Pyrazoles as Potential Histamine H3-Receptor Antagonists

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In search of structure-activity relationships among histamine H3-receptor antagonists, the imidazole ring of known H3-receptor antagonists was replaced by different heteroaromatic ring systems. Thus, pyrazoles with ether (**4**,**5**) and carbamate (**6**,**7**) moieties as functional groups were synthesized. Reaction of the hydrochloride of 4-(3-hydroxypropyl)pyrazole (**1**) with phenyl or benzyl isocyanates mainly gave the carbamates **6** and **7**, whereas a similar reaction with **1** as the free base furnished the *N*-carbamoylpyrazoles **8** and **9**. The bifunctional pyrazoles **10** and **11** were formed as by-products. The compounds obtained did not show significant H3-receptor antagonist activity *in vitro* (rat brain cortex) or *in vivo* (mouse brain). These results demonstrate the importance of the imidazole moiety for H3-receptor antagonists. The new compounds were also screened for H1-receptor antagonist activity on the isolated guinea-pig ileum and for H2-receptor antagonist activity on the isolated spontaneously beating guinea-pig right atrium. The substances showed only weak antagonistic activity at both histamine receptors H1 and H2.

Pyrazole als potentielle Histamin-H3-Rezeptorantagonisten

Im Rahmen von Untersuchungen von Histamin-H3-Rezeptorantagonisten wurde der Imidazolring bekannter H3-Rezeptorantagonisten gegen verschiedene heteroaromatische Ringsysteme ausgetauscht. Es wurden Pyrazole mit Ether-(**4**,**5**) und Urethan-Strukturelementen (**6**,**7**) als funktionelle Gruppen synthetisiert. Die Reaktion des Hydrochlorids von 4-(3-Hydroxypropyl)pyrazol (**1**) mit Phenyl- oder Benzylisocyanaten ergab hauptsächlich die Urethane **6** und **7**, während eine vergleichbare Umsetzung mit **1** als freier Base die *N*-Carbamoylpyrazole **8** und **9** lieferte. Als Nebenprodukte wurden die bifunktionellen Pyrazole **10** und **11** erhalten. Die dargestellten Substanzen zeigten *in vitro* (Zerebralkortex der Ratte) und *in vivo* (Mäusehirn) keine bedeutsame H3-antagonistische Aktivität. Diese Ergebnisse weisen auf die Bedeutung des Imidazolrings für H3-Rezeptorantagonisten hin. Die neuen Verbindungen wurden auch auf H1-antagonistische Aktivität am Meerschweinchendünndarm und auf H2-Antagonismus am isolierten, spontan schlagenden rechten Vorhof des Meerschweinchens getestet. Die Substanzen zeigten an H1 und H2-Rezeptoren nur schwache antagonistische Aktivität.

The existence of a third histamine receptor was reported for the first time in 1983 [1]. It proved to be an autoreceptor with presynaptical location. Interaction of histamine with H3-receptors leads to inhibition of histamine synthesis in and histamine release from histaminergic neurons.

Thioperamide was the first highly potent and selective H3-receptor antagonist to be designed [2], since then H3-receptor antagonists with very different functional groups have been developed [3–5]. So far most of the H3-receptor antagonists have been imidazole derivatives. The very few non-imidazoles with H3-receptor antagonist activity do not reach the potency of compounds like thioperamide. As a general construction pattern for H3-receptor antagonists the existence of a nitrogen-containing heterocycle connected to a polar group *via* an alkyl chain seems to be essential for a potent interaction with H3-receptors. A lipophilic residue linked by a spacer with the polar group seems to enable the molecule to reaching additional binding areas, thereby increasing the H3-receptor antagonist activity of the resulting molecule [3].

In our previous work azine and diazine analogues of known H3-receptor antagonistically active imidazoles were synthesized [6]. The aim of this work was the synthesis of pyrazole analogues of those azines.

Results and Discussion–Synthesis

The starting material in the synthesis of all new compounds was 4-(3-hydroxypropyl)pyrazole (**1**) obtained according to ref. [7]. For the synthesis of the ethers **4** and **5** the *N*-protected pyrazole **3** was used (Scheme 1). The reaction of **1** with a stoichiometric amount of triphenylmethyl chloride in CH_2Cl_2 in the presence of triethylamine gave the *N*-tritylpyrazole **3** and small amounts of the *N*,*O*-ditritylated derivative **2**. As a result of the reaction of **3** with haloalkanes (3-phenylpropyl bromide or 3-cyclohexylpropyl chloride) performed in toluene in the presence of NaH and 15-crown-5 and subsequent acidic hydrolysis, ethers **4** and **5** were obtained. Ether **4** was separated as the hydrochloride, **5** as the free base. The reaction of **1**xHCl with stoichiometric amounts of benzyl or phenyl isocyanate in acetonitrile produced mainly the carbamates **6** and **7** besides minor amounts of the *N*-carbamoylpyrazoles **8** and **9** and the bifunctional pyrazoles **10** and **11**. The same reaction performed with **1** as the free base, gave mainly **8** and **9** and smaller amounts of **6** and **7** as well as **10** and **11**. The compounds **8–11** were separated by column chromatography. The structures of the compounds obtainedwere confirmed on the basis of elemental and spectral analyses (^{1}H-NMR, MS).

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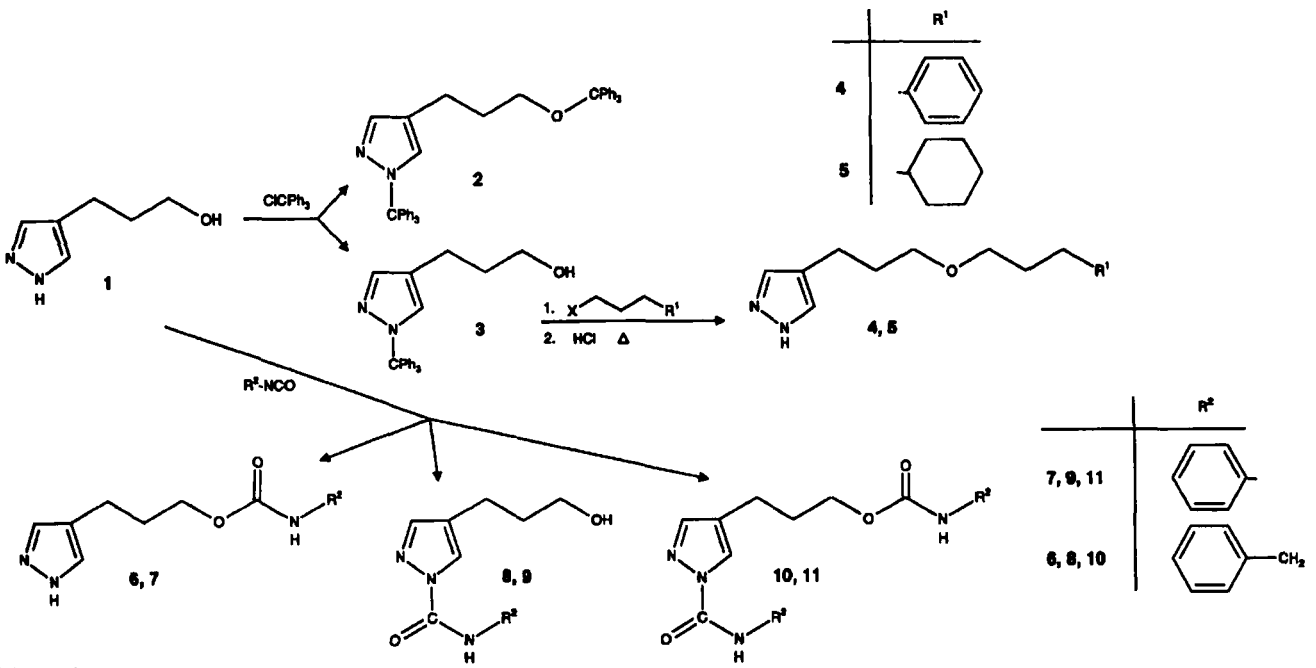

Scheme 1

Pharmacology

Selected pyrazoles were tested for their *in vitro* (rat brain cortex) and *in vivo* (mouse brain) H_3-receptor antagonist (or agonist) activity [1]. Compounds **4–11** also were screened for 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. Results are listed in Table 1.

Table 1: Antagonistic activity of **4–11** on histamine H_3-, H_2-, and H_1-receptors.

Compound	H_3 (brain cortex) K_i (rat) ED_{50}, EC_{50} (mouse)	H_2 (atrium) $-\log K_B$ (guinea pig)	H_1 (ileum) $-\log K_B$ (guinea pig)
4	$K_i > 5 \times 10^{-7}$ M $ED_{50} > 10$ mg/kg p.o.	a)	4.29
5	$K_i > 5 \times 10^{-7}$ M $ED_{50} > 10$ mg/kg p.o.	4.28	4.37
6	$K_i > 5 \times 10^{-7}$ M $ED_{50} > 10$ mg/kg p.o.	a)	4.38
7	$K_i > 5 \times 10^{-7}$ M $EC_{50} > 5 \times 10^{-7}$ M	a)	4.21
8	$K_i > 5 \times 10^{-7}$ M ED50 > 10 mg/kg p.o.	3.62	4.23
9		3.63	4.29
10		4.12	4.15
11		3.85	5.45

a) No effect was observed up to 1×10^{-4} M.

The obtained pyrazoles possess hardly any H_3-receptor antagonist properties. Replacement of the imidazole ring with a pyrazole moiety leads to compounds with negligible *in vitro* activity at histamine H_3-receptors. The results clearly demonstrate the major importance of the imidazole ring for potent antagonism at H_3-receptors. Compounds **4–8** were also tested in *in vivo* experiments with mice after peroral administration. None of the tested compounds showed any central H_3-receptor antagonist activity. Compound **7** at a dose of 10 mg/kg *p.o.* to mice reduced the N^{τ}-methylhistamine level by about 30%. This effect is usually observed with H_3-receptor agonists. Thus, **7** was also screened for H_3-receptor agonist activity, but when tested *in vitro* **7** did not show significant effects (indicated as EC_{50} value in Table 1). The reduction of the N^{τ}-methylhistamine level might be the result of another mechanism, which needs further investigation.

The compounds also showed only weak antagonistic activity at the two other histamine receptors, H_1 and H_2. The antagonism was in most cases of the competitive/non-competitive type. Compound **5** is a partial H_2-agonist, the maximum response was only 48% that of histamine.

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Experimental Part

Chemistry

M.p.s: Büchi 512 (uncorrected).– Elementary analyses: Perkin-Elmer 240 B and 240 C.– IR: Perkin-Elmer 1420 Ratio Recording IR Spectraphotometer (KBr).– ^{1}H-NMR: Bruker AC 300, δ [ppm] ref. to TMS. *– signals exchangeable with D_2O.– MS: Finnigan MAT CH7A (170 °C, EI/70 eV) or MAT 711 (200 °C, EI/80 eV); m/z (%); direct inlet. FAB (FAB, xenon, DMSO/glycerol) Finnigan MAT CH5 DF.– TLC: Al sheets 0.2 mm layer silica gel (60 F_{254}; Merck); solvent systems: I: $CHCl_3$: AcOEt (1:1); II: toluene : acetone (20:1.5).– Rotational chromatography: Chromatotron 7924T (Harrison Research); glass rotors, 4 mm layers of silica gel 60 PF_{254} containing gypsum (Merck); developing systems: $CHCl_3$: AcOEt (1:1).– Column chromatography (cc): silica gel (Baker) 0.05–0.2 mm.

Starting materials: Reaction of 2,3-dihydropyran and ethyl orthoformate in the presence of BF_3 yielded 2-ethoxy-3-tetrahydropyran carbaldehyde diethyl acetal which with hydrazine dihydrochloride gave 4-(3-hydroxypropyl)pyrazole (**1**), see ref. [7].

*Reaction of **1** with chlorotriphenylmethane*

A solution of 2.80 g (10 mmol) chlorotriphenylmethane in CH_2Cl_2 (25 ml) was added dropwise to a stirred mixture of 1.26 g (10 mmol) of **1** and 1.01 g (10 mmol) triethylamine in CH_2Cl_2 (25 ml) with cooling. The reaction mixture was stirred at room temp. for 12 h and then washed with 2 × 50 ml of 2% HCl and 3 × 50 ml of water; the org. layer was dried ($MgSO_4$) and evaporated *in vacuo*. 100 ml of EtOH was added, the mixture was refluxed for 10 min, and after cooling the precipitate of **2** was separated; m.p. 84–86 °C (EtOH); R_F(I) 0.90; yield 19%.– $C_{44}H_{38}N_2O$ (610.8) Calcd. C 86.5 H 6.27 N 4.59 Found C 86.4 H 6.26 N 4.42.– ^{1}H-NMR ($CDCl_3$): 1.82 (quint, J = 7.3 Hz, 2H, $CH_2CH_2CH_2$), 2.54 (t, J = 7.6 Hz, 2H, $PyrCH_2$), 3.05 (t, J = 6.3 Hz, 2H, CH_2O), 7.09–7.43 (m, 32H, 30 Ph-H, Pyr-3-H and Pyr-5-H).– IR: 3048, 3020 (aromat. CH), 2931 (aliphat. CH), 1595 (C=N), 1488, 1445, 1066, 748, 701.– MS: $^+$FAB: 611 ($[M+H]^+$, 0.6), 243 (100, CPh_3), 228(2), 215(2), 202(2), 178(2), 165(17), 154(4), 136(3), 115(2), 107(1), 77(5).

The ethanolic filtrate was evaporated *in vacuo* to dryness, **3** was obtained by addition of diethyl ether.– m.p. 129–131 °C (Et_2O); R_F(I) 0.58; yield 71%; $C_{25}H_{24}N_2O$ (368.4) Calcd. C 81.5 H 6.57 N 7.60 Found C 81.7 H 6.64 N 7.43.– ^{1}H-NMR ($CDCl_3$): 1.28* (br. s, 1H, OH), 1.79 (quint, J = 7.5 Hz, 2H, $CH_2CH_2CH_2$), 2.52 (t, J = 7.6 Hz, 2H, $PyrCH_2$), 3.64 (t, J = 6.3 Hz, 2H, CH_2O), 7.12–7.31 (m, 16H, 15 Ph-H and Pyr-3-H), 7.49 (s, 1H, Pyr-5-H).– IR: 3424 (OH), 3052, 3021 (aromat. CH), 2936 (aliphat. CH) 1595 (C=N), 1489, 1443, 1129, 757, 745, 700.– EI-MS: 368 ($M^{+\bullet}$, 5), 243 (100, CPh_3), 228 (5), 215 (4), 165 (50), 126 (2), 108 (3), 91 (2), 81 (7), 77 (2).

*3-Phenylpropyl-3-(4-pyrazolyl)propyl ether (**4**)*

0.24 g (6 mmol) of NaH (60% suspension in mineral oil) and 0.1 ml (0.5 mmol) of 1,4,7,10,13-pentaoxacylcopentadecane (15-crown-5) were added to a solution of 1.84 g (5 mmol) **3** in dry toluene (10 ml). The reaction mixture was stirred at room temp. for 8 h. 2.0 g (10 mmol) of 1-bromo-3-phenylpropane was then added and the mixture was stirred on an oil bath at 70–80 °C for 20 h (reaction followed by TLC). After cooling, the toluene was evaporated, 30 ml 2N HCl and 20 ml acetone were added and the mixture was warmed on an oil bath at 70 °C for 2 h. After completion of hydrolysis the solution was cooled, and acetone was evaporated *in vacuo*. The separated solid (triphenylmethanol) was filtered off, the water layer washed with 3 × 50 ml diethyl ether, made alkaline with Na_2CO_3 and extracted thoroughly with CH_2Cl_2. The solution was concentrated after drying over Na_2SO_4, and the oily residue purified by rotational chromatography (I). Ethanol, saturated with gas. HCl, was added to the oily product (**4**) and repeatedly evaporated to dryness; on addition of dry diethyl ether a precipitate of **4** × HCl was obtained; m.p. 63–64 °C (Et_2O); R_F(I) 0.37; R_F(II) 0.68; yield 52%; $C_{15}H_{20}N_2OxHCl$ (280.8). Calcd. C 64.2 H 7.54 N 9.98 Found C 64.3 H 7.50 N 9.79.– ^{1}H-NMR ([D6]DMSO): 1.79 (quint, J = 6.6 Hz, 4H, $CH_2CH_2CH_2$), 2.51 (t, 2H, signal under DMSO signals, Pyr-CH_2), 2.61 (t, J = 7.7 Hz, 2H, $PhCH_2$), 3.35 (t, J = 6.3 Hz, 2H, CH_2O), 3.36 (t, J = 6.1 Hz, 2H, CH_2O), 5.34* (br. s, 1H, NH), 7.17 (m, 3H, Ph-3-H, Ph-4-H, and Ph-5-H), 7.26 (d, J = 7.3 Hz, 2H, Ph-2-H and Ph-6-H), 7.93 (s, 2H, Pyr-3-H and Pyr-5-H).– IR: 3016 (aromat. CH), 2935 (aliphat. CH), 2659 (NH^+), 1491, 1451, 1110, 749, 699. EI-MS: 244 ($M^{+\bullet}$, 18), 140(8), 125(9), 118(48), 108(100), 95(9), 91(47), 81(53), 77(4), 65(6).

*3-Cyclohexylpropyl-3-(4-pyrazolyl)propyl ether (**5**)*

Compound **5** was prepared from **3** and 3-chloropropylcyclohexane; reaction time 20 h; purification: rotational chromatography (I); R_F(I) 0.29; R_F(II) 0.74; yield 48%; $C_{15}H_{26}N_2O$ (250.4) Calcd. C 72.0 H 10.5 N 11.2 Found C 71.9 H 10.3 N 11.2.– ^{1}H-NMR ($CDCl_3$): 0.88–1.68 (m, 15H, CH, CH_2), 1,84 (t, J = 6.9 Hz, 2H, $PyrCH_2CH_2$), 2.58 (t, J = 7.6 Hz, 2H, $PyrCH_2$), 3.38 (t, J = 6.2 Hz, 2H, CH_2O), 3.42 (t, J = 6.8 Hz, 2H, CH_2O), 7.41 (s, 2H, Pyr-3-H and Pyr-5-H).– EI-MS: 250 ($M^{+\bullet}$, 5), 167(1), 154(4), 139(11), 126(6), 108(100), 95(8), 83(5), 81(33).

*N-Benzyl-3-[(1-benzylcarbamoyl)-4-pyrazolyl]propyl carbamate (**10**)*

A mixture of 0.81 g (5 mmol) **1**xHCl in dry acetonitrile (20 ml) and 0.67 g benzyl isocyanate (5 mmol) was stirred on an oil bath at 70–80 °C for 3 h. The solvent was evaporated *in vacuo*. The residue was acidified with 20 ml of 1N HCl, the separated precipitate (0.64 g) filtered off, and the water layer washed with diethyl ether (3 × 20 ml). The collected ether extracts were dried over Na_2SO_4, evaporated to dryness, combined with the precipitate, and separated by cc (20 g) ($CHCl_3$: AcOEt, 1:1). Fractions 1–4 were evaporated, recrystallized (EtOH) to afford 0.1 g of **10**; m.p. 98–99 °C; R_F(I) 0.75; yield 5%; $C_{22}H_{23}N_4O_3$ (392.4) Calcd. C 67.3 H 6.17 N 14.3 Found C 66.9 H 6.12 N 14.3.– ^{1}H-NMR ([D6]DMSO): 1.83 (m, 2H, $CH_2CH_2CH_2$), 2.50 (t, 2H, $PyrCH_2$), 3.97 (t, J = 6.3 Hz, 2H, CH_2O), 4.17 (d, J = 5.9 Hz, 2H, $PhCH_2NH$-urethane), 4.41 (d, J = 6.9 Hz, 2H, $PhCH_2NH$-urea), 7.25 (s, 1H, Pyr-3-H), 7.23–7.31 (m, 10 H, Ph-H), 7.32 (s, 1H, Pyr-5-H), 7.71 (s, 1H, CONH-urethane), 8.10 (s, 1H, CONH-urea).– IR: 3345, 3116 (NH), 3053, 3020 (aromat. CH), 2926 (aliphat. CH), 1711 (C=O-urea), 1695 (C=O-urethane), 1527 (C=N), 1241 (O-CO), 740, 697.– MS: $^+$FAB: 393 ($[M+H]^+$, 12), 260(94), 154(98), 136(71), 132(14), 107(41), 91(100), 81(35), 77(40), 63(18).

*1-Benzylcarbamoyl-4-(3-hydroxypropyl)pyrazole (**8**)*

Fractions 5–10 of the above synthesis were evaporated, recrystallized (AcOEt : Et_2O) to afford 0.49 g **8**; m.p. 49–51 °C; R_F(I) 0.35; yield 38%; $C_{14}H_{17}N_3O_2$ (259.3) Calcd. C 64.9 H 6.59 N 16.2 Found C 65.0 H 6.72 N 16.3. ^{1}H-NMR ($CDCl_3$): 1.84 (quint, J = 7.5 Hz, 2H, $PyrCH_2CH_2CH_2$), 2.59 (t, J = 7.6 Hz, 2H, $PyrCH_2$), 3.68 (t, J = 6.3 Hz, 2H, CH_2O), 4.59 (d, J = 6.1 Hz, 2H, $PhCH_2$), 7.34 (s, 1H, Pyr-3-H), 7.28–7.36 (m, 5H, PhH), 7.44 (s, 1H, Pyr-5-H), 8.03 (s, 1H, CONH).– IR: 3391 (OH), 3322, 3113 (NH), 3023 (aromat. CH), 2935 (aliphat. CH), 1714 (C=O), 1527 (C=N), 1384, 751, 699.– MS: $^+$FAB: 260 ($[M+H]^+$, 9), 243(1), 217(2), 206(2), 165(1), 155(1), 139(4), 132(16), 127(100), 109(11), 103(11), 95(13), 91(83), 81(38), 77(9).

*N-Benzyl-3-(4-pyrazolyl)propyl carbamate (**6**)*

The water layer from the synthesis of **10** was made alkaline with solid $NaHCO_3$, extracted with CH_2Cl_2 (3 × 30 ml), the organic layer was dried (Na_2SO_4), evaporated to dryness, recrystallized (AcOEt : cyclohexane) to give 0.66 g **6**; m.p. 108–109 °C; R_F(I) 0.19; yield 52%; $C_{14}H_{17}N_3O_2$ (259.3) Calcd. C 64.9 H 6.59 N 16.2 Found C 64.7 H 6.54 N 16.0.– ^{1}H-NMR ([D6]DMSO): 1.79 (m, 2H, $CH_2CH_2CH_2$), 2.47 (t, J = 7.7 Hz, 2H, $PyrCH_2$), 3.96 (t, J = 6.2 Hz, 2H, CH_2O), 4.17 (d, J = 5.7 Hz, 2H, $PhCH_2$), 7.25 (s, 1H, Pyr-3-H), 7.23–7.31 (m, 5H, Ph-H), 7.41 (s, 1H, Pyr-5-H), 7.69* (br. s, 1H, CONH), 12.50* (br. s, 1 H PyrNH).– IR: 3318, 3171 (NH), 3054, 3023 (aromat. CH), 2931 (aliphat. CH), 1687 (C=O), 1539 (C=N), 1276 (O-CO), 695.– EI-MS: 259 ($M^{+\bullet}$, 1), 213(1), 163(1), 150(4), 133(25), 126(8), 108(100), 104(15), 91(40), 81(66), 77(11).

The reaction above, performed with with free base **1**, gave after cc separation **10**, **6**, and **8** in 10%, 7%, and 79% yield, respectively.

*N-Phenyl-3-[(1-phenylcarbamoyl)-4-pyrazolyl]propyl carbamate (**11**)*

Compound **11** was prepared by reaction of **1**xHCl with phenylisocyanate and similar separation; m.p. 135–137 °C (EtOH); R_F(I) 0.85; yield 16%; $C_{20}H_{20}N_4O_3$ (364.4) Calcd. C 65.9 H 5.54 N 15.4 Found C 65.8 H 5.51 N 15.3.– ^{1}H-NMR ([D6]DMSO): 1.87 (quint, J = 7.5 Hz, 2H, $CH_2CH_2CH_2$), 2.53 (t, 2H, signals under DMSO signals, $PyrCH_2$), 4.06 (t, J = 6.5 Hz, 2H, CH_2O), 6.96 (t, J = 7.0 Hz, 1H, Ph-4-H-urethane), 7.16 (t, J 7.2 Hz, 1H, Ph-4-H-urea), 7.27 (m, 2H, Ph-3-H-urethane and Ph-5-H-urethane), 7.36 (m, 2H, Ph-3-H-urea and Ph-5-H-urea), 7.46 (m, 3H, Ph-2-H-urethane, Ph-6-H-urethane, and Pyr-3-H), 7.60 (d, 2H, Ph-2-H-urea and Ph-6-H-urea), 8.10 (s, 1H, Pyr-5-H), 9.05 (br. s, 1H, CONH-urea), 9.64 (s, 1H, CONH-urethane).– IR: 3354, 3318, 3115 (NH), 3052 (aromat. CH), 2951 (aliphat. CH), 1710 (C=O), 1527 (C=N), 1228 (O-CO), 754.– MS: $^+$FAB: 365 ($[M+H]^+$, 10), 246(100), 138(15), 127(7), 120(17), 109(98), 93(63), 81(87), 77(38), 65(14).

*1-Phenylcarbamoyl-4-(3-hydroxypropyl)pyrazole (**9**)*

Compound **9** was isolated as described for **8**; m.p. 87–88 °C ($CHCl_3$: AcOEt); R_F(I) 0.42; yield 18%; $C_{13}H_{15}N_3O_2$ (245.2) Calcd. C 63.7 H 6.16 N 17.1 Found C 63.9 H 6.19 N 17.1.– ^{1}H-NMR ($CDCl_3$): 1.87 (quint, J = 7.5 Hz, 2H, $CH_2CH_2CH_2$), 2.63 (t, J = 7.6 Hz, 2H, $PyrCH_2$), 3.71 (t, J = 6.3 Hz, 2H, CH_2O), 7.16 (t, J = 7.4 Hz, 1H, Ph-4-H), 7.36 (t, J = 7.9 Hz, 2H, Ph-3-H

and Ph-5-H), 7.53 (s, 1H, Pyr-3-H), 7.60 (d, J = 7.8 Hz, 2H, Ph-2-H and Ph-6-H), 8.10 (s, 1H, Pyr-5-H), 9.05 (br. s, 1H, CONH).– IR: 3340 (OH), 3113 (NH), 3051 (aromat. CH), 2937 (aliphat. CH), 1709 (C=O), 1533 (C=N), 1447, 751. EI-MS: 245 ($M^{+\bullet}$, 0.2), 126(15), 119 (100, PhNHCO), 108(16), 91(21), 81(24), 64(4).

N-Phenyl-3-(4-pyrazolyl)propyl carbamate (7)

Compound **7** was isolated as described for **6**; m.p. 137–138 °C (AcOEt : cyclohexane); R_F(I) 0.25; yield 57%; $C_{13}H_{15}N_3O_2$ (254.2) Calcd. C 63.7 H 6.16 N 17.1 Found C 63.5 H 6.08 N 16.9.– ^{1}H-NMR ([D$_6$]DMSO): 1.87 (quint, J = 7.3 Hz, 2H, $CH_2CH_2CH_2$), 2.53 (t, J = 7.4 Hz, 2H, $PyrCH_2$), 4.08 (t, J = 6.5 Hz, 2H, CH_2O), 6.98 (t, J = 7.3 Hz, 1H, Ph-4-H), 7.27 (t, J = 7.8 Hz, 2H, Ph-3-H and Ph-5-H), 7.46 (d, J = 7.8 Hz, 4H, Ph-2-H, Ph-6-H, Pyr-3-H, and Pyr-5-H), 9.64 (s, 1H, CONH), 12.56* (br. s, 1H, NH).– IR: 3325, 3151 (NH), 3046 (aromat. CH), 2949 (aliphat. CH), 1692 (C=O), 1525 (C=N), 1231 (O-CO). EI-MS: 245 ($M^{+\bullet}$, 5), 137(15), 126(15), 119(88), 108(100), 93(46), 91(27), 81(91), 77(8), 64(14).

The reaction above, performed with free base **1**, gave after cc separation **11**, **7**, and **9** with 20%, 6%, and 69% yield, respectively.

Pharmacology

The new compounds were tested *in vitro* for H_3-receptor antagonist activity in an assay with K^+–evoked release of [^{3}H]histamine with synaptosomes of rat brain cortex [1]. The *in vivo* efficiency of the compounds toward H_3-receptors was evaluated by their effect on the central N^τ–methylhistamine level. This level was measured in whole brain of mice after peroral administration of the compounds. They were also tested for H_1-receptor antagonist activity by in the classical isolated guinea-pig ileum assay according to a modified procedure of *Lennartz et al.* [8] and screened for H_2-receptor antagonism of the histamine-stimulated increase in heart rate on the spontaneously beating guinea-pig right atrium [9,10]. In each case a minimum of two determinations were performed. The presented data are mean values.

Compound **4** was applied as solution in H_2O with an equivalent amount of HCl; compounds **5–7** as solutions in H_2O : EtOH (1:1) mixtures with an equivalent amount of HCl; compounds **8–11** as solutions in DMSO.

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