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Synthesis and Histamine H_3 Receptor Activity of 4-(*n*-Alkyl)-1*H*-imidazoles and 4-(ω-Phenylalkyl)-1*H*-imidazoles

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Abstract—The influence of lipophilic moieties attached to a 4-1*H*-imidazole ring on the histamine H_3 receptor activity was systematically investigated. Series of 4-(*n*-alkyl)-1*H*-imidazoles and 4-(ω-phenylalkyl)-1*H*-imidazoles were prepared, with an alkyl chain varying from 2–9 methylene groups and from 1–9 methylene groups, respectively. The compounds were tested for their activity on the H_3 receptor under in vitro conditions. For the 4-(*n*-alkyl)-1*H*-imidazoles the activity is proportional to chain length, ranging from a pA_2 value of 6.3 ± 0.2 for 4-(*n*-propyl)-1*H*-imidazole to a pA_2 value of 7.2 ± 0.1 for 4-(*n*-decyl)-1*H*-imidazole. For the series 4-(ω-phenylalkyl)-4*H*-imidazoles an optimum in H_3 activity was found for the pentylene spacer: 4-(ω-phenylpentyl)-1*H*-imidazole has a pA_2 value of 7.8 ± 0.1.

Introduction

The histamine H_3 receptor has been shown to regulate the neuronal synthesis of histamine and in addition regulates its release into the synaptic cleft.[1,2] Furthermore, the H_3 receptor acts as heteroreceptor, controlling the release of other neurotransmitters (e.g. dopamine, noradrenaline, serotonin, and acetylcholine).[3] H_3 receptors have been identified in peripheral tissues, but the highest densities of H_3 receptors were found in distinct areas of the central nervous system (e.g. cortex, substantia nigra, and striatum) implying the main pharmacological targets are found in the brain.[4] It has been speculated that H_3 antagonists may provide means for treating Alzheimer's disease, narcolepsy, schizophrenia, epilepsy and obesity.[5] A thorough investigation of the possible use of H_3 ligands as therapeutic agents in brain disorders is hampered by their poor blood–brain-barrier penetration.[6] Therefore, new ligands are needed that can reach the central nervous system. Rational design of compounds with improved pharmacokinetic profiles is only feasible if the molecular structural features that are responsible for affinity and intrinsic activity are resolved.

The most manifest feature of the SAR of H_3 antagonists is the crucial role of the 4-1*H*-substituted imidazole unit present in all potent H_3 ligands.[7] Another pharmacophoric element present in many H_3 antagonists is a basic nitrogen atom in the imidazole side-chain. It has been suggested that this basic nitrogen atom interacts with an aspartic acid residue of the receptor.[8,9] However, a basic group in the imidazole side-chain is not essential for H_3 antagonism and several ligands have been developed that lack a basic group in their imidazole side-chain.[10,11] These compounds are thought to interact at the imidazole binding site and a putative hydrophobic pocket.[8]

Previously, our group has synthesised histamine analogues to investigate the influence of the length of the alkyl chain (spacer), that connects the imidazole ring with the amino group, on the H_3 activity.[12] Elongation of the ethylene spacer of histamine resulted in compounds with antagonistic activity and an optimal activity was found for the pentylene spacer, resulting in the potent and selective H_3 antagonist 4-(5-aminopentyl)-1*H*-imidazole (impentamine).[12] Attachment of lipophilic residues to the amino group significantly increased the H_3 antagonistic activity, for example, attachment of a benzyl group resulted in the potent antagonist VUF4808 (Fig. 1, $pA_2 = 8.9$).[13] However,

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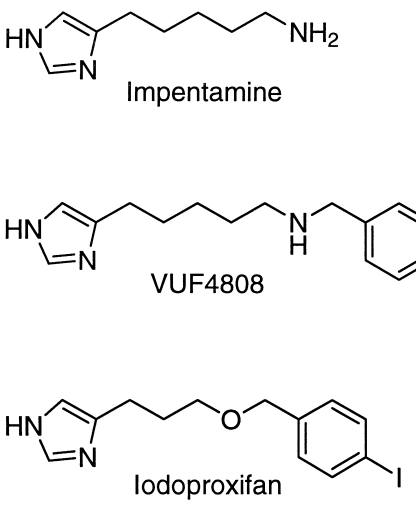


Figure 1. Structures of some H_3 receptor antagonists.

considering the activity of compounds like iodoproxifan ($pA_2 = 8.3$),[14] it is not clear whether the amino group in the impentamine derivatives is involved in binding to a hydrogen-bonding acceptor site point of the receptor or if the affinity of these compounds is merely caused by interaction with the imidazole binding site and a hydrophobic pocket. The role of the lipophilic moiety of H_3 antagonists with respect to their potency has not yet been investigated systematically.

Many new H_3 antagonists have been synthesised using readily available scaffolds like urocanic acid and histamine.[14,15] These approaches do not lead to series that allow thorough SAR studies. However, our ongoing molecular modelling studies prompted us to investigate the role of the lipophilic moiety on H_3 antagonistic activity in more detail.[8] Therefore, two series of compounds were synthesised to explore the SAR of the lipophilic tail of H_3 antagonists. The contribution of simple alkyl groups attached to the imidazole ring to the H_3 antagonistic activity was investigated in the first series. The effect of ω-phenyl-alkyl groups attached to the imidazole ring on the H_3 activity was studied in a second series. With these new series we fill a gap between the SAR of the antagonists with a basic moiety in the imidazole side-chain and the ligands that lack this moiety, thereby enabling evaluation of the contribution of the different molecular structural features that are responsible for affinity and antagonistic activity.

Results

Chemistry

For the synthesis of the target compounds a general and straightforward synthetic route was employed, starting from the aldehyde precursors **1a**–**h** and **2a**–**i** (Scheme 1). These aldehydes were reacted with (*p*-tolylsulfonyl)-methyl isocyanide (TosMIC) in an [3 + 2] anionic cycloaddition.[16,17] The 4-tosyloxazolines **3a**–**h** and **4a**–**i** precipitated from the reaction mixture in high yield and were isolated by filtration. The oxazolines were converted into the corresponding imidazoles with ammonia in ethanol.

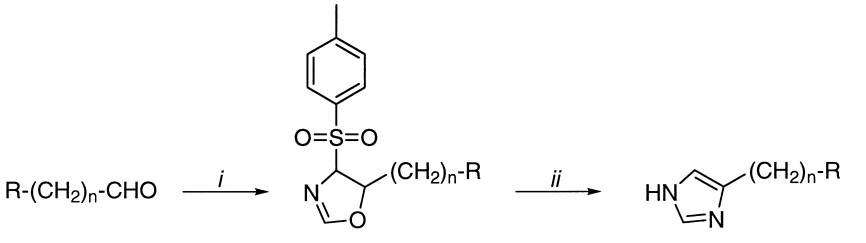
The aldehydes used were either commercially available (aldehydes **1a**–**h** and **2a,b**) or prepared from readily available starting materials (**7**, **8**, **10**, **11** and **12**). Aldehydes **2c**,**e**,**g**,**i** were obtained by Swern oxidation of the corresponding alcohol and aldehyde **2d** was synthesised from the corresponding carboxylic acid **7**, via $LiAlH_4$ reduction and subsequent Swern oxidation (Scheme 2). The aldehydes **2f** and **2h** were prepared by elongation of aldehyde **2d** and **2f**, respectively, via a Wadsworth–Emmons (Horner) reaction, catalytic hydrogenation and subsequent reduction of the carboxylic esters by diisobutylaluminum hydride (DIBALH) (Scheme 3).

Pharmacology

The histamine H_3 antagonistic activities of the compounds **5a**–**h** and **6a**–**i** were determined using an in vitro test system based on the electrically evoked contractile response of isolated guinea pig jejunum segments.[18]

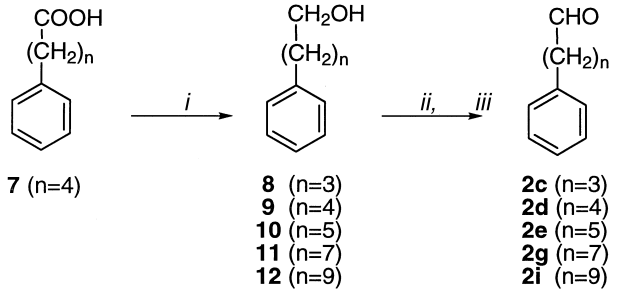
Discussion and Conclusions

The 4-(*n*-alkyl)-1*H*-imidazoles have an antagonistic activity on the histamine H_3 receptor (Table 1) that increases with chain length from $pA_2 = 6.3 \pm 0.2$ (for 4-(*n*-propyl)-1*H*-imidazole (**5a**)) up to $pA_2 = 7.2 \pm 0.1$ (for 4-(*n*-decyl)-1*H*-imidazole (**5h**)). The remarkable activity of such simple imidazole-containing compounds illustrates the important role of the imidazole nucleus for binding to the H_3 receptor. The increasing length of the alkyl chain does not hinder the binding of these flexible ligands. Entropy effects could be responsible for the increase of activity with increasing alkyl chain length. No optimum in activity was found. Further elongation



1a-1h; n=2-9 (R=CH_3) **3a-3h**; n=2-9 (R=CH_3) **5a-5h**; n=2-9 (R=CH_3)
2a-2i; n=1-9 (R=C_6H_5) **4a-4i**; n=1-9 (R=C_6H_5) **6a-6i**; n=1-9 (R=C_6H_5)

Scheme 1. Reagents: (i) TosMIC, NaCN, EtOH, 0°C; (ii) EtOH/NH_3; 120°C; 15 bar.



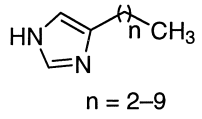
Scheme 2. Reagents: (i) $LiAlH_4$, Et_2O; (ii) $(COCl)_2$/DMSO, CH_2Cl_2, −55°C; (iii) Et_3N, CH_2Cl_2, −55°C.

of the alkyl-chain of this series was not attempted due to the poor solubilities of the higher 4-(*n*-alkyl)-1*H*-imidazoles.

For the 4-(ω-phenylalkyl)-1*H*-imidazole series, a clear optimum in H_3 antagonistic activity was found (Table 2). The low activity of 4-benzyl-1*H*-imidazole (**6a**, $pA_2 = 5.8 \pm 0.1$) is enhanced by elongation of the linker between the two aromatic rings, reaching an optimum in activity for the pentylene linker, 4-(5-phenyl-pentyl)-1*H*-imidazole (**6e**, $pA_2 = 7.8 \pm 0.1$). Further elongation of the linker results in a decrease of H_3 antagonistic activity, leading to the weak antagonist 4-(9-phenyl-nonyl)-1*H*-imidazole (**6i**, $pA_2 = 6.1 \pm 0.2$). During the preparation of this paper compounds **5g**, **6d** and **6f** were described elsewhere by Stark and co-workers.[19] In addition to comparable in vitro activity, the authors reported that these three compounds have high in vivo activity.

The series of compounds presented in our study provide additional insight into the contribution of the different molecular structural features that are responsible for H_3 activity. Thus, by comparing the activities of **6g** ($pA_2 = 7.1$) and VUF4808 (Fig. 1, $pA_2 = 8.9$) it is evident that the activity of the latter is caused not only by the lipophilic moiety but that, in addition, the basic nitrogen in the side-chain is involved in interaction with a hydrogen-bonding acceptor site point of the receptor. Furthermore, the presented series of compounds allow us to determine the relative position (with respect to the imidazole binding site) of a hydrophobic pocket that is available for binding H_3 antagonists. These results enable the construction of a qualitative model for the binding of H_3 antagonists, different from existing models in which the role of the basic nitrogen atom in the imidazole side-chain is still prominent. We plan to use such a model to design new H_3 antagonists, that may have better pharmacokinetic profiles including improved in vivo activities and lower toxicity.

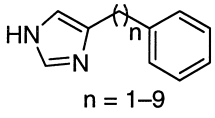
Table 1. Histamine H_3 receptor activity of 4-(*n*-alkyl)-1*H*-imidazoles



Compound	n	pA_2[a] ± SD
Impentamine		8.4 ± 0.2
5a	2	6.3 ± 0.2
5b	3	6.7 ± 0.1
5c	4	6.4 ± 0.2
5d	5	6.3 ± 0.2
5e	6	6.6 ± 0.2
5f	7	6.8 ± 0.1
5g	8	7.1 ± 0.1
5h	9	7.2 ± 0.1

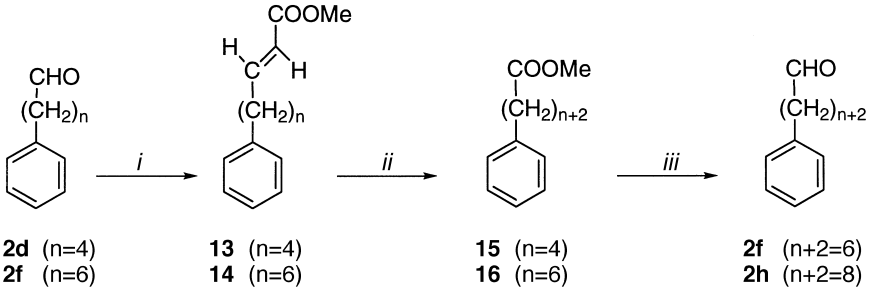
[a] Histamine H_3 receptor activity determined on isolated guinea pig jejunum.[15]

Table 2. Histamine H_3 receptor activity of 4-(ω-phenylalkyl)-1*H*-imidazoles



Compound	n	pA_2[a] ± SD
6a	1	5.8 ± 0.1
6b	2	5.9 ± 0.1
6c	3	6.4 ± 0.3
6d	4	7.5 ± 0.2
6e	5	7.8 ± 0.1
6f	6	7.7 ± 0.1
6g	7	7.1 ± 0.2
6h	8	6.5 ± 0.2
6i	9	6.1 ± 0.2

[a] Histamine H_3 receptor activity determined on isolated guinea pig jejunum.[15]



Scheme 3. Reagents: (i) NaH, $(_2H_5O)_2P(O)CH_2CO_2CH_3$, THF, 0°C; (ii) 10% Pd/C, H_2, MeOH; (iii) DIBALH, CH_2Cl_2, −75°C.

Experimental

General procedure

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer (unless indicated otherwise) with tetramethylsilane as an internal standard. Melting points (mp) were determined on an Electrothermal IA9200 apparatus and are uncorrected. Elemental analyses were performed by the Department of Microanalysis, Groningen University, Groningen, The Netherlands. Solvents were purified and dried by standard procedures.

4-Phenyl-butanal (2c). A solution of oxalyl chloride (3.5 g, 28 mmol) and anhydrous dichloromethane (60 mL) was cooled to −55°C under a nitrogen atmosphere. DMSO (4.3 g, 55 mmol), dissolved in anhydrous dichloromethane (25 mL), was added dropwise. After stirring for 5 min, 4-phenyl-butanol (**8**) (3.8 g, 25 mmol) dissolved in anhydrous dichloromethane (10 mL) was added dropwise. After additional stirring for 15 min, triethylamine (12.7 g, 125 mmol) was added. The mixture was allowed to warm to room temperature and was subsequently washed with an aqueous solution of HCl (1 N, 75 mL). The aqueous layer was extracted with dichloromethane (3×75 mL) and the combined organic layers were washed with saturated aqueous sodium chloride (75 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield a colourless oil. Yield: 3.7 g (99%); ^{1}H NMR ($CDCl_3$) δ 1.95 (m, 2H), 2.44 (dt, J = 2.0, 7.1 Hz, 2H), 2.62 (t, J = 8.1 Hz, 2H), 7.08–7.33 (m, 5H), 9.75 (d, J = 2.0 Hz, 1H).

5-Phenyl-pentanol (9). A suspension of lithiumaluminiumhydride (4.3 g, 0.11 mol) in anhydrous diethyl ether (100 mL) was cooled to 0°C under a nitrogen atmosphere. Gradually, 5-phenyl-pentanoic acid (**7**) (10.1 g, 56 mmol) was added. The suspension was allowed to warm to room temperature and stirred overnight. After cooling to 0°C, water (100 mL) was added cautiously. The reaction mixture was poured into aqueous sulfuric acid (5%, 400 mL). The aqueous layer was extracted with diethyl ether (3×200 mL) and the combined organic layers were washed with saturated aqueous sodium chloride (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield a colourless oil. Yield: 9.3 g (100%); ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 2H), 1.61 (m, 4H), 2.62 (t, J = 8.0 Hz, 2H), 3.62 (t, J = 7.8 Hz, 2H), 7.08–7.37 (m, 5H).

5-Phenyl-pentanal (2d). Analogous to the preparation of **2c**, using 5-phenyl-pentanol (**9**). Yield: 100%; ^{1}H NMR ($CDCl_3$) δ 1.64 (m, 4H), 2.45 (m, 3H), 2.63 (m, 2H), 7.00–7.29 (m, 5H), 9.68 (s, 1H).

6-Phenyl-hexanal (2e). Analogous to the preparation of **2c**, using 6-phenyl-hexanol (**10**). Yield: 67.0%; ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 2H), 1.60 (m, 4H), 2.33 (dt, J = 2.2, 8.0 Hz, 2H), 2.53 (t, J = 7.4 Hz, 2H), 6.98–7.28 (m, 5H), 9.69 (t, J = 2.2 Hz, 1H).

Methyl 7-phenyl-2(*E*)-heptenoate (13). A suspension of THF (75 mL) and NaH (1.9 g of a 60% oil dispersion, 46.7 mmol) was cooled to 0°C under a nitrogen atmosphere. Gradually, methyl diethylphosphonoacetate (8.9 g, 42.4 mmol) was added. After stirring the reaction mixture for 30 min, 5-phenyl-pentanal (**2d**) (6.9 g, 42.4 mmol) was added dropwise. After additional stirring for 15 min, saturated aqueous ammonium chloride (100 mL) was added. The reaction mixture was extracted with diethyl ether (3×100 mL) and the combined organic layers were washed with saturated aqueous sodium chloride (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc:hexane, 1:4, v/v) to yield 8.0 g (86%) of a slightly-yellow oil. R_f 0.66 (EtOAc:hexane, 1:4, v/v). ^{1}H NMR ($CDCl_3$) δ 1.41–1.72 (m, 4H), 2.28 (m, 2H), 2.60 (t, J = 6.7 Hz, 2H), 3.65 (s, 3H), 5.80 (d, J = 16.0 Hz, 1H), 6.94 (dt, J = 16.0, 7.2 Hz, 1H), 7.23 (m, 5H).

Methyl 7-phenyl-heptanoate (15). To methyl 7-phenyl-2(*E*)-heptenoate (**13**) (8.0 g, 37 mmol) in methanol (50 mL) was added 10% Pd/C (800 mg) and the resulting suspension was stirred overnight in a hydrogen atmosphere (10 bar). The Pd(C) catalyst was removed by filtration over hyflo and the volatiles were evaporated in vacuo to yield 7.4 g (91%) of a colourless oil. ^{1}H NMR ($CDCl_3$) δ 1.33 (m, 4H), 1.60 (m, 4H), 2.28 (t, J = 8.0 Hz, 2H), 2.58 (t, J = 7.9 Hz, 2H), 3.65 (s, 3H), 7.32–7.80 (m, 5H).

7-Phenyl-heptanal (2f). To a cooled (−75°C) stirred solution of methyl 7-phenyl-heptanoate (**15**) (7.4 g, 33 mmol) in anhydrous dichloromethane (250 mL) was added DIBALH (35 mL of a 1 M solution in dichloromethane) dropwise. After stirring the solution for 30 min, saturated aqueous Rochelle salt (100 mL) was added. The mixture was allowed to warm up to room temperature and washed with diethyl ether. The combined organic layers were washed with an aqueous HCl solution (1 M, 100 mL) and saturated aqueous sodium chloride (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The product was isolated as a slightly-yellow oil. Yield: 4.9 g (77%); ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 4H), 1.54 (m, 4H), 2.33 (dt, J = 8.0, 2.2 Hz, 2H), 2.52 (t, J = 7.9 Hz, 2H), 7.02–7.28 (m, 5H), 9.69 (t, J = 2.2 Hz, 1H).

8-Phenyl-octanal (2g). Analogous to the preparation of **2c**, using 8-phenyl-octanol (**11**). Yield: 63.3%; R_f 0.67 (EtOA:hexane, 1:4, v/v). ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 6H), 1.59 (m, 4H), 2.39 (dt, J = 2.4, 6.7 Hz, 2H), 2.58 (t, J = 7.0 Hz, 2H), 7.08–7.34 (m, 5H), 9.75 (t, J = 2.4 Hz, 1H).

Methyl 9-phenyl-2(*E*)-nonenoate (14). Analogous to the preparation of **13**, using 7-phenyl-heptanal (**2f**). Yield: 79.3%; R_f 0.67 (EtOAc:hexane, 1:4, v/v); ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 6H), 1.53 (m, 4H), 2.12 (m, 2H), 2.52 (t, J = 8.0 Hz, 2H), 3.63 (s, 3H), 5.73 (d, J = 16.0 Hz, 1H), 6.90 (dt, J = 16.0, 6.9 Hz, 1H), 7.02–7.28 (m, 5H).

Methyl 9-phenyl-nonanoate (16). Analogous to the preparation of **15**, using methyl 9-phenyl-2(*E*)-nonenoate (**14**). Yield: 91.0%; ^{1}H NMR ($CDCl_3$) δ 1.21 (m, 8H), 1.52 (m, 4H), 2.22 (t, J = 7.6 Hz, 2H), 2.51 (t, J = 8.0 Hz, 2H), 3.58 (s, 3H), 7.02–7.25 (m, 5H).

9-Phenyl-nonanal (2h). Analogous to the preparation of **2f**, using methyl 9-phenyl-nonanoate (**16**). Yield: 97%; ^{1}H NMR ($CDCl_3$) δ 1.22 (m, 8H), 1.54 (m, 4H), 2.35 (t, J = 8.2 Hz, 2H), 2.53 (t, J = 7.6 Hz, 2H), 6.99–7.28 (m, 5H), 9.70 (s, 1H).

10-Phenyl-decanal (2i). Analogous to the preparation of **2c**, using 10-phenyl-decanol (**12**). The crude yellow coloured product was purified by column chromatography (EtOAc:hexane, 1:4, v/v) to give 95% of a colourless oil. R_f 0.69 (EtOAc:hexane, 1:4, v/v); ^{1}H NMR ($CDCl_3$) δ 1.27 (m, 10H), 1.60 (m, 4H), 2.40 (dt, J = 2.4, 6.8 Hz, 2H), 2.59 (t, J = 8.2 Hz, 2H), 7.08–7.33 (m, 5H), 9.75 (t, J = 2.4 Hz, 1H).

General procedure for the preparation of 5-(*n*-alkyl)-4-tosyl-2-oxazolines and 5-(ω-phenylalkyl)-4-tosyl-2-oxazolines

To a stirred suspension of tosylmethyl isocyanide (20.0 mmol) and the corresponding aldehyde (20.5 mmol) in absolute ethanol (200 mL) at 0°C was added finely powdered sodium cyanide (30 mg, 1.0 mmol). For a moment the reaction mixture became clear followed by precipitation of the product. Ten min after the addition of sodium cyanide, the suspension was filtered. The product was washed with ether:hexane (20 mL, 1:1, v/v) and dried in vacuo.

5-(*n*-Propyl)-4-tosyl-2-oxazoline (3a). Yield: 83.3%; mp 110.5–111.6°C; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.48 (m, 2H), 1.63 (m, 2H), 2.43 (s, 3H), 4.74 (d, J = 5.4 Hz, 1H), 5.07 (q, J = 5.4 Hz, 1H), 6.94 (s, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H).

5-(*n*-Butyl)-4-tosyl-2-oxazoline (3b). Yield: 77.3%; mp 101.1–103.0°C; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.00 Hz, 3H), 1.38 (m, 4H), 1.68 (m, 2H), 2.43 (s, 3H), 4.72 (d, J = 6.00 Hz, 1H), 5.02 (q, J = 6.00 Hz, 1H), 6.95 (s, 1H), 7.35 (d, J = 7.60 Hz, 2H), 7.80 (d, J = 7.60 Hz, 2H).

5-(*n*-Pentyl)-4-tosyl-2-oxazoline (3c). Yield: 76.7%; mp 117.1–118.3°C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.00 Hz, 3H), 1.31 (m, 6H), 1.64 (m, 2H), 2.42 (s, 3H), 4.73 (d, J = 6.00 Hz, 1H), 5.04 (q, J = 6.00 Hz, 1H), 6.94 (s, 1H), 7.34 (d, J = 8.00 Hz, 2H), 7.80 (d, J = 8.00 Hz, 2H).

5-(*n*-Hexyl)-4-tosyl-2-oxazoline (3d). Yield: 87.2%; mp 104.5–105.6°C; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.00 Hz, 3H), 1.25 (m, 8H), 1.64 (m, 2H), 2.43 (s, 3H), 4.74 (d, J = 6.00 Hz, 1H), 5.04 (q, J = 6.00 Hz, 1H), 6.95 (s, 1H), 7.37 (d, J = 7.40 Hz, 2H), 7.80 (d, J = 7.40 Hz, 2H).

5-(*n*-Heptyl)-4-tosyl-2-oxazoline (3e). Yield: 92.7%; mp 118.2–119.0°C; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 6.67 Hz, 3H), 1.20 (m, 10H), 1.65 (m, 2H), 2.44 (s, 3H), 4.73 (d, J = 6.70 Hz, 1H), 5.04 (q, J = 6.70 Hz, 1H), 6.95 (s, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H).

5-(*n*-Octyl)-4-tosyl-2-oxazoline (3f). Yield: 78.3%; mp 100.4–101.5°C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.21 (m, 12H), 1.64 (m, 2H), 2.42 (s, 3H), 4.73 (d, J = 6.7 Hz, 1H), 5.03 (q, J = 6.7 Hz, 1H), 6.97 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H).

5-(*n*-Nonyl)-4-tosyl-2-oxazoline (3g). Yield: 97.1%; mp 116.9–117.7°C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.25 (m, 14H), 1.68 (m, 2H), 2.42 (s, 3H), 4.75 (d, J = 6.8 Hz, 1H), 5.04 (q, J = 6.8 Hz, 1H), 6.95 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H).

5-(*n*-Decyl)-4-tosyl-2-oxazoline (3h). Yield: 87.8%; mp 105.8–106.4°C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.22 (m, 16H), 1.65 (m, 2H), 2.43 (s, 3H), 4.72 (d, J = 6.7 Hz, 1H), 5.03 (q, J = 6.7 Hz, 1H), 6.98 (s, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H).

5-(Benzyl)-4-tosyl-2-oxazoline (4a). Yield: 95.7%; mp 93.8–96.7°C; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.00 (m, 2H), 4.82 (d, J = 6.7 Hz, 1H), 5.30 (q, J = 6.7 Hz, 1H), 6.91 (s, 1H), 7.11–7.38 (m, 7H), 7.77 (d, J = 8.0 Hz, 2H).

5-(2-Phenyl-ethyl)-4-tosyl-2-oxazoline (4b). Yield: 75.8%; mp 87.2–88.2°C; ^{1}H NMR ($CDCl_3$) δ 1.99 (m, 2H), 2.44 (s, 3H), 2.78 (m, 2H), 4.79 (d, J = 6.7 Hz, 1H), 5.07 (q, J = 6.7 Hz, 1H), 7.00 (s, 1H), 7.01–7.40 (m, 7H), 7.78 (d, J = 8.2 Hz, 2H).

5-(3-Phenyl-propyl)-4-tosyl-2-oxazoline (4c). Yield: 68.7%; mp 113.8–115.4°C, ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 4H), 2.44 (s, 3H), 2.65 (t, J = 7.0 Hz, 2H), 4.71 (d, J = 6.6 Hz, 1H), 5.07 (q, J = 6.6 Hz, 1H), 6.95 (s, 1H), 7.09–7.32 (m, 5H), 7.35 (d, J = 8.0 Hz, 2H), 7.78 (d, 8.0 Hz, 2H).

5-(4-Phenyl-butyl)-4-tosyl-2-oxazoline (4d). Yield: 65.0%; labile product; ^{1}H NMR ($CDCl_3$) δ 1.48 (m, 2H), 1.66 (m, 4H), 2.42 (s, 3H), 2.62 (t, J = 7.5 Hz, 2H), 4.73 (d, J = 4.0 Hz, 1H), 5.03 (q, J = 6.5 Hz, 1H), 6.94 (s, 1H), 7.07–7.44 (m, 7H), 7.79 (d, J = 8.5 Hz, 2H).

5-(5-Phenyl-pentyl)-4-tosyl-2-oxazoline (4e). Yield: 85.6%; mp 104.2–105.4°C; ^{1}H NMR ($CDCl_3$) δ 1.40 (m, 4H), 1.65 (m, 4H), 2.43 (s, 3H), 2.60 (t, J = 7.6 Hz, 2H), 4.72 (d, J = 6.5 Hz, 1H), 5.05 (q, J = 6.5 Hz, 1H), 6.94 (s,1H), 7.08–7.30 (m, 5H), 7.34 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H).

5-(6-Phenyl-hexyl)-4-tosyl-2-oxazoline (4f). Yield: 54%; product unstable; ^{1}H NMR ($CDCl_3$) δ 1.29 (m, 6H), 1.54 (m, 4H), 2.34 (s, 3H), 2.53 (t, J = 7.6 Hz, 2H), 4.69 (d, J = 6.8 Hz, 1H), 5.06 (q, J = 6.8 Hz, 1H), 6.90 (s, 1H), 6.99–7.19 (m, 5H), 7.29 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H).

5-(7-Phenyl-heptyl)-4-tosyl-2-oxazoline (4g). Yield: 88.0%; mp 101.4–102.2°C; ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 8H), 1.61 (m, 4H), 2.45 (s, 3H), 2.60 (t, J = 8.2 Hz, 2H), 4.74 (d, J = 6.8 Hz, 1H), 5.02 (q, J = 6.8 Hz, 1H), 6.95 (s, 1H), 7.08–7.32 (m, 5H), 7.36 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H).

5-(8-Phenyl-octyl)-4-tosyl-2-oxazoline (4h). Yield: 66.4%; mp 98.4–99.3°C; ^{1}H NMR ($CDCl_3$) δ 1.22 (m, 10H), 1.57 (m, 4H), 2.38 (s, 3H), 2.53 (t, J = 7.3 Hz, 2H), 4.68 (d, J = 6.6 Hz, 1H), 4.98 (q, J = 6.6 Hz, 1H), 6.89 (s, 1H),

7.04–7.27 (m, 5H), 7.30 (d, $J=8.0$ Hz, 2H), 7.74 (d, $J=8.0$ Hz, 2H).

5-(9-Phenyl-nonyl)-4-tosyl-2-oxazoline (4i). Yield: 69.3%; mp 94.0–95.1°C; ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 12H), 1.63 (m, 4H), 2.43 (s, 3H), 2.58 (t, $J=7.4$ Hz, 2H), 4.74 (d, $J=6.6$ Hz, 1H), 5.04 (q, $J=6.6$ Hz, 1H), 6.95 (s, 1H), 7.08–7.32 (m, 5H), 7.36 (d, $J=8.0$ Hz, 2H), 7.81 (d, $J=8.0$ Hz, 2H).

General procedure for the preparation of 4-(*n*-alkyl)-1*H*-imidazoles and 4-(ω-phenylalkyl)-1*H*-imidazoles

In a stainless steel bomb, a solution of the corresponding oxazoline (15.0 mmol) and a saturated solution of ammonia in abs ethanol (120 mL) was heated at 120°C for 25 h. The pressure increased to about 12 atm. After cooling, the solvent was removed under reduced pressure. The dark, oily residue was dissolved in ethyl acetate:dichloromethane (150 mL, 4:1, v/v) and washed with saturated aqueous sodium chloride (5×50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The isolated oil was purified on a silica gel column with CH_2Cl_2:MeOH (5:1, v/v) as eluent (for all products: $0.6 < R_f < 0.7$). The product was crystallized as hydrogen oxalate from acetone:CH_3CN.

4-(*n*-Propyl)-imidazole (hydrogen oxalate) VUF 5522 (5a). Yield: 44.7%; mp 153.5–153.9°C; ^{1}H NMR (DMSO-d_6) δ 0.83 (t, $J=7.3$ Hz, 3H), 1.57 (m, 2H), 2.58 (t, $J=6.7$ Hz, 2H), 7.32 (s, 1H), 8.80 (s, 1H), 13.24 (bs, 2.9H); ^{13}C NMR (DMSO-d_6) δ 13.046, 21.158, 25.613, 115.353, 133.142, 135.349, 163.786. Anal. calcd for $C_6H_{10}N_2 \cdot 1.0C_2H_2O_4$: C, 47.62; H, 5.97; N, 13.75. Found: C, 47.64; H, 5.69; N, 13.78.

4-(*n*-Butyl)-imidazole (hydrogen oxalate) VUF 5523 (5b). Yield: 63.1%; mp 155.6°C; ^{1}H NMR (DMSO-d_6) δ 0.89 (t, $J=7.3$ Hz, 3H), 1.30 (m, 2H), 1.58 (m, 2H), 2.62 (t, $J=7.0$ Hz, 2H), 7.28 (s, 1H), 8.69 (s, 1H), 12.23 (bs, 2H); ^{13}C NMR (DMSO-d_6) δ 13.318, 21.226, 23.502, 29.930, 115.402, 133.373, 133.473, 164.012. Anal. calcd for $C_7H_{12}N_2 \cdot 1.0C_2H_2O_4$: C, 49.97; H, 6.50; N, 12.81. Found: C, 50.04; H, 6.66; N, 12.80.

4-(*n*-Pentyl)-imidazole (hydrogen oxalate) VUF 5524 (5c). Yield: 52.8%; mp 179.8–180.4°C, ^{1}H NMR (DMSO-d_6) δ 0.83 (t, $J=7.5$ Hz, 3H), 1.28 (m, 4H), 1.59 (m, 2H), 2.58 (t, $J=7.6$ Hz, 2H), 7.21 (s, 1H), 8.55 (s, 1H), 10.22 (bs, 1.6H); ^{13}C NMR (DMSO-d_6) δ 13.614, 21.511, 24.074, 27.653, 30.356, 115.674, 133.464, 133.776, 164.216. Anal. calcd for $C_8H_{14}N_2 \cdot 0.8C_2H_2O_4$: C, 54.84; H, 7.48; N, 13.32. Found: C, 54.80; H, 7.52; N, 13.22.

4-(*n*-Hexyl)-imidazole (hydrogen oxalate) VUF 5466 (5d). Yield: 39.8%; ^{1}H NMR (DMSO-d_6) δ 0.86 (t, $J=6.8$ Hz, 3H), 1.27 (m, 6H), 1.58 (m, 2H), 2.60 (t, $J=7.7$ Hz, 2H), 7.28 (s, 1H), 8.70 (s, 1H), 11.14 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 13.683, 21.737, 23.855, 27.779, 27,818, 30.616, 115.428, 133.385, 133.517, 163.777. Anal. calcd for $C_9H_{16}N_2 \cdot 1.1\ C_2H_2O_4$: C, 53.54; H, 7.30; N, 11.15. Found: C, 53.62; H, 7.37; N, 11.21.

4-(*n*-Heptyl)-imidazole (hydrogen oxalate) VUF 5526 (5e). Yield: 55.4%; mp 186.1–186.6°C; ^{1}H NMR (DMSO-d_6) δ 0.84 (t, $J=6.7$ Hz, 3H), 1.25 (m, 8H), 1.58 (m, 2H), 2.60 (t, $J=8.0$ Hz, 2H), 7.26 (s, 1H), 8.58 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.713, 21.823, 24.069, 27.954 (2x), 28.109, 30.917, 115.625, 133.454, 133.712, 163.914. Anal. calcd for $C_{10}H_{18}N_2 \cdot 0.8C_2H_2O_4$: C, 58.47; H, 8.29; N, 11.76. Found: C, 58.64; H, 8.38; N, 11.71.

4-(*n*-Octyl)-imidazole (hydrogen oxalate) VUF 5467 (5f). Yield: 47.1%; mp 190.2–190.7°C; ^{1}H NMR (DMSO-d_6) δ 0.85 (t, $J=7.0$ Hz, 3H), 1.23 (bs, 10H), 1.58 (m, 2H), 2.57 (t, $J=6.8$ Hz, 2H), 7.18 (s, 1H), 8.48 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.73, 21.85, 24.32, 28.07 (2×), 28.37, 28.42, 31.01, 115.88, 133.56, 133.96, 164.04. Anal. calcd for $C_{11}H_{20}N_2 \cdot 0.8C_2H_2O_4$: C, 59.98; H, 8.63; N, 11.10. Found: C, 60.12; H, 8.69; N, 11.13.

4-(*n*-Nonyl)-imidazole (hydrogen oxalate) VUF 5528 (5g). Yield: 47.2%; mp 191.0°C; ^{1}H NMR (DMSO-d_6) δ 0.87 (t, $J=6.8$ Hz, 3H), 1.23 (bs, 12H), 1.58 (m, 2H), 2.58 (t, $J=6.9$ Hz, 2H), 7.32 (s, 1H), 8.78 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.723, 21.852, 23.758, 27.803, 28.091 (2×), 28.417, 28.632, 31.029, 115.337, 133.347, 133.430, 163.378. Anal. calcd for $C_6H_{10}N_2 \cdot 1.0C_2H_2O_4$: C, 60.20; H, 8.71; N, 10.17. Found: C, 60.52; H, 8.80; N, 10.15.

4-(*n*-Decyl)-imidazole (hydrogen oxalate) VUF 5529 (5h). Yield: 68.6%; mp 193.7–194.2°C; ^{1}H NMR (DMSO-d_6) δ 0.85 (bs, 3H), 1.20 (bs, 14H), 1.58 (m, 2H), 2.59 (m, 2H), 7.24 (s, 1H), 8.66 (s, 1H); ^{13}C NMR (400 MHz; 80°C; DMSO-d_6) δ 13.425, 21.641, 24.400, 28.0182, 28.0972, 28.2474, 28.2991, 28.5372, 28.5599, 30.893, 115.796, 133.358, 134.182, 163.379. Anal. calcd for $C_{13}H_{24}N_2 \cdot 0.8C_2H_2O_4$: C, 62.55; H, 9.20; N, 9.99. Found: C, 62.59; H, 9.30; N, 10.03.

4-(Benzyl)-imidazole (hydrogen oxalate) VUF 5511 (6a). Yield: 31.4%; mp 172.7–175.4°C; ^{1}H NMR (DMSO-d_6) δ 3.98 (s, 2H), 7.20 (s, 1H), 7.25 (m, 5H), 8.50 (s, 1H), 9.73 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 30.407, 116.341, 126.228, 128.252, 133.273, 134.019, 138.297, 164.572. Anal. calcd for $C_{10}H_{10}N_2 \cdot 0.75C_2H_2O_4$: C, 61.19; H, 5.14; N, 12.41. Found: C, 61.08; H, 4.69; N, 12.28.

4-(2-Phenylethyl)-imidazole (hydrogen oxalate) VUF 5512 (6b). Yield: 55.9%; mp 183.0–183.4°C; ^{1}H NMR (DMSO-d_6) δ 2.91 (m, 4H), 7.13 (s, 1H), 7.14–7.33 (m, 5H), 8.52 (s, 1H), 10.74 (s, 2.2H); ^{13}C NMR (DMSO-d_6) δ 26.196, 33.918, 115.825, 125.818, 128.033, 128.83, 133.261, 133.541, 140.447, 164.548. Anal. calcd for $C_{11}H_{12}N_2 \cdot 0.8C_2H_2O_4$: C, 61.96; H, 5.61; N, 11.47. Found: C, 62.03; H, 5.81; N, 11.42.

4-(3-Phenyl-propyl)-imidazole (hydrogen oxalate) VUF 5513 (6c). Yield: 74.4%; mp 186.1–187.9°C; ^{1}H NMR (DMSO-d_6) δ 1.91 (m, 2H), 2.62 (m, 4H), 7.04–7.38 (m, 5H), 7.41 (s, 1H), 8.78 (s, 1H), 9.45 (bs, 2.8H); ^{13}C NMR (DMSO-d_6) δ 23.372, 29.315, 34.013, 115.262, 125.479, 127.952, 132.920, 133.262, 141.009, 163.541. Anal. calcd for $C_{12}H_{14}N_2 \cdot 1.0C_2H_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.97; H, 5.81; N, 10.08.

4-(4-Phenyl-butyl)-imidazole (hydrogen oxalate) VUF 5514 (6d). Yield: 60.9%; mp 178.9–180.6°C; ^{1}H NMR (DMSO-d_6) δ 1.59 (m, 4H), 2.61 (m, 4H), 6.81 (bs, 1H). 7.09–7.36 (m, 6H), 8.51 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.985, 27.699, 30.117, 34.501, 115.707, 125.432, 128.002, 133.489, 133.694, 141.775, 164.346. Anal. calcd for $C_{13}H_{16}N_2 \cdot 0.75C_2H_2O_4$: C, 65.03; H, 6.59; N, 10.46. Found: C, 65.02; H, 6.64; N, 10.37.

4-(5-Phenyl-pentyl)-imidazole (hydrogen oxalate) VUF 5515 (6e). Yield: 86.2%; mp 167.1–168.2°C; ^{1}H NMR (DMSO-d_6) δ 1.32 (m, 2H), 1.61 (m, 4H), 2.59 (m, 4H), 7.07–7.34 (m, 6H), 7.60 (bs, 1H), 8.73 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.738, 27.637 (2×), 30.308, 34.684, 115.390, 125.386, 127.978, 128.022, 133.299, 133.405, 141.908, 163.709. Anal. calcd for $C_{14}H_{18}N_2 \cdot 1.0C_2H_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.12; H, 6.62; N, 9.15.

4-(6-Phenyl-hexyl)-imidazole (hydrogen oxalate) VUF 5516 (6f). Yield: 40.9%; mp 184.1–185.6°C; ^{1}H NMR (DMSO-d_6) δ 1.30 (m, 4H), 1.56 (m, 4H), 2.68 (m, 4H), 7.08–7.37 (m, 6H), 8.53 (s, 1H), 8.59 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 24.135, 27.920, 27.980, 28.039, 30.632, 34.849, 115.683, 125.349, 127.967, 128.007, 133.424, 133.750, 142.002, 164.311. Anal. calcd for $C_{15}H_{20}N_2 \cdot 0.75$ $C_2H_2O_4$: C, 66.98; H, 7.32; N, 9.47. Found: C, 66.93; H, 7.33; N, 9.44.

4-(7-Phenyl-heptyl)-imidazole (hydrogen oxalate) VUF 5517 (6g). Yield: 83.0%; mp 164.9–166.3°C; ^{1}H NMR (DMSO-d_6) δ 1.28 (m, 6H), 1.56 (m, 4H), 2.58 (m, 4H), 7.08–7.34 (m, 6H), 8.72 (s, 1H), 9.77 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 23.683, 27.762, 28.031, 28.193, 28.282, 30.732, 34.881, 115.270, 125.343, 127.971, 128.002, 133.285, 133.355, 142.039, 163.607. Anal. calcd for $C_{16}H_{22}N_2 \cdot 1.0C_2H_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.12; H, 7.22; N, 8.44.

4-(8-Phenyl-octyl)-imidazole (hydrogen oxalate) VUF 5518 (6h). Yield: 96.4%; mp 139.9–147.1°C; ^{1}H NMR (DMSO-d_6) δ 1.24 (m, 8H), 1.56 (m, 4H), 2.58 (m, 4H), 6.98 (bs, 1.6H), 7.03–7.40 (m, 6H), 8.79 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.651, 27.745, 28.055, 28.362, 28.482, 30.763, 34.902, 115.226, 125.332, 127.963, 127.993, 133.259, 133.319, 142.047, 163.332. Anal. calcd for $C_{17}H_{24}N_2 \cdot 1.0C_2H_2O_4$: C, 65.88; H, 7.56; N, 8.09. Found: C, 65.78; H, 7.61; N, 8.09.

4-(9-Phenyl-nonyl)-imidazole (hydrogen oxalate) VUF 5519 (6i). Yield: 87.4%; mp 157.2–159.5°C; ^{1}H NMR (DMSO-d_6) δ 1.25 (m, 10H), 1.56 (m, 4H), 2.58 (m, 4H), 7.05–7.33 (m, 6H), 8.00 (bs, 1H), 8.72 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.738, 27.787, 28.079, 28.395, 28.582, 28.621, 30.780, 34.910, 115.289, 125.339, 127.965, 128.005, 133.284, 133.384, 142.058, 163.497. Anal. calcd for $C_{18}H_{26}N_2 \cdot 1.0C_2H_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.65; H, 7.81; N, 7.93.

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