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(Partial) Agonist/Antagonist Properties of Novel Diarylalkyl Carbamates on Histamine H_3 Receptors

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Abstract—In the search for new ligands of the histamine H_3 receptor, novel diarylalkyl carbamates (**1**–**19**) were synthesized as derivatives of 3-(1*H*-imidazol-4-yl)propanol and -ethanol. Carbamates were built up via isocyanates either from corresponding amines by reaction with diphosgene or from related carboxylic acid/diphenylphosphoryl azide and the alcoholic component. Sterically hindered amines were prepared in a two-step reaction sequence from corresponding ketones. Some of the title compounds showed (partial) agonist activity at the histamine H_3 receptor in vitro and in vivo. Diphenylmethyl carbamate **2** was identified as a new lead structure ($ED_{50} = 5.3 \pm 2.6$ mg/kg po, $\alpha = 1.0$). Aromatic substitution in *ortho*- or *para*-positions of **2** led to a loss of agonist activity. *meta*-Substitution was tolerated to some extent. These effects seemed to be caused by steric rather than electronic properties of the substituents. An investigation of exchange of one or both phenyl rings of **2** by heterocyclic rings led to the highly active and selective thienyl derivative **18** ($ED_{50} = 3.4 \pm 1.4$ mg/kg po, $\alpha = 1.0$). These new (partial) agonists of the histamine H_3 receptor might serve as pharmacological tools for investigating molecular aspects of the H_3 receptor or as possible centrally acting therapeutic agents with oral bioavailability.

Introduction

The histamine H_3 receptor was discovered in 1983 by Arrang et al. as an inhibitory presynaptic autoreceptor modulating the synthesis and release of histamine.[1,2] H_3 heteroreceptors were also identified on neurons releasing other important neurotransmitters, e.g. dopamine, serotonin, noradrenaline, glutamate, and acetylcholine.[3] Therapeutic targets of histamine H_3-receptor agonists might be, e.g., neurogenic airway inflammation, migraine, and sleep disorders.[4] Very recently, the human histamine H_3 receptor cDNA has been cloned.[5] Research into the existence of receptor subtypes, species variations, and signal transduction of the histamine H_3 receptor has now gained fresh impetus. Highly selective and potent ligands, both agonists and antagonists, are needed as pharmacological tools for such studies.

Classical agonists of the histamine H_3 receptor, e.g., (*R*)-α-methylhistamine[6] and imetit[7,8] (cf. Fig. 1), consist of an imidazole nucleus, an alkyl spacer, and a basic moiety which is protonated under physiological conditions. Apart from this construction pattern, some partial agonists lacking a second basic moiety have also been described recently, e.g., iodoproxyfan[9] and FUB 407[10] (Fig. 1).

Depending on the test model, these compounds have been described as antagonists, partial or even full agonists.[9–11] The aliphatic ether FUB 407 displays full agonism under in vivo conditions after oral administration to Swiss mice,[10] whereas iodoproxyfan is inactive in this test system.[11] Carbamates with partial agonist activity in vitro and in vivo, e.g., FUB 475 (Fig. 1), have also been described.[10] Structure–activity relationships of agonists lacking a second basic moiety do not seem to follow a consistent line, as they are structurally diverse, e.g., carbamates and ethers with aliphatic and aromatic substituents (Fig. 1). Diphenylmethyl ethers have been described as possessing combined histamine H_1- and H_3-receptor antagonist properties without the

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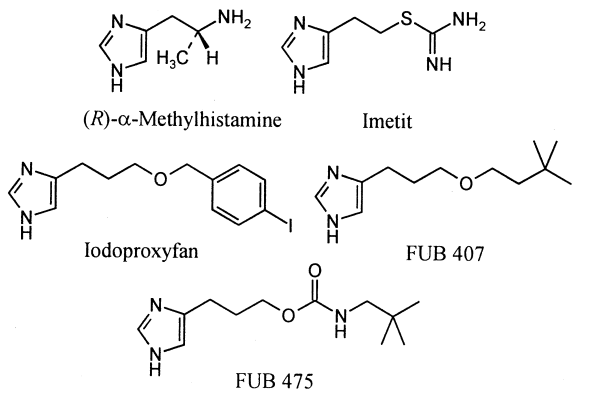


Figure 1.

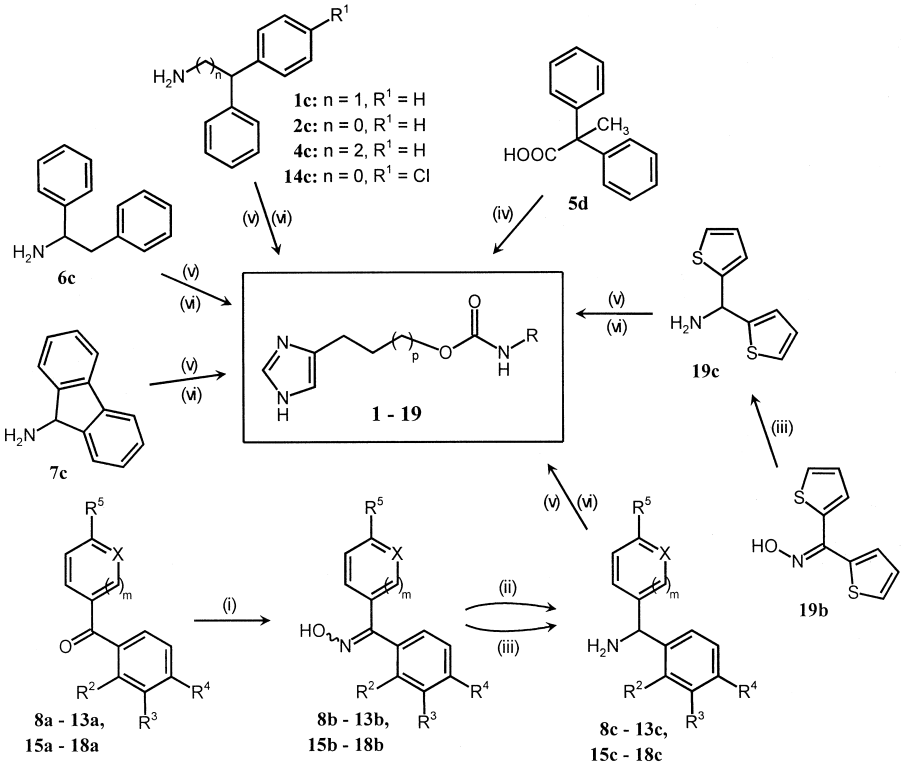
observation of any agonist activity.[12] Due to this fact it was surprising that related diphenylalkylcarbamates (**1**–**3**) possessed (partial) agonist activity at histamine H_3 receptors with high selectivity against H_1 receptors. With these initial results diphenylmethylcarbamate **2** was identified as a new lead structure. In search of histamine H_3-receptor (partial) agonists, we have prepared a series of substituted diphenylmethyl carbamates (**8**–**16**). For these derivatives of the lead **2** structure–activity relationships are discussed. Additionally, heteroaromatic exchange of one or both phenyl rings of the diphenylmethyl residue was investigated. For target carbamates, two functional in vitro and one in vivo test determining the modulatory activity at the histamine H_3 receptor were conducted. Furthermore, the receptor profile of selected compounds regarding histamine H_1 and H_2 receptors was determined.

Results and Discussion

Chemistry

Target molecules (**1**–**19**) were prepared as shown in Scheme 1. 2-(1*H*-Imidazol-4-yl)ethanol hydrochloride (**20**) was obtained from 1,4-dihydroxybutanone and formamidine acetate according to Dziuron and Schunack.[13] 3-(1*H*-Imidazol-4-yl)propanol hydrochloride (**21**) was prepared from urocanic acid as described by Stark et al. in the triphenylmethyl protected form and subsequently deprotected under acidic conditions.[11]

Carbamates **1**–**4** and **6**–**19** were synthesized from the corresponding amines (**1c**, **2c**, **4c**, **6c**–**19c**) by reaction



Scheme 1. Synthesis of compounds **1**–**19**. For residue R of the target molecules please refer to Tables 1 and 2, $p=0$ for **1**, $p=1$ for **2**–**19**; (i) $NH_2OH\times HCl$, Na_2CO_3, EtOH, reflux, 1–96 h; yield: 55–81%; (ii) Pd/C, H_2 (3–4 bar), MeOH, rt, 2–4 h, yield: 33–70%; (iii) $NaBH_4/TiCl_4$, 1,2-dimethoxyethane, 0 °C→rt, 12–168 h, yield: 29–60%; (iv) 3-(1*H*-imidazol-4-yl)propanol×HCl (**21**), diphenylphosphoryl azide, triethylamine, dioxane, reflux, 18 h, yield: 44%; (v) diphosgene, cat. charcoal, ethylacetate, 60 °C, 4 h; (vi) triethylamine (cat.), acetonitrile, reflux, 12 h, yield: 3–92%; **1**: 3-(1*H*-imidazol-4-yl)ethanol×HCl (**20**), **2**–**19**: 3-(1*H*-imidazol-4-yl)propanol×HCl (**21**).

with trichloromethyl chloroformate (diphosgene). The intermediate isocyanate was carefully isolated from solvent-diphosgene mixture by distillation and added to **20** resulting in **1**, and to **21** yielding **2**–**4** and **6**–**19**. Compound **3** was prepared from the same amine (**1c**) as **1**. Appropriate amines were synthesized from corresponding ketones by a two step reaction sequence (Scheme 1). A direct reductive amination of ketones by heterogenous catalysis to amines under standard conditions was not successful (not shown), probably due to steric hindrance of the diaryl ketone structure. Thus, ketones (**8a**–**13a**, **15a**–**18a**) were transformed to oximes (**8b**–**13b**, **15b**–**18b**) with $NH_2OH \times HCl$ in good yields by standard procedures. Oximes were reduced to amines by Pd/C catalyzed hydrogenation under pressure or by using $NaBH_4/TiCl_4$. The reduction procedure depended on the nature of substitution of diphenylmethyl oximes. Chlorine-substituted diphenylmethanone oximes (**12b, 13b, 15b**), and thienyl-substituted methanone oximes (**18b**, **19b**) were reduced by $NaBH_4/TiCl_4$ as they could not be prepared by catalytic reduction. Utilizing Pd/C-catalyzed reduction, aromatic chlorine substituents (**12b**, **13b**, **15b**) were cleaved off and thienyl containing methanone oximes (**18b**, **19b**) poisoned the catalyst. Methyl- (**8b**–**11b**), fluorosubstituted (**16b**) diphenylmethanone oximes, and phenyl-(3-pyridyl)methanone oxime (**17b**) were hydrogenated smoothly with Pd/C under pressure (3–4 bar).

A different approach of carbamate synthesis was performed for compound **5**. Starting with the corresponding carboxylic acid (**5d**), **5** was built up in a two-step, one-pot reaction with diphenylphosphoryl azide (DPPA) according to a modified Curtius reaction, and then with **21** (Scheme 1).[14]

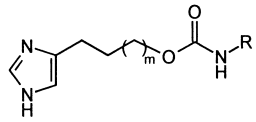
Since pharmacological testing revealed no significant differences between mono- or disubstituted diarylmethyl derivatives, separation into enantiomers of chiral compounds was not considered worth while.

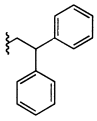
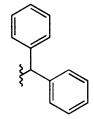
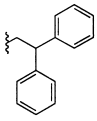
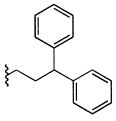
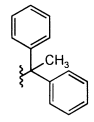
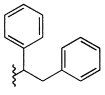
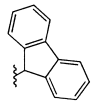
In vitro and in vivo potency on histamine H_3 receptors in rodents

Novel carbamates were tested in vitro on synaptosomes of rat cerebral cortex on their ability to modulate K^+-evoked depolarization-induced [^{3}H]histamine release after preloading of synaptosomes with [^{3}H]L-histidine.[7] Modulation of in vivo N^τ-methylhistamine (N^τ-MeHA) levels in cerebral cortex was determined after po administration to Swiss mice.[7] As activation of the histamine H_3 autoreceptor inhibits synthesis and release of histamine, agonists decrease whereas antagonists increase the level of N^τ-MeHA, the main metabolite of histamine in the central nervous system. Whereas changes in N^τ-MeHA levels might reflect actions of the drugs at targets other than the H_3 receptor (e.g., histidine decarboxylase or histamine *N*-methyltransferase), the latter seem very unlikely taking into account their structure and activity in vitro.

As shown in Table 1, compound **1** showed some agonist activity in vitro as well as in vivo, which could not be determined exactly due to low intrinsic activity and affinity for the histamine H_3 receptor. 3-(1*H*-Imidazol-4-yl)propyl homologue of **1**, compound **3**, displayed calculable partial agonist activity on both test systems in vitro and in vivo. When tested as an antagonist **3** showed high potency at the histamine H_3 receptor

Table 1. Chemical structures and potencies of **1**–**7** at histamine H_3 receptors in vitro and in vivo in rodents



No.	m	R	EC_{50} (nM)[a] ± SEM	α[b]	K_i (nM)[c] ± SEM	ED_{50} (mg/kg)[d] ± SEM	α[b]
1	0		> 10,000	n.c.[e]	> 1500	~20	≤1
2	1		n.c.[e]	0.20	26 ± 14	5.3 ± 2.6	1.0
3	1		43 ± 27	0.28	17 ± 3	2.0 ± 0.3	0.8
4	1		n.c.[e]	0.22	29 ± 18	> 10	—
5	1		—[f]		≥500	> 10	—
6	1		—[f]		13 ± 8[g]	> 10	—
7	1		—[f]		13 ± 3	2.3 ± 0.5	—
Imetit[h]			2.8 ± 0.7[i]	1.0		1.0 ± 0.3[i]	1.0

[a]Functional assay on synaptosomes of rat cerebral cortex;[7] compounds tested as agonists.
[b]Intrinsic activity.
[c]Functional assay on synaptosomes of rat cerebral cortex; [7] compounds tested as antagonists.
[d]Central assay with po administration of compounds to mice.
[e]n.c. = not calculable.
[f]No agonism evidenced.
[g]57% of maximum effect.
[h]Refs 7 and 8.
[i]Ref 7.

($K_i = 17$ nM). Thus, all of the following compounds contained 3-(1*H*-imidazol-4-yl)propyl as a central building block. Further variations in chain length of the substituent on the carbamate nitrogen (**2** and **4**) led to the diphenylmethyl substituted lead compound **2**, which showed full intrinsic activity under in vivo conditions ($ED_{50} = 5.3$ mg/kg po, $\alpha = 1.0$). The corresponding 3,3-diphenylpropyl homologue **4** was inactive under in vivo conditions.

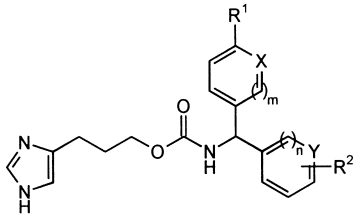
Quaternization of the carbon atom next to the carbamate nitrogen of the new lead structure **2** by an additional methyl group led to in vitro and in vivo inactive **5** (Table 1). 1,2-Diphenylethyl substituted derivative **6** showed only antagonist behaviour in vitro; interestingly the maximum antagonist effect reached was only 57%. As this compound displays non-competitive antagonist behaviour, terminal diaryl substitutition in this series seemed to be important for either competitive antagonist or (partial) agonist activity. Increased rigidity of the diphenylmethyl substituent of **2** as accomplished in **7** led to pure antagonist behaviour.

Aromatic substitution of the diphenylmethyl residue of **2** with methyl (**8**–**11**), chloro (**12**–**15**), and fluoro (**16**) groups led to interesting structure–activity relationships (Table 2). Methyl substitution in *ortho*- or *para*-positions (**8**, **10** and **11**) led to a dramatic decrease in H_3-receptor affinity in vitro and inactivity under in vivo conditions. The same effect was observed with chloro substituted analogues (**12**, **14** and **15**). The mesomeric as well as the inductive effects of methyl and chloro substituents are clearly different, nevertheless substitution in *ortho*- or *para*-positions led to the same pharmacological effect, suggesting that steric rather than electronic effects may be responsible for the low potency or inactivity at the histamine H_3 receptor. In agreement with this hypothesis *para,para*-difluoro-substituted derivative **16** retained at least in vitro antagonist potency ($K_i = 54$ nM). However, no agonist activity was observed for **16**. Obviously, the rather small fluoro substituents did not detract **16** from interaction with the receptor protein, although induction of a large conformational change was prevented, thus **16** showed purely antagonist behaviour.

meta-Substituted derivatives of **2**, e.g., **9** and **13**, showed weak agonist activity under in vitro conditions. However, due to low intrinsic activities of **9** and **13** EC_{50}-values were not calculable. *meta*-Methyl-substituted **9** displayed weak agonist action in vivo, whereas the other *meta*-substituted derivative **13** was not active. Aromatic substitution of lead compound **2** in various positions led in each case to a less active compound in vivo. Only *meta*-substitution was tolerated as agonist activity was retained to some extent (**9**).

Replacement of one or both phenyl rings by heterocycles was achieved with compounds **17**–**19**. However, pyridyl-substituted **17** displayed only antagonist properties in vitro and in vivo. Introduction of thiophene (**18**, **19**) led to (partial) agonists in vitro and in vivo. Monothienyl substituted **18** was equipotent to **2** with full intrinsic activity in vivo ($ED_{50} = 3.4$ mg/kg po, $\alpha = 1$). Partial agonist activity was observed for the dithienyl derivative **19** in vivo ($ED_{50} = 3.0$ mg/kg po, $\alpha = 0.8$).

Table 2. Chemical structures and potencies of lead compound **2** and analogues **8**–**19** at histamine H_3 receptors in vitro and in vivo in rodents



No.	R^1	R^2	m	n	X	Y	EC_{50} (nM)[a] ± SEM	α[b]	K_i (nM)[c] ± SEM	ED_{50} (mg/kg)[d] ± SEM	α[b]
2	H	H	1	1	CH	CH	n.c.[e]	0.2	26 ± 14	5.3 ± 2.6	1.0
8	H	*ortho*-CH_3	1	1	CH	CH	> 10,000	—	≥1500	> 10	—
9	H	*meta*-CH_3	1	1	CH	CH	n.c.[e]	0.21	31 ± 10	~30	~1
10	H	*para*-CH_3	1	1	CH	CH		—[f]	279 ± 140	> 10	—
11	CH_3	*para*-CH_3	1	1	CH	CH	> 10,000	—	> 1500	> 10	—
12	H	*ortho*-Cl	1	1	CH	CH		—[f]	380 ± 100	> 10	—
13	H	*meta*-Cl	1	1	CH	CH	n.c.[e]	0.10	21 ± 5	> 10	—
14	H	*para*-Cl	1	1	CH	CH		—[f]	137 ± 36	> 10	—
15	Cl	*para*-Cl	1	1	CH	CH		—[f]	258 ± 61	> 10	—
16	F	*para*-F	1	1	CH	CH		—[f]	54 ± 22	~10	—
17	H	H	1	1	N	CH		—[f]	96 ± 35	> 10	—
18	H	H	0	1	S	CH	557 ± 196	0.27	14 ± 4	3.4 ± 1.4	1.0
19	H	H	0	0	S	S	n.d.[g]		n.d.[g]	3.0 ± 1.9	0.8

[a]Functional assay on synaptosomes of rat cerebral cortex;[7] compounds tested as agonists.
[b]Intrinsic activity.
[c]Functional assay on synaptosomes of rat cerebral cortex; [7] compounds tested as antagonists.
[d]Central assay with po administration of compounds to mice.
[e]n.c. = not calculable.
[f]No agonism evidenced.
[g]n.d. = not determined.

Steric requirements for (partial) agonists of diarylmethyl carbamates at the histamine H_3 receptor seem to be very distinct. Aromatic substitution or increasing rigidity of the lead diphenylmethyl carbamate **2** was not tolerated well, except for *meta*-substitution (**9**, **13**), which retained some agonist activity. Phenylthienylmethyl exchange (**18**) of the diphenylmethyl moiety of **2** was tolerated, however. Partial agonist activity was observed for dithienylmethyl substituted **19** in vivo.

Since partial agonists generally cause lower receptor down regulation or desentization, these novel receptor activating agents might display potential beneficial effects from a therapeutic point of view.[15]

Histamine receptor profile of selected compounds

The receptor profile regarding other histamine receptors (H_1 and H_2) of selected compounds was determined on functional models of the guinea pig (Table 3).[16] For determination of histamine H_3 receptor modulation a second functional in vitro model on guinea pig ileum was conducted (Table 3).[17,18] With this peripheral model no partial agonism was evidenced with any of the new compounds. These differences in pharmacological action in vivo (mouse) and in vitro (rat, guinea pig) might be caused by a varying receptor reserve or species variants of the histamine H_3-receptor protein as well as by different experimental conditions within the assays.

Comparable antagonist potencies were observed for most compounds in these two functional H_3-receptor models ($|pA_2$ (guinea pig) $-pK_i$ (rat)$| \leq 0.4$ log units). Only **4**, **6**, and *meta*-substituted **9** and **13** showed different antagonist potencies in the two test models. Similar discrepancies in the two functional test models of the histamine H_3 receptor have been observed for alkyl cabamates.[19] Structural similarity of the new compounds to histamine H_1-receptor antagonists[3] due to the presence of diarylalkyl moieties did not generally lead to low selectivity (H_3 versus H_1). Highest potency on histamine H_1-receptors was observed for **4** ($pA_2 = 6.5$). Most compounds showed non-competitive antagonist behaviour on histamine H_1 and H_2 receptors ($pD'_2 \leq 5.4$). Highest selectivity was determined for the new lead compound **2** and its monothienyl analogue **18** (440:1, 1000:1, respectively) for H_3 versus H_1 and H_2 receptors.

Table 3. Receptor profile of selected compounds (**1**–**7**, **9**, **12**–**15** and **18**)

	H_3		H_2	H_1
No.	pK_i[a]	pA_2[b]	pD'_2[c]	pD'_2[d]
1	< 5.8	6.2	4.9	4.7
2	7.6	7.2	4.6	4.5
3	7.8	7.5	5.1	4.7
4	7.5	6.7	5.3	6.5[e]
5	< 6.3	6.3	5.2	4.9
6	7.9[f]	6.4	5.0	5.0
7	7.9	7.8	4.9	5.4[e]
9	7.5	6.8	5.0	5.0
12	6.4	6.1	< 5.0[e]	5.1[e]
13	7.7	6.9	< 5.0[e]	5.0[e]
14	6.9	6.8	5.1	5.4
15	6.6	6.3	5.0	5.4
18	7.9	8.0	4.8	4.6

[a]H_3-receptor assay on synaptosomes of rat cerebral cortex.[7]
[b]H_3-receptor assay on guinea pig ileum.[17,18]
[c]H_2-receptor test on guinea pig atrium.[16]
[d]H_1-receptor test on guinea pig ileum.[16]
[e]pA_2-value.
[f]57% of maximum effect.

Conclusions

Novel carbamates with diarylalkyl structure were synthesized. Some of the new compounds showed (partial) agonist activity in vitro and in vivo at the histamine H_3 receptor despite their structural difference to classical H_3-receptor agonists. Diphenylmethyl carbamate **2** was identified as a new lead ($ED_{50} = 5.3 \pm 2.6$ mg/kg po, $\alpha = 1.0$). Increased rigidity of the diphenylmethyl substituent (**7**) led to a loss of agonist activity. Substitution in *ortho*- and *para*-position of the diphenylmethyl moiety revealed that steric rather than electronic effects were responsible for the decreased antagonist affinity and lost agonist activity at the histamine H_3 receptor. Only *meta*-substitution was tolerated as decreased partial agonist activity was maintained. Replacement of one or both phenyl rings by thiophene (**18**, **19**) led to equieffective derivatives of **2** in vivo. Full agonism was observed for monothienyl substituted **18** ($ED_{50} = 3.4 \pm 1.4$ mg/kg po, $\alpha = 1.0$). Under in vitro conditions on synaptosomes of rat cerebral cortex partial agonism was observed for **2** and **18**. Selectivity of (partial) agonists **2** and **18** for H_3 receptors was high with respect to histamine H_1 and H_2 receptors. These diphenylmethyl and phenylthienylmethyl carbamates seem to be the parent compounds for a new class of histamine H_3-receptor (partial) agonists as pharmacological tools and as possible therapeutic agents with central activity after po administration.

Experimental

Chemistry

General procedures. Melting points were determined on an Electrothermal IA 9000 digital or a Büchi 512 apparatus and are uncorrected. For all compounds ^{1}H NMR spectra were recorded on a Bruker DPX 400 Avance (400 MHz) spectrometer. Chemical shifts are expressed in ppm downfield from internal TMS as reference. ^{1}H NMR data are reported in the following order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet; m, multiplet; *, exchangeable by D_2O; Im, imidazole; Mal, maleic acid; Ph, phenyl; Pyr, Pyridyl; Th, thienyl), number of protons, and approximate coupling constants in hertz (Hz). Mass spectra were obtained on a Finnigan MAT CH7A (EI–MS) and a Finnigan MAT CH5DF (FAB–MS). IR spectra were recorded with a 1420 Ratio-Recording or a 297 spectral photometer (Perkin–Elmer) in KBr (br, broad; m, medium; s, strong). Elemental analyses (C, H, N) for all compounds were measured on Perkin–Elmer 240 B or Perkin–Elmer 240

C instruments and were within 0.4% of theoretical values. Preparative, centrifugally accelerated, rotatory chromatography was performed using a Chromatotron 7924T (Harrison Research) and glass rotors with 4 mm layers of silica gel 60 PF_{254} containing gypsum (Merck).

Synthesis of oximes (8b–13b, 15b–18b)

(2-Methylphenyl)phenylmethanone Oxime (8b). A solution of (2-methylphenyl)phenylmethanone (3.9 g, 20 mmol), $NH_2OH \times HCl$ (4.2 g, 60 mmol) and Na_2CO_3 (6.4 g, 60 mmol) in 50 mL of ethanol was heated to reflux for 72 h. The solvent was evaporated under reduced pressure, the residue dissolved in an aqueous solution of K_2CO_3 and filtered. The crystalline residue was dissolved in CH_2Cl_2, filtered, and the solvent evaporated. Crude **8b** was crystallized from hot ethanol. (72%). Mp 108 °C.[20] ^{1}H NMR (DMSO-d_6) δ 11.28* (s, 1H, =N-OH), 7.35–7.01 (m, 9H, 9Ph–H), 2.08 (s, 3H, CH_3); MS (70 eV), *m/z* (%) 211 ([M^+], 75); IR (cm^{-1}) 3398br (ν[OH]), 1626m (ν[C=N]). Anal. ($C_{14}H_{13}NO$) calcd C: 79.6, H: 6.20, N: 6.63; found C: 79.6, H: 6.20, N: 6.62.

(3-Methylphenyl)phenylmethanone oxime (9b). Synthesized, as described for **8b** from (3-methylphenyl)phenylmethanone. Reaction was stopped after 6 h. **9b** crystallized from hot methanol (78%). Mp 114/139°C.[20] ^{1}H NMR (DMSO-d_6) δ 11.26*/11.25* (2s, 1H, =N–OH), 7.39–7.04 (m, 9H, 9Ph–H), 2.33–2.27 (2s, 3H, CH_3); MS (70 eV), *m/z* (%) 211 ([M^+], 100); IR (cm^{-1}) 3250br (ν[OH]), 1629m (ν[C=N]). Anal. ($C_{14}H_{13}NO$) calcd C: 79.6, H: 6.20, N: 6.63; found C: 79.4, H: 6.17, N: 6.63.

(4-Methylphenyl)phenylmethanone oxime (10b). Synthesized, as described for **8b** from (4-methylphenyl)phenylmethanone. Reaction was stopped after 6 h. **10b** crystallized from hot methanol (75%). Mp 142 °C.[21] ^{1}H NMR (DMSO-d_6) δ 11.28* (s, 1H, =N–OH), 7.50–7.20 (m, 9H, 9Ph–H), 2.40–2.35 (m, 3H, CH_3); MS (70 eV), *m/z* (%) 211 ([M^+], 100); IR (cm^{-1}) 3234br (ν[OH]), 1611 m (ν[C=N]). Anal. ($C_{14}H_{13}NO$) calcd C: 79.6, H: 6.20, N: 6.63; found C: 79.6, H: 6.18, N: 6.58.

Bis(4-methylphenyl)methanone oxime (11b). Synthesized, as described for **8b** from bis(4-methylphenyl)methanone. Reaction was stopped after 6 h. **11b** crystallized from hot methanol (81%). Mp 168 °C.[22] ^{1}H NMR (DMSO-d_6) δ 11.13* (s, 1H, =N–OH), 7.26 (s, 4H, 4Ph-3,3′,5,5′-H), 7.17 (s, 4H, 4Ph-2,2′,6,6′-H), 2.35–2.30 (s, 6H, 2×CH_3); MS (70 eV), *m/z* (%) 225 ([M^+], 100); IR (cm^{-1}) 3275br (ν[OH]), 1631m (ν[C=N]). Anal. ($C_{15}H_{15}NO$) calcd C: 80.0, H: 6.71, N: 6.22; found C: 80.0, H: 6.67, N: 6.14.

(2-Chlorophenyl)phenylmethanone oxime (12b). Synthesized, as described for **8b** from (2-chlorophenyl)phenylmethanone. Reaction was stopped after 16 h. **12b** crystallized from hot ethanol (73%). Mp 126 °C.[23] ^{1}H NMR (DMSO-d_6) δ 11.55* (s, 1H, =N–OH), 7.62–7.30 (m, 9H, 9Ph–H); MS (70 eV), *m/z* (%) 231 ([M^+], 100); IR (cm^{-1}) 3253br (ν[OH]), 1621m (ν[C=N]). Anal. ($C_{13}H_{10}ClNO$) calcd C: 67.4, H: 4.35, N: 6.05; found C: 67.3, H: 4.37, N: 5.95.

(3-Chlorophenyl)phenylmethanone oxime (13b). Synthesized, as described for **8b** from (3-chlorophenyl)phenylmethanone. Reaction was stopped after 15 h. **13b** crystallized from hot ethanol (69%). Mp 109–114 °C.[21] ^{1}H NMR (DMSO-d_6) δ 11.51* (s, 1H, =N–OH), 7.48–7.21 (m, 9H, 9Ph–H); MS (70 eV), *m/z* (%) 231 ([M^+], 100); IR (cm^{-1}) 3234br (ν[OH]), 1622m (ν[C=N]). Anal. ($C_{13}H_{10}ClNO$) calcd C: 67.4, H: 4.35, N: 6.05; found C: 67.3, H: 4.35, N: 5.99.

Bis(4-chlorophenyl)methanone oxime (15b). Synthesized, as described for **8b** from bis(4-chlorophenyl)methanone. Reaction was stopped after 72 h. **15b** crystallized from hot ethanol (55%). Mp 138 °C.[24] ^{1}H NMR (DMSO-d_6) δ 11.59* (s, 1H, =N–OH), 7.53 (d, 2H, J = 8.3 Hz, 2Ph–3,5–H), 7.44 (d, 2H, J = 8.6 Hz, 2Ph-3′,5′-H), 7.38 (d, 2H, J = 8.6 Hz, 2Ph–2,6–H), 7.33 (d, 2H, J = 8.3 Hz, 2Ph-2′,6′-H); MS (70 eV), *m/z* (%) 265 ([M^+], 66); IR (cm^{-1}) 3279br (ν[OH]), 1655m (ν[C=N]). Anal. ($C_{13}H_9Cl_2NO$) calcd C: 58.7, H: 3.41, N: 5.26; found C: 58.7, H: 3.47, N: 5.17.

Bis(4-fluorophenyl)methanone oxime (16b). Synthesized, as described for **8b** from bis(4-fluorophenyl)methanone. Reaction was stopped after 6 h. **16b** crystallized from hot methanol (68%). Mp 142 °C.[25] ^{1}H NMR (DMSO-d_6) δ 11.43* (s, 1H, =N–OH), 7.43–7.18 (m, 8H, 8Ph–H); MS (70 eV), *m/z* (%) 233 ([M^+], 100); IR (cm^{-1}) 3414br (ν[OH]), 1620m (ν[C=N]). Anal. ($C_{13}H_9F_2NO$) calcd C: 67.0, H: 3.89, N: 6.01; found C: 66.8, H: 3.86, N: 5.97.

Phenyl-(3-pyridyl)methanone oxime (17b). Synthesized, as described for **8b** from phenyl(3-pyridyl)methanone. Reaction was stopped after 1 h. **17b** crystallized from hot methanol (78%). Mp 142/165 °C.[26] ^{1}H NMR (DMSO-d_6) δ 11.66*/11.62* (2s, 1H, =N–OH), 8.63 (m, 1H, Pyr-6-H), 8.51 (m, 1H, Pyr-2-H), 7.74 (m, 1H, Pyr-4-H), 7.53–7.49 (m, 6H, 5Ph–H, Pyr-5-H); MS (70 eV), *m/z* (%) 198 ([M^+], 61); IR (cm^{-1}) 3406br (ν[OH]), 1625m (ν[C=N]). Anal. ($C_{12}H_{10}N_2O$) calcd C: 72.7, H: 5.08, N: 14.1; found C: 72.7, H: 5.22, N: 14.1.

Phenyl-(2-thienyl)methanone oxime (18b). Synthesized, as described for **8b** from phenyl(2-thienyl)methanone. Reaction was stopped after 96 h. **18b** crystallized from hot ethanol (62%). Mp 95 °C.[21] ^{1}H NMR (DMSO-d_6) δ 12.22/11.28* (s, 1H, =N–OH), 7.81 (m, 1H, Th–H-), 7.47 (s, 5H, 5Ph–H), 7.10 (m, 2H, 2Th–H); MS (70 eV), *m/z* (%) 203 ([M^+], 100); IR (cm^{-1}) 3239br (ν[OH]), 1604m (ν[C=N]). Anal. ($C_{11}H_9NOS$) calcd C: 65.0, H: 4.46, N: 6.89; found C: 65.0, H: 4.50, N: 6.82.

Synthesis of amines (8c–13c, 15c–19c)

(RS)-(2-Methylphenyl)phenylmethylamine (8c). A solution of **8b** (3.2 g, 15 mmol), Pd/C (10%, 200 mg) in 50 mL of methanol was hydrogenated under pressure at 3–4 bar for 2 h. The catalyst was filtered and the residue concentrated under reduced pressure. The crude product was dissolved in 2 N HCl and washed with ethyl acetate. The aqueous layer was alkalized with K_2CO_3 and extracted with ethyl acetate. The organic layer was

dried with Na_2SO_4 and evaporated under reduced pressure. Compound **8c** was crystallized as hydrochloride salt from EtOH/Et_2O (40%). Mp 268 °C (decomp.).[20] ^{1}H NMR (DMSO-d_6) δ 9.09* (s, 3H, NH_3^+), 7.67–7.22 (m, 9H, 9Ph–H), 5.70 (s, 1H, CH), 2.26 (s, 3H, CH_3); FAB$^+$–MS (Xe, MeOH/glycerol), *m/z* (%) 198 ([M + H$^+$], 13); IR (cm^{-1}) 3431br (ν[NH]), 3181s (ν[NH_3^+]). Anal. ($C_{14}H_{15}N\times$HCl) calcd C: 71.9, H: 6.90, N: 5.99; found C: 72.0, H: 6.81, N: 5.91.

(RS)-(3-Methylphenyl)phenylmethylamine (9c). Synthesized, as described for **8c** from **9b** (70%). Mp 268 °C (decomp.).[20] ^{1}H NMR (DMSO-d_6) δ 9.17* (s, 3H, NH_3^+), 7.55–7.15 (m, 9H, 9Ph–H), 5.56 (s, 1H, CH), 2.30 (s, 3H, CH_3); MS (70 eV), *m/z* (%) 197 ([M$^+$], 72); IR (cm^{-1}) 3422br (ν[NH]), 3190s (ν[NH_3^+]). Anal. ($C_{14}H_{15}N\times$HCl) calcd C: 71.9, H: 6.90, N: 5.99; found C: 71.8, H: 6.94, N: 5.88.

(RS)-(4-Methylphenyl)phenylmethylamine (10c). Synthesized, as described for **8c** from **10b** (33%). Mp 250 °C (decomp.).[20] ^{1}H NMR (DMSO-d_6) δ 9.08* (s, 3H, NH_3^+), 7.50–7.23 (m, 9H, 9Ph–H), 5.57 (s, 1H, CH), 2.29 (s, 3H, CH_3); MS (70 eV), *m/z* (%) 197 ([M$^+$], 53); IR (cm^{-1}) 3426br (ν[NH]), 3150s (ν[NH_3^+]). Anal. ($C_{14}H_{15}N\times$HCl) calcd C: 71.9, H: 6.90, N: 5.99; found C: 71.9, H: 7.00, N: 5.88.

Bis(4-methylphenyl)methylamine (11c). Synthesized, as described for **8c** from **11b**. The reaction was stopped after 4 h (43%). Mp 246 °C (decomp.).[20] ^{1}H NMR (DMSO-d_6) δ 9.02* (s, 3H, NH_3^+), 7.37 (d, J = 8.0 Hz, 4H, 4Ph-2,2′,6,6′-H), 7.22 (d, J = 8.0 Hz, 4H, 4Ph-3,3′,5,5′-H), 5.53 (d, J = 5.1 Hz, 1H, CH), 2.29 (s, 6H, 2×CH_3); MS (70 eV), *m/z* (%) 211 ([M$^+$], 38); IR (cm^{-1}) 3397br (ν[NH]), 3034s (ν[NH_3^+]). Anal. ($C_{15}H_{17}N\times$HCl) calcd C: 72.7, H: 7.32, N: 5.65; found C: 72.8, H: 7.33, N: 5.53.

(RS)-(2-Chlorophenyl)phenylmethylamine (12c). To a solution of **12b** (2.3 g, 10 mmol) in 10 mL of 1,2-dimethoxyethane, $NaBH_4$ (1.59 g, 41 mmol) was added. $TiCl_4$ (4.0 g, 21 mmol) was added slowly under nitrogen atmosphere at 0 °C. The mixture was warmed up to room temperature and stirred for 24 h. 100 mL of cold water was added, the solution alkalized with ammonia, and extracted with ethyl acetate. The organic layer was washed with a saturated solution of NaCl, dried over Na_2SO_4, and evaporated under reduced pressure. **12c** was crystallized as hydrochloride salt from EtOH/Et_2O (29%). Mp 246 °C (decomp.).[27] ^{1}H NMR (DMSO-d_6) δ 9.34* (s, 3H, NH_3^+), 7.99–7.34 (m, 9H, 9Ph–H), 5.82 (s, 1H, CH); MS (70 eV), *m/z* (%) 217 ([M$^+$], 50); IR (cm^{-1}) 3441br (ν[NH]), 3150m (ν[NH_3^+]). Anal. ($C_{13}H_{12}ClN\times$HCl) calcd C: 61.4, H: 5.16, N: 5.51; found C: 61.3, H: 5.22, N: 5.44.

(RS)-(3-Chlorophenyl)phenylmethylamine (13c). Synthesized, as described for **12c** from **13b** (45%). Mp 251 °C (decomp.).[27] ^{1}H NMR (DMSO-d_6) δ 9.13* (s, 3H, NH_3^+), 7.65–7.36 (m, 9H, 9Ph-H), 5.69 (s, 1H, CH); MS (70 eV), *m/z* (%) 217 ([M$^+$], 28); IR (cm^{-1}) 3429br (ν[NH]), 3183m (ν[NH_3^+]). Anal. ($C_{13}H_{12}ClN\times$HCl) calcd C: 61.4, H: 5.16, N: 5.51; found C: 61.4, H: 5.43, N: 5.47.

Bis(4-chlorophenyl)methylamine (15c). Synthesized, as described for **12c** from **15b** (43%). Mp 262 °C (decomp.).[27] ^{1}H NMR (DMSO-d_6) δ 9.25* (s, 3H, NH_3^+), 7.55 (d, J = 8.7 Hz, 4H, 4Ph-3,3′,5,5′-H), 7.51 (d, J = 8.6 Hz, 4H, 4Ph-2,2′,6,6′-H), 5.72 (s, 1H, CH); MS (70 eV), *m/z* (%) 251 ([M$^+$], 17); IR (cm^{-1}) 3433br (ν[NH]), 3024br (ν[NH_3^+]). Anal. ($C_{13}H_{11}Cl_2N\times$HCl) calcd C: 54.1, H: 4.19, N: 4.85; found C: 53.9, H: 4.45, N: 4.71.

Bis(4-fluorophenyl)methylamine (16c). Synthesized, as described for **8c** from **16b** (63%). Mp 250 °C (decomp.).[28] ^{1}H NMR (DMSO-d_6) δ 9.25* (s, 3H, NH_3^+), 7.37 (m, 4H, 4Ph-2,2′,6,6′-H), 7.22 (m, 4H, 4Ph–3,3′,5,5′-H), 5.71 (s, 1H, CH); MS (70 eV), *m/z* (%) 219 ([M$^+$], 25); IR (cm^{-1}) 3395br (ν[NH]), 2911br (ν[NH_3]). Anal. ($C_{13}H_{11}F_2N\times$HCl) calcd C: 61.0, H: 4.73, N: 5.48; found C: 61.0, H: 4.87, N: 5.30.

(RS)-Phenyl-(2-pyridyl)methylamine (17c). Synthesized, as described for **8c** from **17b**. The reaction was stopped after 4 h (72%). Mp 230 °C (decomp.).[26] ^{1}H NMR (DMSO-d_6) δ 9.17* (s, 3H, NH_3^+), 8.96* (s, 1H, Pyr$^+$-H), 8.66 (d, J = 4.0 Hz, 1H, Pyr-6-H), 7.90 (m, 1H, Pyr-4-H), 7.56–7.34 (m, 7H, 5Ph-H, 2Pyr-3,5-H), 5.75 (d, J = 5.4 Hz, 1H, CH); MS (70 eV), *m/z* (%) 184 ([M$^+$], 40); IR (cm^{-1}) 3428br (ν[NH]), 3261s (ν[NH_3^+]). Anal. ($C_{12}H_{12}N_2\times$2 HCl) calcd C: 56.1, H: 5.49, N: 10.9; found C: 56.0, H: 5.58, N: 10.7.

(RS)-Phenyl-(2-thienyl)methylamine (18c). Synthesized, as described for **12c** from **18b**. The reaction was stopped after 48 h (60%). Mp 200 °C (decomp.).[29] ^{1}H NMR (DMSO-d_6) δ 9.23* (s, 3H, NH_3^+), 7.61–7.36 (m, 7H, 5Ph–H, 2Th-3,5-H), 7.08 (m, 1H, Th-4-H), 5.91 (s, 1H, CH); MS (70 eV), *m/z* (%) 189 ([M$^+$], 100); IR (cm^{-1}) 3428br (ν[NH]), 2946br (ν[NH_3^+]). Anal. ($C_{11}H_{11}NS\times$HCl×$\frac{1}{4}$ H_2O) calcd C: 57.4, H: 5.47, N: 6.08; found C: 57.6, H: 5.51, N: 6.00.

Bis(2-thienyl)methylamine (19c). Synthesized, as described for **12c** from bis(2-thienyl)methanone oxime. The reaction was stopped after 168 h (34%). Mp 146 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ 9.27* (s, 3H, NH_3^+), 7.60 (dd, ^3J = 5.1 Hz, ^4J = 1.1 Hz, 2H, 2Th-5,5′-H), 7.42 (d, J = 3.4 Hz, 2H, 2Th-3,3′-H), 7.10 (dd, ^3J = 5.0 Hz, ^4J = 3.6 Hz, 2H, 2Th-4,4′-H), 6.27 (s, 1H, CH); MS (70 eV), *m/z* (%) 195 ([M$^+$], 79); IR (cm^{-1}) 3434br (ν[NH]), 2975br (ν[NH_3^+]). Anal. ($C_9H_9NS_2\times$HCl) calcd C: 46.6, H: 4.35, N: 6.04; found C: 46.6, H: 4.26, N: 5.92.

Synthesis of carbamates (1–19)

2-(1*H*-Imidazol-4-yl)ethyl *N*-(2,2-Diphenylethyl)carbamate (1). To a solution of trichloromethyl chloroformate (1.2 g, 6 mmol) and a catalytic amount of charcoal in 30 mL of dry ethyl acetate was added rapidly 2,2-diphenylethylamine (**1c**) (1.0 g, 5 mmol). The reaction mixture was heated to reflux for 4 h. Then the black

Table 4. Physical properties and elemental analysis of target carbamates (**1**–**19**)

Compound no.	Formula	M_w (g/mol)	Mp (°C)	Calcd (%)			Found (%)		
				C	H	N	C	H	N
1	$C_{20}H_{21}N_3O_2\times C_4H_4O_4$	451.5	136	63.9	5.58	9.31	63.7	5.77	9.13
2	$C_{20}H_{21}N_3O_2\times C_4H_4O_4\times\frac{1}{4}H_2O$	456.0	127	65.2	5.64	9.22	65.5	5.64	9.19
3	$C_{21}H_{23}N_3O_2\times C_4H_4O_4$	465.5	106	64.5	5.85	9.03	64.5	5.75	8.94
4	$C_{22}H_{25}N_3O_2\times C_4H_4O_4$	479.5	126	65.1	6.10	8.76	65.2	6.20	8.85
5	$C_{21}H_{23}N_3O_2\times C_2H_2O_4\times\frac{1}{4}H_2O$	444.0	132	62.2	5.79	9.46	62.4	5.80	9.46
6	$C_{21}H_{23}N_3O_2\times C_4H_4O_4\times\frac{1}{4}H_2O$	470.0	140	63.9	5.90	8.94	64.0	5.83	8.96
7	$C_{20}H_{19}N_3O_2\times C_4H_4O_4\times\frac{1}{4}H_2O$	454.0	175	63.5	5.22	9.26	63.3	5.23	9.38
8	$C_{21}H_{23}N_3O_2\times C_2H_2O_4$	439.5	134	62.9	5.73	9.56	62.9	5.76	9.61
9	$C_{21}H_{23}N_3O_2\times C_2H_2O_4$	439.5	132	62.9	5.73	9.56	62.8	5.97	9.61
10	$C_{21}H_{23}N_3O_2\times 0.8\ C_2H_2O_4\times\frac{1}{4}H_2O$	426.0	131	63.7	5.94	9.86	63.8	5.75	9.69
11	$C_{22}H_{25}N_3O_2\times C_4H_4O_4$	379.5	134	65.1	6.10	8.76	65.0	6.06	8.70
12	$C_{20}H_{20}ClN_3O_2\times C_2H_2O_4$	459.9	135	57.5	4.82	9.14	57.3	4.96	9.16
13	$C_{20}H_{20}ClN_3O_2\times C_2H_2O_4\times\frac{1}{2}H_2O$	468.9	107	56.4	4.94	8.96	56.5	5.06	8.83
14	$C_{20}H_{20}ClN_3O_2\times C_2H_2O_4\times\frac{1}{2}H_2O$	468.9	104	56.4	4.94	8.96	56.6	4.91	8.85
15	$C_{20}H_{19}Cl_2N_3O_2\times C_4H_4O_4$	520.4	147	55.4	4.45	8.07	55.2	4.58	8.12
16	$C_{20}H_{19}F_2N_3O_2\times C_4H_4O_4\times\frac{1}{4}H_2O$	492.0	141	58.6	4.81	8.54	58.5	4.83	8.43
17	$C_{19}H_{20}N_4O_2\times\frac{1}{2}H_2O$	345.4	141	66.1	6.13	16.2	66.4	5.97	16.1
18	$C_{18}H_{19}N_3O_2S\times C_2H_2O_4$	431.5	121	55.7	4.91	9.74	55.6	4.91	9.55
19	$C_{16}H_{17}N_3O_2S_2\times 0.9\ C_2H_2O_4$	428.5	126	49.9	4.42	9.81	50.1	4.60	9.82

solution was cooled, filtered, and the solvent was evaporated under reduced pressure. The freshly prepared isocyanate was dissolved in 30 mL of dry acetonitrile and added to 2-(1*H*-imidazol-4-yl)ethanol×HCl[13] (**20**) (0.7 g, 5 mmol) in 10 mL of dry acetonitrile. The solution was heated to reflux for 4 h and concentrated in vacuo. The residue was purified by rotatory chromatography (eluent: CH_2Cl_2:MeOH (gradient from 99:1 to 90:10), ammonia atmosphere]. The pure fractions were concentrated in vacuo and dried (40%). The yellow oil was crystallized as hydrogenmaleate. ^{1}H NMR (DMSO-d_6) δ 8.83 (s, 1H, Im-2-H), 7.32–7.19 (m, 12H, 10Ph-H + Im-5-H + CONH), 6.06 (s, 2H, Mal), 4.20–4.10 (m, 3H, NHCH_2C*H*), 3.62 (m, 2H, CH_2O), 2.87 (t, J = 6.3 Hz, 2H, Im-CH_2); MS (70 eV), m/z (%) 335 ([M$^+$], 2); IR (cm^{-1}) 1720s (ν[C=O]).

3-(1*H*-Imidazol-4-yl)propyl *N*-(diphenylmethyl)carbamate (2). Synthesized as described for **1** with diphenylmethylamine and 3-(1*H*-imidazol-4-yl)propanol×HCl[11] (**21**) (85%). ^{1}H NMR (DMSO-d_6) δ 8.87 (s, 1H, Im-2-H), 8.29* (d, J = 9.2 Hz, 1H, CONH), 7.39–7.20 (m, 11H, 10Ph-H + Im-5-H), 6.05 (s, 2H, Mal), 5.86 (d, J = 9.2 Hz, 1H, CH), 4.01 (t, J = 6.4 Hz, 2H, CH_2O), 2.69 (m, 2H, Im-CH_2), 1.91 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 335 ([M$^+$], 26); IR (cm^{-1}) 1722s (ν[C=O]).

(1*H*-Imidazol-4-yl)propyl *N*-(2,2-diphenylethyl)carbamate (3). Synthesized as described for **1** from **1c** and **21**[11] (61%). ^{1}H NMR (DMSO-d_6) δ 8.87 (s, 1H, Im-2-H), 7.35–7.17 (m, 12H, 10Ph-H + Im-5-H + CONH), 6.06 (s, 2H, Mal), 4.20 (m, 1H, CH), 3.93 (t, J = 6.4 Hz, 2H, CH_2O), 3.63 (m, 2H, NHCH_2), 2.61 (t, J = 7.5 Hz, 2H, Im-CH_2), 1.83 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 349 ([M$^+$], 19); IR (cm^{-1}) 1690s (ν [C=O])

3-(1*H*-Imidazol-4-yl)propyl *N*-(3,3-diphenylpropyl)carbamate (4). Synthesized as described for **1** from 3,3-diphenylpropylamin and **21**[11] (61%). ^{1}H NMR (DMSO-d_6) δ 8.89 (s, 1H, Im-2-H), 7.40 (s, 1H, Im-5-H), 7.29–7.17 (m, 11H, 10Ph-H + CONH), 6.07 (s, 2H, Mal), 3.98–3.94 (m, 3H, CH_2O + CH), 2.89 (m, 2H, NHCH_2), 2.68 (t, J = 7.5 Hz, 2H, Im-CH_2), 2.17 (m, 2H, CH_2CH), 1.89 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 363 ([M$^+$], 47); IR (cm^{-1}) 1718s (ν[C=O]).

3-(1*H*-Imidazol-4-yl)propyl *N*-(1,1-diphenylethyl)carbamate (5). A mixture of 2,2-diphenylpropionic acid (1.1 g, 5 mmol), triethylamine (0.5 g, 5 mmol), and diphenylphosphoryl azide (1.4 g, 5 mmol) was stirred for 45 min in 30 mL of dry acetonitrile at room temperature. The reaction mixture was heated to reflux for 30 min, **21**[11] (0.8 g, 5 mmol) was added, and the solution was refluxed for 4 h. The solvent was removed under reduced pressure, the residue dissolved in Et_2O and extracted with a saturated solution of K_2CO_3 and $NaHCO_3$. After concentration of the combined organic fractions the residue was purified by rotatory chromatography [eluent: $CHCl_3$/MeOH (gradient from 95/5 to 90/10), ammonia atmosphere]. The combined fractions were concentrated, dried, and crystallized as hydrogenoxalate (44%). ^{1}H NMR (DMSO-d_6) δ 8.64 (s, 1H, Im-2-H), 7.75 (s, 1H, Im-5-H), 7.33–7.19 (m, 11H, 10Ph-H + CONH), 3.87 (t, J = 7.5 Hz, 2H, CH_2O), 2.65 (m, 2H, Im-CH_2), 1.98 (s, 3H, CH_3), 1.84 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 349 ([M$^+$], 29); IR (cm^{-1}) 1722s (ν[C=O]).

(RS)-3-(1*H*-Imidazol-4-yl)propyl *N*-(1,2-diphenylethyl)-carbamate (6). Synthesized as described for **1** from 1,2-diphenylethylamine and **21**[11] (70%). ^{1}H NMR (DMSO-d_6) δ 8.85 (s, 1H, Im-2-H), 7.80* (d, J = 8.9 Hz, 1H, CONH), 7.33–7.15 (m, 11H, 10Ph-H + Im-5-H), 6.05 (s, 2H, Mal), 4.74 (m, 1H, CH), 3.85 (t, J = 6.4 Hz, 2H, CH_2O), 2.92 (t, J = 7.6 Hz, 2H, CHCH_2), 2.58 (t, J = 7.5 Hz, 2H, Im-CH_2), 1.81 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 349 ([M$^+$], 8); IR (cm^{-1}) 1690s (ν [C=O]).

***N*-(9-Fluorenyl)3-(1*H*-imidazol-4-yl)propylcarbamate (7).** Synthesized as described for **1** from 9-fluorenylamine and **21**[11] (49%). ^{1}H NMR (DMSO-d_6) δ 8.87 (s, 1H, Im-2-H), 7.85–7.31 (m, 10H, 8Ph-H + Im-5-H + CONH), 6.05 (s, 2H, Mal), 5.70 (d, J = 8.5 Hz, 1H, CH), 4.12 (t, J = 6.5 Hz, 2H, CH_2O), 2.72 (t, J = 7.5 Hz, 2H, Im-CH_2), 1.97 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 333 ([M$^+$], 39); IR (cm^{-1}) 1690s (ν[C=O]).

(RS)-3-(1*H*-Imidazol-4-yl)propyl *N*-[(2-methylphenyl)-phenylmethyl]carbamate (8). Synthesized as described for **1** from **8c** and **21**[11] (13%). The product was crystallized as hydrogenoxalate from EtOH/Et_2O. ^{1}H NMR (DMSO-d_6) δ 8.88 (s, 1H, Im-2-H), 8.17* (d, J = 8.1 Hz, 1H, CONH), 7.32–7.12 (m, 10 H, 9Ph-H + Im-5-H), 6.02 (d, J = 8.7 Hz, 1H, CH), 3.99 (m, 2H, CH_2O), 2.63 (m, 2H, Im-CH_2), 2.25 (s, 3H, CH_3), 1.88 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 349 ([M$^+$], 48); IR (cm^{-1}) 1713s (ν[C=O]).

(RS)-3-(1*H*-Imidazol-4-yl)propyl *N*-[(3-methylphenyl)-phenylmethyl]carbamate (9). Synthesized as described for **1** from **9c** and **21**[11] (11%). The product was crystallized as hydrogenoxalate from EtOH/Et_2O. ^{1}H NMR (DMSO-d_6) δ 8.48 (s, 1H, Im-2-H), 8.24* (d, J = 8.6 Hz, 1H, CONH), 7.31–7.03 (m, 10 H, 9Ph-H + Im-5-H), 5.80 (d, J = 9.3 Hz, 1H, CH), 3.99 (t, J = 6.2 Hz, 2H, CH_2O), 2.65 (t, J = 7.3 Hz, 2H, Im-CH_2), 2.26 (s, 3H, CH_3), 1.88 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 349 ([M$^+$], 62); IR (cm^{-1}) 1702s (ν[C=O]).

(RS)-3-(1*H*-Imidazol-4-yl)propyl *N*-[(4-methylphenyl)-phenylmethyl]carbamate (10). Synthesized as described for **1** from **10c** and **21**[11] (40%). The product was crystallized as hydrogenoxalate from EtOH/Et_2O. ^{1}H NMR (DMSO-d_6) δ 8.36 (s, 1H, Im-2-H), 8.21* (d, J = 8.9 Hz, 1H, CONH), 7.31–7.11 (m, 10 H, 9Ph-H + Im-5-H), 5.81 (d, J = 9.2 Hz, 1H, CH), 4.00 (t, J = 6.4 Hz, 2H, CH_2O), 2.62 (t, J = 6.6 Hz, 2H, Im-CH_2), 2.26 (s, 3H, CH_3), 1.89 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 349 ([M$^+$], 46); IR (cm^{-1}) 1699s (ν[C=O]).

***N*-[Bis(4-methylphenyl)methyl]3-(1*H*-imidazol-4-yl)propylcarbamate (11).** Synthesized as described for **1** from **11c** and **21**[11] (73%). ^{1}H NMR (DMSO-d_6) δ 8.83 (s, 1H, Im-2-H), 8.15* (d, J = 9.3 Hz, 1H, CONH), 7.37 (s, 1H, Im-5-H), 7.16 (d, J = 8.1 Hz, 4H, 4Ph-2,2′,6,6′-H), 7.10 (d, J = 8.1 Hz, 4H, 4Ph-3,3′,5,5′5-H), 6.04 (s, 2H, Mal), 5.75 (d, J = 9.4 Hz, 1H, CH), 3.99 (t, J = 6.3 Hz, 2H, CH_2O), 2.67 (m, 2H, Im-CH_2), 2.25 (s, 6H, 2CH_3), 1.90 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 363 ([M$^+$], 53); IR (cm^{-1}) 1696s (ν[C=O]).

(RS)-*N*-[(2-Chlorophenyl)phenylmethyl]3-(1*H*-imidazol-4-yl)propylcarbamate (12). Synthesized as described for **1** from **12c** and **21**[11] (22%). The product was crystallized as hydrogenoxalate from EtOH/Et_2O. ^{1}H NMR (DMSO-d_6) δ 8.33 (m, 2H, Im-2-H + CONH), 7.53–7.13 (m, 10 H, 9Ph-H + Im-5-H), 6.22 (d, J = 9.1 Hz, 1H, CH), 3.99 (t, J = 6.3 Hz, 2H, CH_2O), 2.63 (t, J = 7.2 Hz, 2H, Im-CH_2), 1.88 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 369 ([M$^+$], 13); IR (cm^{-1}) 1704s (ν[C=O]).

(RS)-*N*-[(3-Chlorophenyl)phenylmethyl]3-(1*H*-imidazol-4-yl)propylcarbamate (13). Synthesized as described for **1** from **13c** and **21**[11] (92%). The product was crystallized as hydrogenoxalate from EtOH/Et_2O. ^{1}H NMR (DMSO-d_6) δ 8.41 (m, 1H, Im-2-H), 8.30* (d, J = 8.2 Hz, 1H, CH), 7.39–7.15 (m, 10 H, 9Ph-H + Im-5-H), 5.86 (d, J = 9.2 Hz, 1H, CH), 3.98 (t, J = 6.4 Hz, 2H, CH_2O), 2.63 (t, J = 8.0 Hz, 2H, Im-CH_2), 1.88 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 369 ([M$^+$], 18); IR (cm^{-1}) 1699s (ν[C=O]).

(RS)-*N*-[(4-Chlorophenyl)phenylmethyl]3-(1*H*-imidazol-4-yl)propylcarbamate (14). Synthesized as described for **1** from (4-chlorophenyl)phenylmethylamine and **21**[11] (57%). The product was crystallized as hydrogenoxalate from EtOH/Et_2O. ^{1}H NMR (DMSO-d_6) δ 8.51 (s, 1H, Im-2-H), 8.29* (d, J = 8.4 Hz, 1H, CH), 7.40–7.21 (m, 10H, 9Ph-H + Im-5-H), 5.87 (d, J = 8.8 Hz, 1H, CH), 4.01 (m, 2H, CH_2O), 2.66 (m, 2H, Im-CH_2), 1.90 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 369 ([M$^+$], 19); IR (cm^{-1}) 1701s (ν[C=O]).

***N*-[Bis(4-chlorophenyl)methyl]3-(1*H*-imidazol-4-yl)propylcarbamate (15).** Synthesized as described for **1** from **15c** and **21**[11] (33%). ^{1}H NMR (DMSO-d_6) δ 8.81 (s, 1H, Im-2-H), 8.31* (d, J = 8.8 Hz, 1H, CH), 7.39 (d, J = 8.5 Hz, 4H, 4Ph-3,3′,5,5′-H), 7.39 (s, 1H, Im-5-H), 7.32 (d, J = 8.5 Hz, 4H, 4Ph-2,2′,6,6′-H), 6.04 (s, 2H, Mal), 5.88 (d, J = 9.2 Hz, 1H, CH), 4.00 (t, J = 6.5 Hz, 2H, CH_2O), 2.86 (m, 2H, Im-CH_2), 1.90 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 403 ([M$^+$], 8); IR (cm^{-1}) 1696s (ν[C=O]).

***N*-[Bis(4-fluorophenyl)methyl]3-(1*H*-imidazol-4-yl)propylcarbamate (16).** Synthesized as described for **1** from **16c** and **21**[11] (75%). Mp 141 °C. ^{1}H NMR (DMSO-d_6) δ 8.83 (s, 1H, Im-2-H), 8.29* (d, J = 9.0 Hz, 1H, CONH), 7.34 (m, 5H, 4Ph-2,2′,6,6′-H + Im-5-H), 7.16 (m, 4H, 4Ph-3,3′,5,5′-H), 6.04 (s, 2H, Mal), 5.88 (d, J = 9.1 Hz, 1H, CH), 4.00 (t, J = 6.5 Hz, 2H, CH_2O), 2.68 (m, 2H, Im-CH_2), 1.91 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 371 ([M$^+$], 41); IR (cm^{-1}) 1704s (ν[C=O]).

(RS)-3-(1*H*-Imidazol-4-yl)propyl *N*-[phenyl(3-pyridyl)methyl]carbamate (17). Synthesized as described for **1** from **17c** and **21**[11] (23%). The product was crystallized as free base. ^{1}H NMR (DMSO-d_6) δ 8.56 (s, 1H, Im-2-H), 8.44 (m, 1H, Pyr-6-H), 8.36* (d, J = 8.7 Hz, 1H, CONH), 7.71 (m, 1H, Pyr-4-H), 7.50 (s, 1H, Pyr-2-H), 7.37–7.23 (m, 9H, 8Ph-H + Pyr-4-H), 6.73 (s, 1H, Im-5-H), 5.94 (d, J = 9.1 Hz, 1H, CH), 4.00 (t, J = 6.5 Hz, 2H, CH_2O), 2.54 (m, 2H, Im-CH_2), 1.85 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 339 ([M$^+$], 21); IR (cm^{-1}) 1692s (ν[C=O]).

(RS)-3-(1*H*-Imidazol-4-yl)propyl *N*-[phenyl(2-thienyl)methyl]carbamate (18). Synthesized as described for **1** from **18c** and **21**[11] (29%). The product was crystallized as hydrogenoxalate from EtOH/Et_2O. ^{1}H NMR (DMSO-d_6) 8.50 (m, 1H, Im-2-H), 8.42* (d, J = 8.6 Hz, 1H, CH), 7.71-7.21 (m, 7 H, 5Ph-H + Im-5-H + Th-5-H), 6.94 (m, 1H, Th-4-H), 6.79 (m, 1H, Th-3-H), 6.04 (d, J = 9.2 Hz, 1H, CH), 4.00 (m, 2H, CH_2O), 2.66 (m, 2H, Im-CH_2), 1.91 (m, 2H, Im-$CH_2C\mathit{H}_2$); MS (70 eV), m/z (%) 341 ([M$^+$], 35); IR (cm^{-1}) 1700s (ν[C=O]).

***N*-[Bis(2-thienyl)methyl]3-(1*H*-imidazol-4-yl)propylcarbamate (19).** Synthesized as described for **1** from **19c** and **21**[11] (3%). The product was crystallized as hydrogenoxalate from EtOH/Et_2O. ^1H NMR (DMSO-d_6) δ 8.51 (m, 1H, CONH), 8.35 (m, 1H, Im-2-H), 7.45 (dd, $^3J = 4.6$ Hz, $^4J = 1.4$ Hz, 2H, 2Th-5,5′-H), 7.13 (s, 1H, Im-5-H), 6.98 (m, 4H, 4Th-3,4-H), 6.30 (d, $J = 9.0$ Hz, 1H, CH), 4.02 (t, J = 6.5 Hz, 2H, CH_2O), 2.64 (m, 2H, Im-CH_2), 1.90 (m, 2H, Im-CH_2CH_2); MS (70 eV), *m*/*z* (%) 347 ([M^+], 34); IR (cm^{-1}) 1701s (ν[C=O]).

Pharmacology

Histamine H_3-receptor assay on synaptosomes of rat cerebral cortex. Compounds were tested for their H_3-receptor agonist/antagonist activity in an assay with K^+-evoked depolarization-induced release of [^{3}H]histamine from rat synaptosomes according to Garbarg et al.[7] A synaptosomal fraction from rat cerebral cortex prepared according to the method of Whittaker[30] was preincubated for 30 min with L-[^{3}H]histidine (0.4 μM) at 37 °C in a modified Krebs-Ringer solution. The synaptosomes were washed extensively, resuspended in fresh 2 mM K^+ Krebs-Ringer's medium, and incubated for 2 min with 2 or 30 mM K^+ (final concentration). Antagonists and 1 μM histamine or the agonist in increasing concentrations were added 5 min before depolarization stimulus. Incubations were stopped by rapid centrifugation, and [^{3}H]histamine levels were determined after purification by liquid scintillation spectrometry.[7] K_i values were determined according to the Cheng–Prussoff equation.[31] The data presented are given as mean values with standard error of the mean (SEM)[32] for a minimum of three separate determinations each. The intrinsic activity (α) of agonists was expressed as percent of the maximal effect of the compounds over the maximal effect of histamine.

Histamine H_3-receptor antagonist activity on guinea pig ileum. For selected compounds H_3-receptor activity was measured by concentration-dependent inhibition of electrically evoked twitches of isolated guinea pig ileum segments induced by (*R*)-α-methylhistamine in the presence of the antagonist according to Ligneau et al.[33] Longitudinal muscle strips were prepared from the small intestine, 20–50 cm proximal to the ileocecal valve. The muscle strips were mounted between two platinum electrodes (4 mm apart) in 20 mL of Krebs buffer, containing 1 μM of mepyramine, connected to an isometric transducer, continuously gassed with oxygen containing 5% CO_2 at 37 °C. After equilibration of the muscle segments for 1 h with washing every 10 min, they were stimulated continuously with rectangular pulses of 15 V and 0.5 ms at a frequence of 0.1 Hz. After 30 min of stimulation, a cumulative dose–response curve was recorded. Subsequently the preparations were washed three times every 10 min without stimulation. The antagonist was incubated 20 min before redetermination of the dose–response curve of (*R*)-α-methylhistamine.[18] After addition of the investigated compounds, no depression of contraction, e.g., agonist activity, was observed. The values presented represent the mean of a minimum of three separate determinations.

Histamine H_3-receptor agonist/antagonist potency in vivo in mouse. In vivo testing was performed after peroral administration to Swiss mice as described by Garbarg et al.[7] Brain histamine turnover was assessed by measuring the level of the main metabolite of histamine, N^τ-MeHA. Mice were fasted for 24 h before po treatment. Animals were decapitated 90 min after treatment, and the cerebral cortex was prepared out. The cortex was homogenized in 10 vol of ice-cold perchloric acid (0.4 M). The N^τ-MeHA level was measured by radioimmunoassay.[34] By treatment with 10 mg/kg of thioperamide or imetit the maximum/minimum N^τ-MeHA levels were obtained and related to the level reached with the administered antagonist/agonist. The ED_{50} value was calculated as mean with SEM.[32]

In vitro screening at other histamine receptors. Selected compounds were screened for histamine H_2-receptor activity on the isolated spontaneously beating guinea pig right atrium as well as for H_1-receptor activity on the isolated guinea pig ileum by standard methods described by Hirschfeld et al.[16] The given values represent the mean.

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