as high as histamine for the human H_3 receptor.[25] Interestingly, the compound exhibited a 10-fold increase in functional activity (pEC_{50} = 9.17). The activities of two rigid analogues of histamine (**7** and **8**) confirmed that a small group on the chain between the imidazole ring and the side chain amine is tolerated. The (*S*,*S*)-diastereomer **8**, however, has higher affinity and functional activity on the receptor (pK_i = 8.03, pEC_{50} = 8.23) than the (*R*,*R*)-diastereomer **7** (pK_i = 7.17, pEC_{50} = 7.24). On the histamine H_4 receptor, an additional group on the ethylene chain of histamine led to a decrease in affinity and functional activity. For

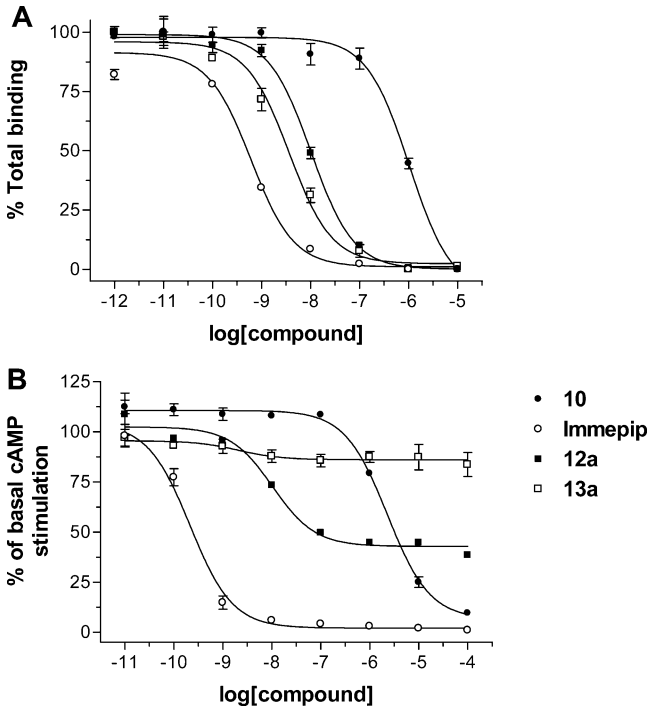


Figure 3. Affinities and functional activities of immepip and its homologues with variations in the spacer between the imidazole and the piperidine ring, on the histamine H_3 receptor. (A) Receptor affinities were determined by displacement of [^{3}H]-N^{α}-methylhistamine binding to membranes of SK-N-MC cells stably expressing the human H_3 receptor. (B) Histamine H_3 agonistic responses were measured by CRE-mediated β-galactosidase reporter gene assay.

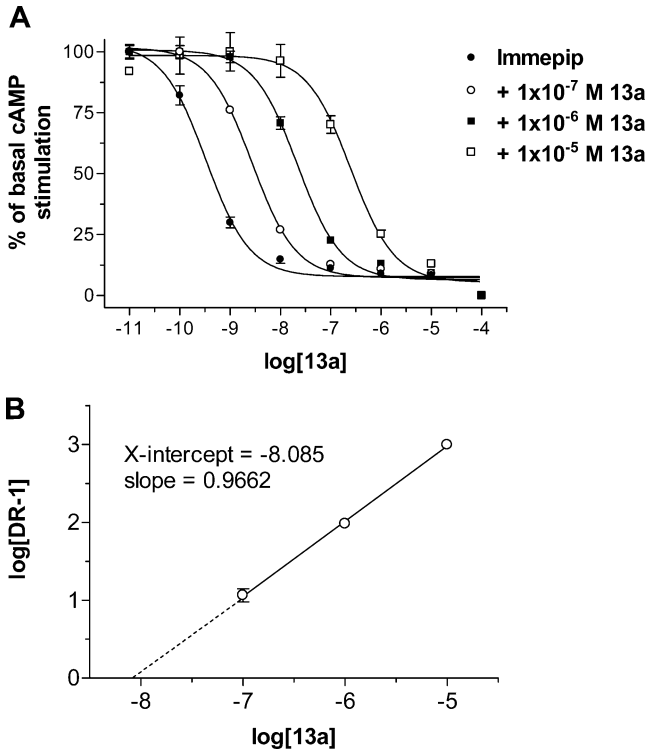


Figure 4. (A) Rightward shift of concentration−response curves of immepip in the presence of various concentration of **13a** determined by the inhibition of the CRE-stimulated β-galactosidase transcription in SK-N-MC cell expressing the human H_3 receptor. (B) Schild plot demonstrating the determination of the antagonist potency (pA_2 value) of **13a** at the human H_3 receptor.

instance (*R*)-α-methylhistamine (**6**) possessed a 15-fold decrease in affinity and a 20-fold decrease in functional activity ($pK_i = 6.62$, $pEC_{50} = 5.95$) at histamine H_4 receptor.

In the series of ligands containing a 4-piperidine ring, immepip (**11a**) exhibited the highest affinity and functional activity on both histamine H_3 and H_4 receptors. Increasing or decreasing in the spacer length between the imidazole and piperidine ring of immepip (**10**, **12a**, **13a**) led to a decrease in affinity and functional activity (Figure 3). The shorter homologue (**10**), however, retained full agonistic activity on the H_3 receptor, whereas the longer homologues behaved as partial agonist (**12a**, $\alpha = 0.60$) or did not show any agonistic response (**13a**). Nevertheless, compound **13a** exhibited a nanomolar affinity for the H_3 receptor ($pK_i = 8.35$).

The histamine H_3 receptor shows a high level of constitutive activity, i.e., it signals via G_i proteins without the presence of an H_3 agonist.[49,50] Currently, the H_3 receptor is one of the few examples of GPCRs for which constitutive activity has been reported to appear in vivo (rat and mouse brain). The occurrence of constitutive activity leads to a reclassification of H_3 antagonists into inverse agonists (i.e. they inhibit constitutive H_3 receptor signaling) and neutral antagonists (i.e. they do not affect constitutive signaling, but competitively block the effect of agonists and inverse agonists). So far only two ligands have been recognized as neutral antagonists. We previously reported on *N*-isopropylimpentamine as a neutral antagonist at the human H_3 receptor ($pK_i = 7.89$),[50] while proxyfan has been shown to be a neutral antagonist in both rat and mouse brain but acts as a full agonist at the human H_3 receptor.[49,51]

In view of the high affinity and lack of pharmacological responses, we hypothesized that compound **13a** could be a novel neutral antagonist at the human H_3 receptor. As can be seen in Figure 4, compound **13a** effectively antagonizes the response to immepip, yielding a pA_2 value of 8.1 ± 0.1 ($n = 6$). In our current experimental model system, the known inverse agonistic actions of thioperamide and clobenpropit are easily detectable (data not shown), indicating that compound **13a** acts as a high-affinity neutral antagonist on the human H_3 receptor, indeed. Moreover, characterization of **13a** on the human H_4 receptor ($pK_i = 6.21$) implied selectivity of the ligand on the H_3 receptor. On the basis of these observations, we conclude that elongation of the spacer between the imidazole ring and the side chain nitrogen does not significantly influence the affinity but obviously reduces the agonistic activity of the ligand.

Alterations of the nitrogen position in the piperidine ring resulted in a decrease of affinity and functional activity independent of the length of the spacer in the side chain (**11a**→**b**→**c**, **12a**→**b**→**c**, and **13a**→**b**→**c**). Although in **11a**, **12b**, **13c**, and **3**, the distances between the side chain nitrogen and the imidazole ring are not significantly different (five methylene units), **12b** and **13c** showed a 100-fold decrease in affinity at both the H_3 and H_4 receptor (Tables 1 and 3). The results not only indicate the crucial role of the side chain nitrogen in the binding, but also imply that the steric environment around the side chain nitrogen affects the interaction between the piperidine nitrogen and the binding

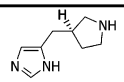
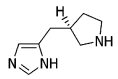
Table 1. Affinities and Functional Activities of Histamine, Homologues of Histamine, and Some Conformationally Constrained Ligands on the Human Histamine H_3 Receptors[d]

No	VUF	R	n	Human histamine H_3 receptor		
				pK_i ± SEM[a]	pEC_{50} ± SEM[b]	Intrinsic activity (α)
1	histamine		2	8.03 ± 0.06	8.01 ± 0.03	1.00
2	8326		3	7.31 ± 0.02	7.37 ± 0.17	0.86
3	imbutamine		4	8.39 ± 0.03	8.13 ± 0.08	0.89
4	impentamine		5	8.29 ± 0.14	8.63 ± 0.08	0.87
5	4732		6	8.00 ± 0.17	7.48 ± 0.23	0.61
6	RAMH		-	8.36 ± 0.07	9.17 ± 0.03	0.95
7	5296		-	7.17 ± 0.09	7.24 ± 0.04	0.90
8	5297		-	8.03 ± 0.08	8.23 ± 0.14	0.97
9	(±) 4899		-	7.45 ± 0.07	7.71 ± 0.05	0.88
10	4735		0	6.06 ± 0.07	5.74 ± 0.05	0.95
11a	immepip		1	9.32 ± 0.04	9.88 ± 0.02	0.96
12a	4929		2	7.70 ± 0.13	7.88 ± 0.13	0.60
13a	5681		3	8.35 ± 0.11	8.08 ± 0.03[c]	0
11b	(±) 4858		1	7.17 ± 0.09	7.31 ± 0.03	0.91
12b	(±) 5655		2	6.74 ± 0.11	6.29 ± 0.18	0.34
13b	(±) 5682		3	7.08 ± 0.11	7.59 ± 0.34	-0.29
11c	(±) 4888		1	5.94 ± 0.09	6.10 ± 0.08	0.96
12c	(±) 5656		2	5.55 ± 0.02	< 5	n.d.
13c	(±) 5683		3	7.03 ± 0.02	6.49 ± 0.01	0.74
14	(±) 4848		-	8.44 ± 0.06	8.88 ± 0.09	0.96
15	4736		-	5.37 ± 0.03	5.82 ± 0.13	0.96
16	5510		-	8.23 ± 0.02	8.50 ± 0.01	0.90
17	5465		-	8.40 ± 0.14	8.63 ± 0.08	0.92
18	5464		-	5.41 ± 0.09	5.56 ± 0.11	0.98

[a] The pK_i values were measured by [^{3}H]-N^{α}-methylhistamine binding to membranes of SK-N-MC cells expressing the human H_3 receptor. [b] The pEC_{50} values were determined by the inhibition of the cAMP-stimulated β-galactosidase transcription in SK-N-MC cell expressing the human H_3 receptor. The results were presented as the mean ± SEM of at least three independent experiments, otherwise the number of experiments is mentioned in parentheses. [c] The pA_2 value was determined from the Schild plot (Figure 4). The results are represented as the mean ± SEM of three independent experiments. [d] n.d. = not determined.

site on both the H_3 and H_4 receptors. Replacement of the piperidine ring of **11b** by a pyrrolidine ring (**14**), which due to the reduced ring size provides less steric interference, leads to an improved affinity and functional activity (pK_i = 8.44, pEC_{50} = 8.88). Characterization of the enantiomers of **14** (**19** and **20**) on the histamine H_3 receptor showed that the (*S*)-enantiomer (**19**), the absolute configuration of which was identified by X-ray crystallography (Figure 2), exhibits a higher affinity and functional activity than (*R*)-enantiomer (**20**). Intriguingly, reverse results were obtained on the H_4 receptor, since the (*R*)-enantiomer **20** possesses higher affinity and functional activity than (*S*)-enantiomer **19**.

Table 2. Affinities and Functional Activities of the Two Enantiomers of **14** on the Human Histamine H_3 Receptor

No	VUF	Structures	Human histamine H_3 receptor		
			pK_i ± SEM[a]	pEC_{50} ± SEM[b]	Intrinsic activity (α)
19	(+,*S*) 4848		8.85 ± 0.03	9.41 ± 0.07	0.96
20	(-,*R*) 4848		8.28 ± 0.05	8.68 ± 0.09	0.96

[a] The pK_i values were measured by [^{3}H]-N^{α}-methylhistamine binding to membranes of SK-N-MC cells expressing the human H_3 receptor. [b] The pEC_{50} values were determined by the inhibition of the cAMP-stimulated β-galactosidase transcription in SK-N-MC cell expressing the human H_3 receptor. The results are presented as the mean ± SEM of at least three independent experiments.

Table 3. Affinities and Functional Activities of Histamine, Homologues of Histamine and Some Conformationally Constrained Ligands on the Human Histamine H_4 Receptors

no.	human histamine H_4 receptor			selectivity (Δ)[c]
	pK_i ± SEM[a]	pEC_{50} ± SEM[b]	intrinsic activity (α)	
1	7.84 ± 0.03	7.26 ± 0.12	1.00	1.6
2	7.46 ± 0.12	6.67 ± 0.17	0.82	0.7
3	7.84 ± 0.09	7.05 ± 0.04	0.96	3.6
4	6.43 ± 0.08	<5	n.d[d]	72.4
5	6.12 (1)	<5	n.d.	75.8
6	6.62 ± 0.04	5.95 ± 0.09	1.04	55.0
7	5.42 ± 0.04	<5	n.d.	56.2
8	5.96 ± 0.01	5.15 ± 0.27	0.61	117.5
9	6.95 ± 0.10	5.96 ± 0.26	0.56	3.2
10	5.66 ± 0.05	<5	n.d.	2.5
11a	7.66 ± 0.04	7.25 ± 0.16	0.73	45.7
12a	6.43 ± 0.05	<5	n.d.	18.6
13a	6.21 ± 0.02	<5	n.d.	138.0
11b	6.21 ± 0.04	5.40 ± 0.17	0.64	9.1
12b	6.49 ± 0.04	5.69 ± 0.15	0.48	1.8
13b	6.41 ± 0.02	<5	n.d.	4.7
11c	5.05 ± 0.10	<5	n.d.	7.8
12c	5.35 ± 0.01	<5	n.d.	1.6
13c	6.24 ± 0.04	<5	n.d.	6.2
14	7.29 ± 0.13	6.13 ± 0.18	0.83	14.1
15	3.58 ± 0.25	<5	n.d.	61.6
16	5.76 ± 0.03	<5	n.d.	295.1
17	5.55 ± 0.03	<5	n.d.	707.9
18	3.32 ± 0.22	<5	n.d.	123.0
19	6.85 ± 0.06	5.99 ± 0.07	0.80	100.0
20	7.43 ± 0.13	6.38 ± 0.05	0.85	7.1

[a] The pK_i values were measured by [^{3}H]histamine binding to membranes of SK-N-MC cells expressing the human H_4 receptor. [b] The pEC_{50} values were determined by the inhibition of the cAMP-stimulated β-galactosidase transcription in SK-N-MC cell expressing the human H_4 receptor. The results were presented as the mean ± SEM of at least three independent experiments, otherwise the number of experiments is mentioned in parentheses. [c] Selectivity was calculated from equation $\Delta = 1/[K_i(H_3)/K_i(H_4)]$. [d] n.d. = not determined.

A further reduction of the conformational flexibility as in **15**−**18** led to a decrease in affinity and functional activity both on the human H_3 and H_4 receptors (Tables 1 and 3) compared to their prototypes (**10** and **11a**). Although compounds **16** and **17** exhibited decreased affinity and functional activity at the histamine H_3 receptor as full agonists, the selectivity for the histamine H_3 receptor over the H_4 receptor is increased (300- and 700-fold, respectively; Table 3). In contrast, compounds **15** and **18** lost affinity and functional activity at both the human histamine H_3 and H_4 receptors. Comparing **18** with **17** might indicate the crucial role of the basic properties of the imidazole ring in the binding, since an earlier report shows that incorporation of a carbonyl adjacent to an imidazole ring results in massive decreased basicity.[52] Surprisingly, this modification does not affect the (full) agonistic activity at the histamine H_3 receptor ($\alpha = 0.98$) but only affects the binding affinity.

Conclusions

Characterization of a series of compounds containing a basic amine in the side chain indicates that additional substituents on α and/or β positions are tolerated at the human H_3 receptor but not at the human H_4 receptor. On the H_3 receptor, the optimum chain length between an imidazole ring and the basic nitrogen in the side chain is five methylene units. Elongation of the spacer between the imidazole ring and the nitrogen in the side chain did not tremendously affect the affinity and functional activity, but a reduction of intrinsic activity was clearly observed. In most cases, a more rigid side chain improved the affinity and functional activity of the ligands. The 4-piperidinyl analogues possess the highest affinity and functional activity on the receptor compared to other isomers. In this study immepip (**11a**), a conformationally constrained analogue of **3**, is the most potent agonist on both human H_3 and H_4 receptors. Elongation of the spacer between the imidazole ring and the piperidine ring results in a decrease of intrinsic activity at the histamine H_3 receptor. Compound **13a**, a propylene homologue of immepip, indeed behaves as a high-affinity neutral antagonist on the human histamine H_3 receptor. Although more conformationally constrained analogues of **11a** (**16**−**18**) do not show an improved affinity and efficacy, they could become valuable for molecular modeling studies. The loss of affinity of **18** at both the histamine H_3 and H_4 receptors might indicate the crucial role of the basic properties of the imidazole ring in the binding.

Experimental Section

Materials. Reagents were obtained from commercial suppliers and used without further purification, except the pyridinepropanols and the pyridinecarboxylaldehydes, which were purified by distillation under reduce pressure. Solvents used were either AR or HPLC grade. Dry THF and DCM were distilled from $LiAlH_4$ and CaH_2, respectively. Compounds **1**−**8** were obtained from laboratory stock,[30,53] compounds **10** and **15** were synthesized according to the method of Lange et al.[54] All structure confirmations and purities are presented in Table 4. Thin-layer chromatography was carried out on Merck Kieselgel 60 F_{254} on aluminum sheets, and flash chromatography was performed using J. T. Baker Kieselgel 60 under pressure. Melting points were determined on an Electrothermal IA9200 apparatus. ^{1}H spectra were recorded on a Bruker AC-200 spectrometer at 200 MHz using the residual undeuterated solvent peak as reference. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Elemental analyses were performed at Mikroanalytisches Labor Pascher (Remagen-Bandorf, Germany).

Methods. 2-(1-Triphenylmethylimidazol-4-yl)cyclopropylmethanol (21). Ethyl 2-(1-triphenylmethylimidazol-4-yl)-cyclopropanecarboxylate (13.1 mmol) was added to a suspension of 25.8 mmol of $LiAlH_4$ in 100 mL of dry ether and heated under reflux for 3 h. Slowly, 100 mL 0.1 M NaOH was added and the mixture was extracted with $CHCl_3$ (3 × 100 mL). The organic layers were washed with 100 mL of $NaHCO_3$ and 100 mL of brine and dried with Na_2SO_4. Concentration in vacuo gave **21** (70%) as white crystals. ^{1}H NMR ($CDCl_3$): δ 7.03−7.37 (m, 16H), 6.50 (s, 1H), 3.41−3.64 (m, 1H), 2.15 (br, 1H), 1.67−1.78 (m, 1H), 1.38−1.49 (m, 1H), 0.89−0.98 (m, 1H), 0.68−0.77 (m, 1H).

***N*-[2-(1-Triphenylmethylimidazol-4-yl)cyclopropylmethyl]phthalimide (22).** Diethyl diazodicarboxylate (3.65 mmol) was added to a solution of 2.26 mmol of **21**, 3.64 mmol of phthalimide, and 3.46 mmol of triphenylphosphine in 50 mL of THF and stirred for 2 h at ambient temperature under an atmosphere of dry nitrogen. The mixture was washed with 50 mL water and the aqueous layer was extracted DCM (2 × 50 mL). The combined organic layers were washed with 50 mL of brine and dried with Na_2SO_4. Concentration in vacuo gave an oil which was purified by column chromatography using DCM/EtOAc (4:1) as eluent to give **22** (99%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.78−7.86 (m, 2H), 7.64−7.72 (m, 2H), 7.01−7.31 (m, 16H), 6.49 (s, 1H), 3.83 (dd, 1H, J = 7.0 and 13.9 Hz), 3.50 (dd, 1H, J = 7.0 and 13.9 Hz), 1.81−1.91 (m, 1H), 1.40−1.50 (m, 1H), 0.88−0.98 (m, 2H).

2-(1-Triphenylmethylimidazol-4-yl)cyclopropylmethylamine (23). Compound **22** (1.49 mmol) and 0.29 mL of hydrazine hydrate in 50 mL of EtOH were heated under reflux for 6 h. The reaction mixture was cooled to 0 °C and filtered. Evaporation of the mother liquor gave **23** (88%) as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 7.03−7.35 (m, 16H), 6.50 (s, 1H), 2.67 (d, 2H, J = 7.2 Hz), 2.10 (br, 2H), 1.57−1.68 (m, 1H), 1.19−1.31 (m, 1H), 0.82−0.94 (m, 1H), 0.61−0.72 (m, 1H).

2-(1*H*-Imidazol-5-yl)cyclopropylmethylamine Dihydrochloride (9). Compound **23** (1.24 mmol) was dissolved in 25 mL of EtOH and 25 mL of 0.5M HCl and heated at reflux for 1.5 h. The ethanol was evaporated completely and the solid, triphenylmethanol, was filtered. The mother liquor was further concentrated and the product (**9**) was recrystallized from 2-propanol as an off-white solid (44%). ^{1}H NMR (D_2O): δ 8.5 (s, 1H), 7.2 (s, 1H), 3.0−3.1 (m, 2H), 2.0 (m, 1H), 1.5 (m, 1H), 1.1−1.2 (m, 2H).

3-(Piperidinyl)propan-1-ol Acetate Salt (24a−c). Pyridinepropanol (0.15 mol) was dissolved in 100 mL of glacial acetic acid, and 1 g of 10% Pd/C and 0.5 g of 5% Rh/C were added. The suspension was hydrogenated under 100 atm of H_2 for 2 h in a stainless steel bomb. The mixture was filtered through a short column of Hyflo super cel and the solvent was evaporated under reduced pressure to obtain the product as an oil, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): **24a** (95%), δ 3.7 (t, 2H), 3.0 (m, 2H), 2.7 (m, 2H), 2.0 (s, 3H), 1.8 (m, 2H), 1.3−1.6 (m, 7H); **24b** (92%), δ 3.7 (t, 2H), 3.3 (m, 2H), 2.7 (m, 1H), 2.4 (m, 1H), 2.0 (s, 3H), 1.8 (m, 4H), 1.5 (m, 2H), 1.3 (m, 2H), 1.1 (m, 1H); **24c** (95%), δ 3.7 (t, 2H), 3.4 (m, 1H), 2.9 (m, 1H), 2.7 (m, 1H), 1.9 (s, 3H), 1.4−1.8 (m, 10H).

3-(*N*-Benzylpiperidinyl)propan-1-ol (25a−c). Compound **24 (**0.11 mol), 0.11 mol of benzyl bromide, and 0.50 mol of potassium carbonate were stirred in 150 mL of absolute ethanol at room temperature for 1 h and then heated at reflux for 2 h. The solvent was removed under reduced pressure. Saturated potassium carbonate solution (100 mL) was added and the mixture was extracted with DCM (3 × 100 mL). The organic layers were dried with anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified using flash column chromatography (EtOAc/EtOH, 1:2), and the product was obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): **25a** (75%), δ 7.2−7.3 (m, 5H), 3.6 (t, 2H), 3.5 (s, 2H), 2.8 (m, 2H),

Table 4. Structural Characterization and Purity of Compounds

no.	mp	NMR (D_2O)	[α]	formula	elemental analysis
7[a]	207	δ 8.6 (s, 1H), 7.2 (s, 1H), 3.0 (ddd, 1H, *J* = 3.6, 4.5, and 8.2 Hz), 2.5 (ddd, 1H, *J* = 3.4, 6.5, and 10.1 Hz), 1.6 (ddd, 1H, *J* = 4.7, 7.2 and 10.2 Hz), 1.4 (ddd, 1H, *J* = 6.7, 6.9 and 8.2 Hz)	+54.4		
8[a]	207	δ 8.6 (s, 1H), 7.2 (s, 1H), 3.0 (ddd, 1H, *J* = 3.6, 4.5, and 8.2 Hz), 2.5 (ddd, 1H, *J* = 3.4, 6.5, and 10.1 Hz), 1.6 (ddd, 1H, *J* = 4.7, 7.2 and 10.2 Hz), 1.4 (ddd, 1H, *J* = 6.7, 6.9 and 8.2 Hz)	−54.2		
9	265	δ 8.5 (s, 1H), 7.2 (s, 1H), 3.0−3.1 (m, 2H), 2.0 (m, 1H), 1.5 (m, 1H), 1.1−1.2 (m, 2H)		$C_7H_{13}N_3Cl_2$	Anal. (40.27% C, 6.33% H, 19.9% N) Calcd (40.0% C, 6.2% H, 20.0% N)
10	279	δ 8.8 (s, 1H), 7.5 (s, 1H), 3.6 (m, 2H), 3.3 (m, 3H), 2.4 (m, 2H), 2.0 (m, 2H)		$C_8H_{15}N_3Br_2$	Anal. (30.50% C, 4.73% H, 13.3% N) Calcd (30.7% C, 4.8% H, 13.4% N)
11a	230	δ 8.5 (s, 1H), 7.3 (s, 1H), 3.4 (m, 2H), 2.8−3.0 (m, 2H), 2.7 (d, 2H, *J* = 7 Hz), 1.8−2.0 (m, 3H), 1.3−1.5 (m, 2H)		$C_9H_{17}N_3Br_2$	Anal. (33.11% C, 5.13% H, 12.8% N) Calcd (33.1% C, 5.2% H, 12.8% N)
12a	224	δ 8.5 (s, 1H), 7.2 (s, 1H), 3.4 (m, 2H), 2.8−2.9 (m, 2H), 2.7 (m, 2H), 1.9 (m, 2H), 1.6 (m, 3H), 1.4 (m, 2H)		$C_{10}H_{19}N_3Br_2$	Anal. (35.34% C, 5.53% H, 12.4% N) Calcd (35.2% C, 5.6% H, 12.3% N)
13a	179	δ 8.5 (s, 1H), 7.2 (s, 1H), 3.4 (m, 2H), 2.9 (m, 2H), 2.7 (t, 2H), 1.9 (d, 2H), 1.6 (m, 3H), 1.3 (m, 4H)		$C_{11}H_{21}N_3Br_2$	Anal. (37.43% C, 6.11% H, 11.6% N) Calcd (37.2% C, 6.0% H, 11.8% N)
11b	244	δ 8.6 (s, 1H), 7.3 (s, 1H), 3.3−3.6 (m, 2H), 2.6−3.0 (m, 4H), 2.0−2.2 (m, 1H), 1.5−2.0 (m, 3H), 1.2−1.4 (m, 1H)		$C_9H_{17}N_3Br_2$	Anal. (32.94% C, 5.26% H, 12.9% N) Calcd (33.1% C, 5.2% H, 12.8% N)
12b	162	δ 8.5 (s, 1H), 7.2 (s, 1H), 3.3 (m, 2H), 2.6−2.9 (m, 4H), 1.8 (m, 2H), 1.6 (m, 4H), 1.1−1.3 (m, 1H)		$C_{10}H_{19}N_3Br_2$	Anal. (35.54% C, 5.79% H, 12.8% N) Calcd (35.2% C, 5.6% H, 12.3% N)
13b	157	δ 8.5 (s, 1H), 7.2 (s, 1H), 3.4 (m, 2H), 2.9 (m, 1H), 2.5−2.7 (m, 3H), 1.9 (d, 2H), 1.7 (m, 4H), 1.1−1.3 (m, 3H)		$C_{11}H_{21}N_3Br_2$	Anal. (37.96% C, 6.22% H, 11.6% N) Calcd (37.2% C, 6.0% H, 11.8% N)
11c	197	δ 8.6 (s, 1H), 7.4 (s, 1H), 3.3−3.6 (m, 2H), 2.9−3.2 (m, 3H), 1.4−2.0 (m, 6H)		$C_9H_{17}N_3Br_2$	Anal. (33.27% C, 5.48% H, 12.9% N) Calcd (33.1% C, 5.2% H, 12.8% N)
12c	200	δ 8.5 (s, 1H), 7.2 (s, 1H), 3.4 (m, 1H), 3.2 (m, 1H), 2.7−3.0 (m, 3H), 1.8−2.0 (m, 5H), 1.4−1.7 (m, 3H)		$C_{10}H_{19}N_3Br_2$	Anal. (35.83% C, 5.85% H, 12.9% N) Calcd (35.2% C, 5.6% H, 12.3% N)
13c	167	δ 8.5 (s, 1H), 7.2 (s, 1H), 3.4 (m, 1H), 3.2 (m, 1H), 3.0 (m, 1H), 2.8 (t, 2H), 1.2−1.8 (m, 10H)		$C_{11}H_{21}N_3Br_2$	Anal. (37.29% C, 6.14% H, 11.9% N) Calcd (37.2% C, 6.0% H, 11.8% N)
14	147	δ 8.6 (s, 1H), 7.2 (s, 1H), 3.2−3.5 (m, 3H), 2.8−3.0 (m, 3H), 2.7 (m, 1H), 2.1 (m, 1H), 1.7 (m, 1H)		$C_8H_{15}N_3Br_2$	Anal. (30.68% C, 4.82% H, 13.6% N) Calcd (30.7% C, 4.8% H, 13.4% N)
15	273	δ 8.7 (s, 1H), 7.5 (s, 1H), 6.4 (m, 1H), 3.9 (s, 2H), 3.5 (t, 2H, *J* = 7 Hz), 2.8 (m, 2H)		$C_8H_{13}N_3Br_2$	Anal. (30.58% C, 4.19% H, 13.3% N) Calcd (30.9% C, 4.2% H, 13.5% N)
16	250	δ 8.7 (s, 1H), 7.5 (s, 1H), 6.4 (s, 1H), 3.3 (m, 4H), 2.8 (m, 4H)		$C_9H_{15}N_3Cl_2$	Anal. (45.51% C, 6.45% H, 17.6% N) Calcd (45.8% C, 6.4% H, 17.8% N)
17	257	δ 8.6 (s, 1H), 7.5 (s, 1H), 5.6 (s, 1H), 5.3 (s, 1H), 3.5 (m, 2H), 3.1 (m, 2H), 2.7 (m, 1H), 2.1 (m, 2H), 1.5−1.7 (m, 2H)		$C_{10}H_{17}N_3Cl_2$	Anal. (48.06% C, 6.90% H, 17.1% N) Calcd (48.0% C, 6.8% H, 16.8% N)
18	328	δ 8.8 (s, 1H), 8.3 (s, 1H), 3.5 (m, 3H), 3.1 (m, 2H), 2.1 (m, 2H), 1.0 (m, 2H)		$C_9H_{15}N_3OCl_2$	Anal. (42.50% C, 6.00% H, 16.7% N) Calcd (42.9% C, 6.0% H, 16.7% N)
19	147	δ 8.6 (s, 1H), 7.2 (s, 1H), 3.2−3.5 (m, 3H), 2.8−3.0 (m, 3H), 2.7 (m, 1H), 2.1 (m, 1H), 1.7 (m, 1H)	+5.0[b]	$C_8H_{15}N_3Br_2$	Anal. (30.75% C, 4.78% H, 13.5% N) Calcd (30.7% C, 4.8% H, 13.4% N)
20	147	δ 8.6 (s, 1H), 7.2 (s, 1H), 3.2−3.5 (m, 3H), 2.8−3.0 (m, 3H), 2.7 (m, 1H), 2.1 (m, 1H), 1.7 (m, 1H)	−5.0[b]	$C_8H_{15}N_3Br_2$	Anal. (30.62% C, 4.77% H, 13.4% N) Calcd (30.7% C, 4.8% H, 13.4% N)

[a] See ref 30. [b] $[\alpha]_D^{22}$ (*c* = 0.52, MeOH).

1.9 (m, 2H), 1.5−1.6 (m, 5H), 1.1−1.2 (m, 4H); **25b** (83%), δ 7.2−7.3 (m, 5H), 3.6 (t, 2H), 3.5 (s, 2H), 2.7 (m, 2H), 1.5−1.9 (m, 8H), 1.2 (m, 2H), 0.9 (m, 1H); **25c** (75%), δ 7.2−7.3 (m, 5H), 4.0 (d, 1H, *J* = 14 Hz), 3.6 (t, 2H), 3.3 (d, 1H, *J* = 14 Hz), 2.8 (m, 1H), 2.4 (m, 1H), 1.2−2.1 (m, 11H).

3-(*N*-Benzylpiperidinyl)propionaldehyde (26a−c). A solution of oxalyl chloride (80 mmol) in 100 mL of DCM, was cooled to −60 °C under nitrogen atmosphere. A solution of 160 mmol of dimethyl sulfoxide in 100 mL of DCM was added dropwise and stirred for an additional 15 min at −60 °C. A solution of 64 mmol of **25** in 100 mL of DCM was added dropwise and stirred at −60 °C for 45 min. Subsequently, 200 mmol of triethylamine was added and the mixture was warmed to ambient temperature. The reaction mixture was washed with water (3 × 200 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. After the purification by flash column chromatography (EtOAc), a yellow oil was obtained. ^{1}H NMR ($CDCl_3$): **26a** (64%), δ 9.7 (t, 1H), 7.2−7.3 (m, 5H), 3.5 (s, 2H), 2.8 (m, 2H), 2.4 (m, 2H), 1.9 (m, 2H), 1.5 (m, 4H), 1.2 (m, 3H); **26b** (63%), δ 9.7 (t, 1H), 7.2−7.3 (m, 5H), 3.5 (s, 2H), 2.7 (m, 2H), 2.4 (m, 2H), 1.9 (m, 1H), 1.5−1.8 (m, 7H), 0.9 (m, 1H); **26c** (65%), δ 9.7 (t, 1H), 7.2−7.3 (m, 5H), 4.0 (d, 1H, *J* = 14 Hz), 3.3 (d, 1H, *J* = 14 Hz), 2.8 (m, 1H), 2.5 (m, 2H), 2.3 (m, 1H), 1.8−2.1 (m, 3H), 1.3−1.7 (m, 6H).

1-Benzyl-{2-[4-(toluene-4-sulfonyl)-4,5-dihydrooxazol-5-yl]ethyl}piperidine (27a−c). Finely powdered sodium cyanide (6.5 mmol) was added in one portion to a stirred suspension of tosylmethyl isocyanide (TosMIC) (40 mmol) and **26** (40 mmol) in 500 mL of absolute ethanol. In a moment the reaction mixture became clear. For **27a**, the product precipitated. Filtration and washing with 50 mL of ether/*n*-hexane (1:1 v/v) yielded **27a** as a pale yellow solid. For the synthesis of **27b** and **27c**, the mixture was stirred for 2 h and the solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (250 mL) and washed with saturated sodium carbonate solution (3 × 250 mL). The organic layer was collected and concentrated in vacuo. The product was obtained as a yellow oil and used immediately for the next step without further purification. ^{1}H NMR ($CDCl_3$): **27a** (88%), δ 7.8 (d, 2H), 7.4 (d, 2H), 7.2−7.3 (m, 5H), 6.9 (s, 1H), 5.1 (dt, 1H), 4.8 (d, 1H), 3.5 (s, 2H), 2.8−2.9 (m, 2H), 2.5 (s, 3H), 1.8−1.9 (m, 2H), 1.4−1.6 (m, 6H), 1.1−1.3 (m, 3H); **27b** (99%), δ 7.8 (d, 2H), 7.4 (d, 2H), 7.2−7.3 (m, 5H), 6.9 (s, 1H), 5.0 (dt, 1H), 4.7 (d, 1H), 3.5 (s, 2H), 2.8 (m, 2H), 2.4 (s, 3H), 1.1−1.9 (m, 11H); **27c** (97%), δ 7.8 (d, 2H), 7.4 (d, 2H), 7.2−7.3 (m, 5H), 6.9 (d, 1H), 5.0 (m, 1H), 4.7 (m, 1H), 3.9 (m, 1H), 3.2 (m, 1H), 2.8 (m, 1H), 2.5 (s, 3H), 2.3 (m, 1H), 1.3−2.1 (m, 11H).

1-Benzyl-[2-(1*H*-Imidazol-5-yl)ethyl]piperidine (28a−c). In a stainless steel bomb, a solution of 17.5 mmol of **27** in 120 mL of absolute ethanol saturated with ammonia was heated at 90−110 °C for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in DCM (100 mL) and washed with a 5% K_2CO_3 solution (100 mL) and water (2 × 100 mL). The organic layer was dried with anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, a dark brown oil was obtained. Purification using flash column

chromatography (MeOH) gave the product as a brown oil. ^{1}H NMR ($CDCl_3$): **28a** (57%), δ 7.5 (s, 1H), 7.2−7.3 (m, 5H), 6.7 (s, 1H), 3.5 (s, 2H), 2.8−2.9 (m, 2H), 2.5−2.6 (m, 2H), 1.8−1.9 (m, 2H), 1.4−1.6 (m, 6H), 1.1−1.3 (m, 3H); **28b** (54%), δ 7.5 (s, 1H), 7.2−7.3 (m, 5H), 6.7 (s, 1H), 3.5 (s, 2H), 2.8−2.9 (m, 2H), 2.5−2.6 (m, 2H), 1.4−1.8 (m, 11H); **28c** (85%), δ 7.5 (s, 1H), 7.2−7.3 (m, 5H), 6.7 (s, 1H), 3.9 (d, 1H, J = 14 Hz), 3.2 (d, 1H, J = 14 Hz), 2.6−2.9 (m, 3H), 2.5 (m, 1H), 1.3−2.1 (m, 8H).

2-(1*H*-Imidazol-5-yl)ethylpiperidine Dihydrogen Bromide (12a−c). A suspension of **28** (8 mmol in 100 mL of MeOH), 0.25 g of 10% Pd/C, and 80 mmol of ammonium formate was heated under reflux for 5 h. The mixture was filtered through short column of Hyflo super cel and the filtrate was concentrated under reduced pressure. To remove excess ammonium formate, 2-propanol was added to the residue and the ammonium formate was filtered off. The filtrate was titrated with 1 N hydrobromic acid solution until the pH of the solution was acidic (pH ≈ 3). The solvents were evaporated under reduced pressure and the product was recrystallized from EtOH/$(Et)_2O$. ^{1}H NMR (D_2O): **12a** (61%), δ 8.5 (s, 1H), 7.2 (s, 1H), 3.4 (m, 2H), 2.8−2.9 (m, 2H), 2.7 (m, 2H), 1.9 (m, 2H), 1.6 (m, 3H), 1.4 (m, 2H); **12b** (45%), δ 8.5 (s, 1H), 7.2 (s, 1H), 3.3 (m, 2H), 2.6−2.9 (m, 4H), 1.8 (m, 2H), 1.6 (m, 4H), 1.1−1.3 (m, 1H); **12c** (55%), δ 8.5 (s, 1H), 7.2 (s, 1H), 3.4 (m, 1H), 3.2 (m, 1H), 2.7−3.0 (m, 3H), 1.8−2.0 (m, 5H), 1.4−1.7 (m, 3H).

(3-[1,3]Dioxolan-2-ylpropenyl)pyridine (29a−c). A solution of 15 mmol of [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide in 100 mL of THF was cooled to −30 °C and 15 mmol of 1.6 M *n*-BuLi in hexane was added dropwise. The orange solution was stirred for 45 min at −30 °C. Next, a solution of 14 mmol of the corresponding pyridinecarboxaldehyde in 25 mL of THF was added dropwise and stirred at −30 °C for 30 min. The cooling bath was removed and the mixture was stirred at room temperature for 3 h, after which time 25 mL of $CHCl_3$ was added. The resulting mixture was washed with saturated ammonium chloride solution (3 × 25 mL). The organic layer was separated and dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (ether) to give a yellow oil. ^{1}H NMR ($CDCl_3$): **29a** (80%), δ 8.5 (d, 2H), 7.2 (d, 2H), 6.5 (d, 1H), 5.9 (dt, 1H), 5.0 (t, 1H), 3.9 (m, 4H), 2.7 (m, 2H); **29b** (83%), δ 8.6 (s, 1H), 8.5 (m, 1H), 7.5 (m, 1H), 7.2 (m, 1H), 6.5 (d, 1H), 5.9 (dt, 1H), 5.0 (t, 1H), 3.9 (m, 4H), 2.7 (m, 2H); **29c** (80%), δ 8.6 (d, 1H), 7.6 (m, 1H), 7.1−7.3 (m, 2H), 6.5 (d, 1H), 5.9 (dt, 1H), 5.0 (t, 1H), 3.9 (m, 4H), 2.7 (m, 2H).

(3-[1,3]Dioxolan-2-ylpropyl)pyridine (30a−c). Compound **29** (10 mmol) and 0.25 g of 5% Pd/C were added to 25 mL of EtOH. The suspension was stirred under an atmosphere of hydrogen gas at room temperature for 24 h. The mixture was filtered through a short column of Hyflo super cel and concentrated under reduced pressure. The product was obtained as a yellow oil and used directly in the next step. ^{1}H NMR ($CDCl_3$): **30a** (96%), δ 8.5 (d, 2H), 7.1 (d, 2H), 4.8 (t, 1H), 3.9 (m, 4H), 2.7 (t, 2H), 1.7 (m, 4H); **30b** (95%), δ 8.5 (m, 2H), 7.5 (d, 1H), 7.2 (m, 1H), 4.9 (t, 1H), 3.9 (m, 4H), 2.7 (t, 2H), 1.7 (m, 4H); **30c** (95%), δ 8.5 (d, 1H), 7.5 (m, 1H), 7.1−7.3 (m, 2H), 4.9 (t, 1H), 3.9 (m, 4H), 2.7 (t, 2H), 1.7 (m, 4H).

4-Pyridinylbutyraldehyde (31a−c). Compound **30** (9 mmol) was dissolved in 50 mL of 1 N HCl solution. The solution was stirred for 30 min and subsequently washed with $CHCl_3$ (3 × 50 mL). The aqueous layer was basified with sodium carbonate (pH ≈ 12) and extracted with $CHCl_3$ (3 × 50 mL). The organic layer was dried with anhydrous sodium sulfate and evaporated under reduced pressure to give a yellow oil. ^{1}H NMR ($CDCl_3$): **31a** (99%), δ 9.8 (t, 1H), 8.5 (d, 2H), 7.1 (d, 2H), 2.7 (t, 2H), 2.5 (t, 2H), 2.0 (tt, 2H); **31b** (99%), δ 9.8 (t, 1H), 8.5 (m, 2H), 7.5 (d, 1H), 7.2 (m, 1H), 2.7 (t, 2H), 2.5 (t, 2H), 2.0 (tt, 2H); **31c** (99%): δ 9.8 (t, 1H), 8.5 (d, 1H), 7.5 (t, 1H), 7.2 (m, 2H), 2.7 (t, 2H), 2.5 (t, 2H), 2.0 (tt, 2H).

3-[4-(Toluene-4-sulfonyl)-4,5-dihydrooxazol-5-yl]propylpyridine (32a−c). The compounds were synthesized using the procedure described for the synthesis of **27b** and **27c**, but 9 mmol of **31** was used as starting chemical. ^{1}H NMR ($CDCl_3$): **32a** (97%), δ 8.5 (d, 2H), 7.8 (d, 2H), 7.3 (d, 2H), 7.1 (d, 2H), 6.9 (s, 1H), 5.1 (dd, 1H), 4.7 (d, 1H), 2.6 (t, 2H), 2.4 (s, 3H), 1.7 (m, 4H); **32b** (98%), δ 8.5 (s, 2H), 7.8 (d, 2H), 7.5 (d, 1H), 7.3 (d, 2H), 7.2 (m, 1H), 6.9 (s, 1H), 5.1 (dd, 1H), 4.7 (d, 1H), 2.6 (t, 2H), 2.4 (s, 3H), 1.7 (m, 4H); **32c** (97%), δ 8.5 (d, 1H), 7.8 (d, 2H), 7.5 (t, 1H), 7.3 (d, 2H), 7.1 (m, 2H), 6.9 (s, 1H), 5.1 (dd, 1H), 4.7 (d, 1H), 2.8 (t, 2H), 2.4 (s, 3H), 1.7−1.9 (m, 4H).

3-(1*H*-Imidazol-5-yl)propylpyridine (33a−c). The compounds were synthesized using the procedure described for the synthesis of **28a−c**, but 9 mmol of **32** was used as starting chemical. ^{1}H NMR ($CDCl_3$): **33a** (62%), δ 8.5 (d, 2H), 7.6 (s, 1H), 7.1 (d, 2H), 6.8 (s, 1H), 2.6 (m, 4H), 1.9 (tt, 2H); **33b** (67%), δ 8.5 (d, 2H), 7.6 (s, 1H), 7.5 (d, 1H), 7.2 (m, 2H), 6.8 (s, 1H), 2.7 (m, 4H), 2.0 (tt, 2H); **33c** (64%), δ 8.5 (d, 1H), 7.5 (m, 2H), 7.2 (m, 2H), 6.8 (s, 1H), 2.7 (t, 2H), 2.6 (t, 2H), 2.0 (tt, 2H).

3-(1*H*-Imidazol-5-yl)propylpiperidine Dihydrogen Bromide (13a−c). A mixture of 5 mmol of **33**, 50 mL of EtOH, and 10 mL of a 1 N HBr solution was stirred with 0.1 g of 10% Pd/C and 0.05 g of 5% Rh/C under 100 atm of H_2 for 48 h in a stainless steel bomb. Next, the mixture was filtered through a short column of Hyflo super cel and concentrated under reduced pressure. The product was obtained by trituration with acetone. ^{1}H NMR (D_2O): **13a** (52%), δ 8.5 (s, 1H), 7.2 (s, 1H), 3.4 (m, 2H), 2.9 (m, 2H), 2.7 (t, 2H), 1.9 (d, 2H), 1.6 (m, 3H), 1.3 (m, 4H); **13b** (42%), δ 8.5 (s, 1H), 7.2 (s, 1H), 3.4 (m, 2H), 2.9 (m, 1H), 2.5−2.7 (m, 3H), 1.9 (d, 2H), 1.7 (m, 4H), 1.1−1.3 (m, 3H); **13c** (48%), δ 8.5 (s, 1H), 7.2 (s, 1H), 3.4 (m, 1H), 3.2 (m, 1H), 3.0 (m, 1H), 2.8 (t, 2H), 1.2−1.8 (m, 10H).

***N*-Benzyl-3-[hydroxy(triphenylmethylimidazol-4-yl)-methyl]pyrrolidin-2-one (34).** *N*-Benzylpyrrolidinone (35.4 mmol) dissolved in 100 mL of THF was cooled to −60 °C under an atmosphere of dry nitrogen gas, 22.2 mL of *n*-BuLi (1.6M in hexanes) was added dropwise, and the mixture stirred for another 30 min at −60 °C. 1-(Triphenylmethyl)imidazol-4-yl-carboxaldehyde (29.5 mmol) in 100 mL of THF was added dropwise and the mixture was allowed to warm to ambient temperature. Water (100 mL) was added and the THF was evaporated under reduced pressure. The residue was extracted with DCM (3 × 50 mL) and dried with Na_2SO_4. Concentration in vacuo gave an oil which was purified by crystallization from EtOAc to give **34** (76%) as an off-white crystals. ^{1}H NMR ($CDCl_3$): δ 7.00−7.40 (m, 16H), 6.76+6.83 (s, 1H, ImH5 diastereomers), 5.25 + 5.42 (s, 1H, CH−O diastereomers), 4.46 (d, 1H, J = 14.0 Hz), 4.33 (d, 1H, J = 14.0 Hz), 3.45 (br, 1H), 2.95−3.20 (m, 2H), 1.70−2.10 (m, 3H).

***N*-Benzyl-3-(triphenylmethylimidazol-4-ylmethylene)-pyrrolidin-2-one (35).** Compound **34** (22.66 mmol) was dissolved in 75 mL of dry pyridine and cooled in an ice-bath. $POCl_3$ (25 mmol) was added dropwise and the mixture was stirred at ambient temperature for 1 h. Next, 68 mmol of DBU was added and the mixture was stirred for 3 h. Then, 250 mL of water was added and the mixture was extracted with DCM (3 × 50 mL). The organic layers were washed with 50 mL of 1 M NaOH and 50 mL of water and dried with Na_2SO_4. Concentration in vacuo gave an oil which was dissolved in 200 mL of DCM/EtOAc (1:1) and filtered through 150 g of silica gel. The column was washed with DCM/EtOAc until the entire product was recovered. The crude product was recrystallized from EtOAc to give **35** (87%) as white crystals. ^{1}H NMR ($CDCl_3$): δ 7.49 (s, 1H), 7.05−7.40 (m, 15H), 6.98 (s, 1H), 4.59 (s, 2H), 3.32 (t, 2H, J = 6.6 Hz), 2.95−3.15 (m, 2H).

***N*-Benzyl-3-(triphenylmethylimidazol-4-ylmethylene)-pyrrolidine (36).** $LiAlH_4$ (50 mmol) was suspended in 100 mL of THF and cooled to 0 °C. H_2SO_4 (25 mmol, 97%) was added dropwise over a period of 30 min and stirred an additional 30 min. Compound **35** (19.6 mmol) in 100 mL of THF was added dropwise and the mixture was stirred at ambient temperature for 1 h. Next, the mixture was cooled in an ice-bath and the excess $LiAlH_4$ was destroyed by an addition of 5 mL of THF/water (1:1) and 30 mL of 5% NaOH. The white solids were filtered and washed with THF (2 × 50

mL). The filtrate was dried with Na_2SO_4. Concentration in vacuo gave **36** in a quantative yield as an oil. ^{1}H NMR ($CDCl_3$): δ 7.38 (s, 1H), 7.00−7.50 (m, 15H), 6.63 (s, 1H), 6.22 (s, 1H), 3.62 (s, 2H), 3.35 (s, 2H), 2.21 (t, 2H, J = 6.5 Hz), 2.40−2.60 (m, 2H).

3-[(1*H*-Imidazol-5-yl)methyl]pyrrolidine Dihydrogen Bromide (14). Compound **36** (18.7 mmol) was dissolved in 100 mL of MeOH with 1 g of $Pd(OH)_2$ (20% on carbon) and hydrogenated under 50 atm hydrogen gas for 72 h. The mixture was filtered through Hyflo super cel and concentrated in vacuo. The residue was dissolved in 100 mL of 2 M HCl, washed with ether (3 × 50 mL), and concentrated in vacuo to give an oil. The oil was subsequently dissolved in 100 mL of MeOH and 10 mL of triethylamine and treated with 45 mmol of di-*tert*-butyl dicarbonate. After stirring of the mixture at ambient temperature overnight, the solvents were evaporated, and the residue was extracted with 100 mL of water and EtOAc (3 × 75 mL). The organic layer was washed with brine and dried with Na_2SO_4. Concentration in vacuo gave an oil which was purified by column chromatography using a gradient of EtOAc and MeOH to give *tert*-butyl 4-(1-*tert*-butoxycarbonylpyrrolidin-3-yl)imidazole-1-carboxylate (66%) as a white solid. The solid was dissolved in 10 mL of 2 M HBr and stirred overnight. The mixture was evaporated and recrystallized from EtOH to give **14** (96%) as a white solid. ^{1}H NMR (D_2O): δ 8.6 (s, 1H), 7.2 (s, 1H), 3.2−3.5 (m, 3H), 2.8−3.0 (m, 3H), 2.7 (m, 1H), 2.1 (m, 1H), 1.7 (m, 1H).

Pyridin-4-yl-(1-trityl-1*H*-imidazol-4-yl)methanol (37). 1-Trityl-4-iodo imidazole[41] (12 mmol) was dissolved in 100 mL of DCM, 13.2 mmol of ethylmagnesium bromide (3.0 M in THF) was added, and the mixture was stirred at room temperature for 45 min. 4-Pyridinecarboxaldehyde (12 mmol) was added dropwise and stirred for 16 h. The mixture was washed with saturated sodium carbonate solution (3 × 100 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent and recrystallization from EtOAc yielded a pale yellow solid (89%). NMR ($CDCl_3$): δ 8.5 (d, 2H), 7.4 (s, 1H), 7.1−7.3 (m, 17H), 6.6 (s, 1H), 5.7 (s, 1H).

(1*H*-Imidazol-5-yl)piperidin-4-ylmethanol Dihydrogen Chloride (38). Compound **37** (10 mmol) was dissolved in 10 mL of 5 N HCl and added to a suspension of 0.5 g of 10% Pd/C and 0.25 g of 5% Rd/C in 100 mL of MeOH. The mixture was hydrogenated under 100 atm of hydrogen gas for 48 h in a stainless steel bomb. The organic solvent was evaporated under reduced pressure. The residue was dissolved in 100 mL of water and washed with ether (3 × 100 mL). The aqueous layer was concentrated in vacuo and recrystallized from EtOH to give a pale yellow solid (85%). NMR (MeOH-d_4): δ 8.7 (s, 1H), 7.4 (s, 1H), 4.8 (d, 1H), 3.5 (t, 2H), 3.0 (t, 2H), 2.0 (d, 2H), 1.5−1.7 (m, 3H).

4-[1-*tert*-Butoxycarbonyl-1*H*-imidazol-4-yl]hydroxymethyl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (39). To a solution of **38** (8 mmol) and triethylamine (30 mmol) in 100 mL of MeOH was added di-*tert*-butyl dicarbonate (17 mmol) and the mixture stirred at room temperature for 24 h. The solvent was evaporated and the residue was suspended in 100 mL of ether. The mixture was washed with a saturated sodium carbonate solution (100 mL) and subsequently with water (2 × 100 mL). The organic layer was dried with anhydrous sodium sulfate. The product was obtained as a yellow oil and used directly in the next step (95%). NMR ($CDCl_3$): δ 7.9 (s, 1H), 7.2 (s, 1H), 4.3 (d, 1H), 4.1 (m, 2H), 2.6 (t, 2H), 1.8−2.0 (m, 3H), 1.5 (s, 9H), 1.4 (s, 9H), 1.1 (m, 2H).

4-[(1-*tert*-Butoxycarbonyl-1*H*-imidazol-4-yl)methanesulfonyloxymethyl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (40). A solution of **39** (7 mmol) and triethylamine (17.5 mmol) in 50 mL of dry DCM was cooled in an ice bath and methanesulfonyl chloride (7.7 mmol) was added. The ice bath was removed and the mixture was stirred at room temperature for 12 h. The mixture was washed with brine (3 × 50 mL) and the organic layer was dried with anhydrous sodium sulfate. After evaporation under reduced pressure, the residue was purified using flash column chromatography (EtOAc). The product was obtained as a white solid (89%). NMR ($CDCl_3$): δ 7.9 (s, 1H), 7.2 (s, 1H), 4.7 (d, 1H), 4.1 (m, 2H), 2.6−2.7 (m, 5H), 2.3 (m, 1H), 1.8−1.9 (m, 2H), 1.6 (s, 9H), 1.5 (s, 9H), 1.1 (m, 2H).

4-(1*H*-Imidazol-5-ylmethylene)piperidine-1-carboxylic Acid *tert*-Butyl Ester (41). A mixture of **40** (6 mmol) and calcium carbonate (15 mmol) in 50 mL of dimethylformamide was heated at reflux temperature for 2 h. After cooling, the solvent was evaporated under reduced pressure. Ether (50 mL) was added and the suspension was washed with saturated sodium carbonate solution (3 × 50 mL). The ether layer was dried with anhydrous sodium sulfate and concentrated in vacuo. After purification using flash column chromatography (EtOAc), the product was obtained as a white solid (85%). NMR ($CDCl_3$): δ 7.6 (s, 1H), 6.9 (s, 1H), 6.1 (s, 1H), 3.5 (m, 4H), 2.7 (t, 2H), 2.3 (t, 2H), 1.5 (s, 9H).

4-(1*H*-Imidazol-5-ylmethylene)piperidine Dihydrogen Chloride (16). A solution of **41** (5 mmol) in 10 mL of 2 N HCl solution was stirred at room temperature for 2 h and concentrated under reduced pressure. The product was recrystallized from EtOH/$(Et)_2O$ as a pale yellow solid (45%). NMR (D_2O): δ 8.7 (s, 1H), 7.5 (s, 1H), 6.4 (s, 1H), 3.3 (m, 4H), 2.8 (m, 4H).

4-(1-*tert*-Butoxycarbonyl-1*H*-imidazol-4-carbonyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (42). The compound was synthesized using the procedure described for the synthesis of **26**, but 7.1 mmol of **39** was used as starting chemical. The crude product was purified by flash column (EtOAc:hexane, 1:3), to give a white solid (95%). ^{1}H NMR ($CDCl_3$): δ 8.1 (s, 1H), 8.0 (s, 1H), 4.1 (m, 2H), 3.5 (m, 1H), 2.9 (m, 2H), 1.5−2.0 (m, 4H), 1.6 (s, 9H), 1.4 (s, 9H).

(1*H*-Imidazol-5-yl)piperidin-4-ylmethanone Dihydrogen Chloride (18). Compound **42** (1.2 mmol) was dissolved in 10 mL of acetone. The solution was added to 10 mL of 1 N HCl and stirred at room temperature for 2 h. After concentration under reduced pressure, a white solid was obtained (100%). ^{1}H NMR (D_2O): δ 8.8 (s, 1H), 8.3 (s, 1H), 3.5 (m, 3H), 3.1 (m, 2H), 2.1 (m, 2H), 1.0 (m, 2H).

4-[1-(1-*tert*-Butoxycarbonyl-1*H*-imidazol-4-yl)vinyl]-piperidine-1-carboxylic Acid *tert*-Butyl Ester (43). To a solution of methyl triphenylphosphonium bromide (15 mmol) in 150 mL of toluene was added potassium-*tert*-butoxide (15 mmol). After stirring for 1 h at room temperature, a solution of **42** (7.5 mmol) in 100 mL of toluene was added dropwise. The solution was stirred for 3 h and subsequently quenched with a saturated solution of Na_2CO_3 (150 mL). The water layer was extracted with toluene (3 × 100 mL), and the combined organic layers were washed with brine (2 × 150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified using flash column (EtOAc:hexane, 1:2) to yield a white solid (50%). ^{1}H NMR ($CDCl_3$): δ 8.0 (s, 1H), 7.3 (s, 1H), 5.7 (s, 1H), 5.0 (s, 1H), 4.0−4.3 (m, 2H), 2.6−2.9 (m, 2H), 2.4−2.6 (m, 1H), 1.7−1.9 (m, 2H), 1.2−1.5 (m, 2H), 1.6 (s, 9H), 1.4 (s, 9H).

4-[1-(1*H*-Imidazol-5-yl)vinyl]piperidine Dihydrogen Chloride (17). Compound **43** (1.2 mmol) was dissolved in 10 mL of acetone. The solution was added to 10 mL of 1 N HCl and stirred at room temperature for 2 h. After concentration under reduced pressure, a white solid was obtained (100%). ^{1}H NMR (D_2O): δ 8.6 (s, 1H), 7.5 (s, 1H), 5.6 (s, 1H), 5.3 (s, 1H), 3.5 (m, 2H), 3.1 (m, 2H), 2.7 (m, 1H), 2.1 (m, 2H), 1.5−1.7 (m, 2H).

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