Synthesis and Pharmacology of Combined Histamine H_1-/H_2-Receptor Antagonists Containing Diphenhydramine and Cyproheptadine Derivatives ☆

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Key Words: *histamine H_1-receptor antagonism; histamine H_2-receptor antagonism; diphenhydramine; cyproheptadine; tiotidine*

Summary

The classical histamine H_1-receptor antagonists diphenhydramine (**3a**) and cyproheptadine (**9**) and their derivatives (**3b–d**, **10**) were connected with a 2-guanidinothiazole containing structure (**28**) derived from the H_2-receptor antagonist tiotidine in order to obtain combined H_1-/H_2-receptor antagonists. The two moieties were not directly linked together, but were separated by a polymethylene spacer and a polar group (nitroethenediamine or urea). Thus 12 compounds were obtained that proved *in vitro* to possess high H_1- and H_2-receptor antagonist activity at the isolated guinea-pig ileum (H_1) and the isolated guinea-pig right atrium (H_2), respectively. The incorporation of the diphenhydramine as well as the cyproheptadine component provides high affinity to H_1-receptors. The tricyclic cyproheptadine and its 10,11-dihydro derivative (**30–32**, **34**), however, cause a decrease of H_2-receptor antagonist potency compared to the diphenhydramines (**29a–d**, **33a–d**). Using nitroethenediamine as the polar group is apparently more favourable to H_1- and H_2-receptor affinity as the urea function. All compounds elicit a dual mode of competitive and noncompetitive antagonism. Among the novel compounds the nitroethenediamines with 4-fluoro- or 4-methyl-substituted diphenhydramine as H_1-receptor antagonist moiety (**29c**, **d**) display the most potent H_1- and H_2-receptor antagonist effects. The presented concept is a very promising way to combine H_1- and H_2-receptor antagonist properties in one molecule.

Introduction

Histamine is an important mediator in allergic and inflammatory diseases. It is released e.g. from mast cells and basophils by immunological and non-immunological mechanisms. Histamine for example causes contraction of smooth muscles of the uterus, the gastro-intestinal tract, and bronchia and an increase of capillary permeability by stimulating the H_1-receptor. Interaction with the H_2-receptor leads to e.g. relaxation of the bronchia, increase of gastric acid secretion, and increase in heart rate and contractility. In order to inhibit these pathophysiological reactions numerous drugs have been developed which either antagonize the H_1- *or* H_2-receptor. Nevertheless, H_1- *and* H_2-receptors are often involved simultaneously.

Both receptors have been detected in blood vessels of the skin[1] and clinical studies have shown that the combined application of H_1- and H_2-receptor antagonists reduced skin lesions and itching in chronic urticaria more effectively than a therapy using only H_1-receptor antagonists[2–4]. Another field of application for the simultaneous H_1-/H_2-receptor blockade is the prevention of anaphylactic/anaphylactoid reactions during premedication and anaesthesia. Plasma expanders, muscle relaxants, analgetics, narcotics, for example, are well known histamine liberating drugs leading to clinically severe incidents. Several studies have shown the effectiveness of a prophylactic application of H_1- together with H_2-receptor antagonists (for a survey see[5]). Finally, the Mainz-Marburg study has once again confirmed the usefulness of such a prophylaxis[6].

Icotidine (SK&F 93319)[7] was the first compound that displayed both H_1- and H_2-receptor antagonist activity across a similar concentration range. Its ability to antagonize both histamine receptor subtypes was interesting, because it differs physicochemically from classical H_1-receptor antagonists in lacking a basic amino function and from known H_2-receptor antagonists in being really lipophilic[7]. Since the combination of H_1-receptor *antagonist* and H_2-receptor *agonist* activity in one molecule has been successfully realized by Buschauer[8], it has been the aim of our study to combine H_1- and H_2-receptor *antagonist* properties in a similar way connecting structural parts of classical H_1-receptor antagonists (diphenhydramine, cyproheptadine) with an H_2-receptor antagonist element derived from tiotidine. Its cyanoguanidino function has been replaced by nitroethenediamine or urea as polar groups. Such an exchange of polar groups has already been described for H_2-receptor antagonists of the imidazolyl[9] and of the guanidinothiazolyl series[10]. Finally, a polymethylene spacer is introduced separating the H_1- and H_2-receptor antagonist components. Similar compounds have been published by one of us (W.S.)[11] combining the H_1-receptor antagonists mepyramine and cyclizine with different H_2-receptor antagonists (tiotidine, ranitidine, lamtidine) without an alkyl chain, thus loosing the basic tertiary amino function of the H_1-receptor antagonists. As a consequence thereof, H_1-receptor antagonist activity was considerably reduced and the affinity to H_2-receptors was also more or less affected[11].

We will now present the synthesis and *in vitro* H_1- and H_2-receptor antagonist activity of the newly developed compounds.

Results and Discussion

Chemistry. The mono 4-substituted diphenhydramine derivatives **3b–d** were prepared in a *Williamson* ether synthesis using the respective diphenylmethanols **1b–d** and 2-chloro-*N*,*N*-dimethylethanamine **2** according to ref.[12] (Scheme 1).

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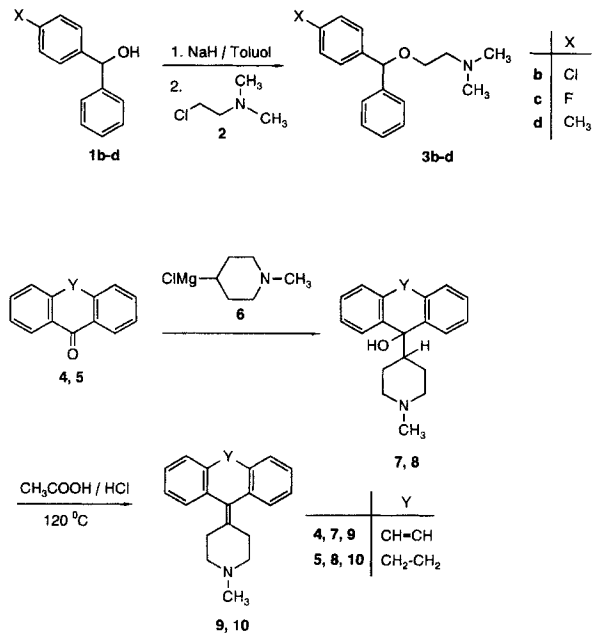
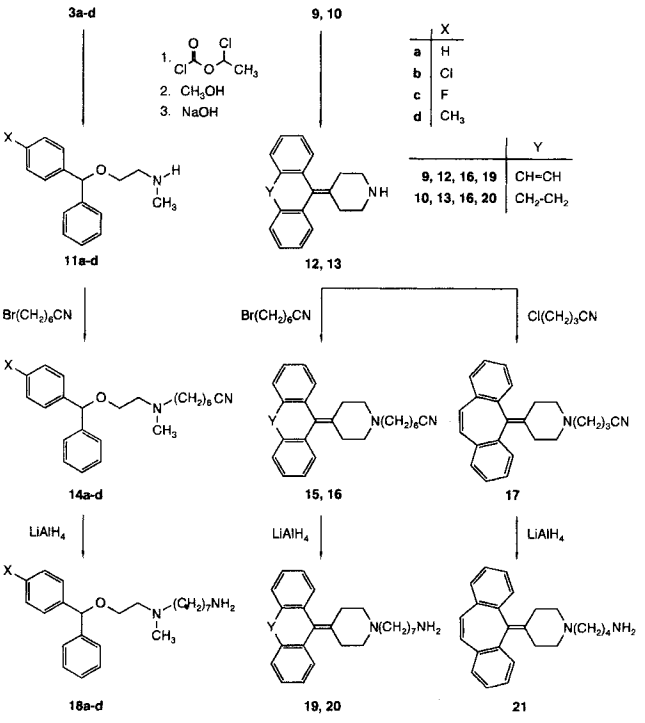


Scheme 1

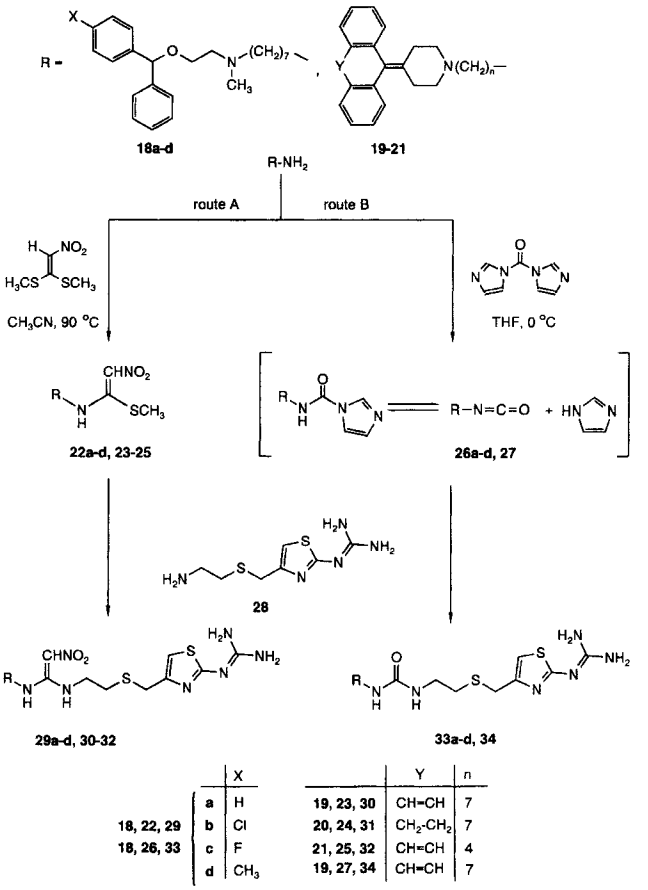


Scheme 2

Diphenhydramine **3a** itself was commercially available. Cyproheptadine **9** and its 10,11-dihydro derivative **10** could be obtained by a *Grignard* reaction of 5*H*-dibenzo[*a,d*]cyclohepten-5-one **4** and 10,11-dihydro-5*H*-dibenzo[*a,d*]-cyclohepten-5-one **5** respectively and 4-(1-methyl)piperidylmagnesium chloride **6** (Scheme 1)[13]. After hydrolysis the tertiary alcohols **7, 8** were dehydrated to the alkenes **9, 10** by heating them in a mixture of anhydrous acetic acid and concentrated hydrochloric acid (Scheme 1)[13]. One methyl group of the tertiary amino function of the diphenhydramines **3a–d** and the methyl group of the piperidine nitrogen in **9, 10** were split off by the method of Olofson and Martz (Scheme 2)[14]. The secondary amines **11a–d** and **12, 13** were subsequently alkylated by 7-bromoheptanonitrile to **14a–d** and **15, 16** and reduced with $LiAlH_4$ to the 1,7-heptanediamines **18a–d** and 7-piperidino-heptanamines **19, 20** (Scheme 2). Analogously, the cyproheptadine derivative **12** was alkylated by 4-chlorobutanonitrile and reduced to 4-piperidinobutanamine **21** (Scheme 2).

The structural element contributing the H_2-receptor antagonist activity is a 2-guanidinothiazole containing molecule derived from tiotidine (**28**, Scheme 3) and was prepared according to Yellin et al.[15].

In the final step the primary amines **18a–d** and **19–21** were at first converted to the ketene-*N,S*-acetals **22a–d, 23–25** by reaction with 1,1-bis(methylthio)-2-nitroethene at 90 °C and then connected with **28** to provide the nitroethenediamines **29a–d** and **30–32** (Scheme 3, route A). The compounds **22a, b** have been prepared by using the free base of **28** and working in a highly concentrated solution of acetonitrile following literature[16]. In order to improve the yields, the reaction conditions were modified. Changing the solvent to ethanol and reducing the reaction temperature to 50 °C in the synthesis of **22c** and **d** the yields dropped down to about 10 % (Table 1). Comparable results to **22a, b** were obtained for the nitroethenediamines **30–32** by a procedure applying the di-



Scheme 3

hydrochloride salt of **28** in a mixture of methanol and triethylamine (Table 1). The 1,7-heptanediamines **18a–d** and **19** were furthermore treated with 1,1′-carbonyldiimidazole at 0 °C to give *N*-imidazole amides which dissociate rather quickly to imidazole and isocyanates **26a–d, 27** (Scheme 3, route B)[17, 18]. The 2-guanidinothiazole derivative **28** was added and after 24 h at ambient temperature the urea analogues **33a–d, 34** were obtained (Scheme 3, route B). Preparative and analytical data of the nitroethenediamines **29a–d, 30–32** and the ureas **33a–d, 34** are presented in Table 1; ^{1}H-NMR data of these compounds are shown in Table 2.

Pharmacology. The newly developed compounds were investigated *in vitro* for histamine H_1-receptor antagonist activity at the isolated guinea-pig ileum (inhibition of the histamine induced contraction) and for H_2-receptor antagonist activity at the isolated spontaneously beating guinea-pig right atrium (inhibition of the histamine induced increase in heart rate)[19, 20]. According to *van Rossum* cumulative concentration-response curves were recorded[21]. All compounds induced a shift of the concentration-response curves to the right with a concomitant depression of the maximal agonist response at higher concentrations. These depressions, in some cases rather considerable, could be observed in both histamine receptor assays and indicate a dualism in action[22, 23]: The test compounds display a competitive antagonist behaviour at low concentrations (10^{-8} M) and a more or less marked noncompetitive interaction at higher concentrations. In Figure 1 the concentration-response curves of histamine in the absence and presence of the diphenhydramine derivative **29d** (Figure 1A) and of the cyproheptadine containing compound **32** (Figure 1B) at the isolated guinea-pig ileum (H_1-

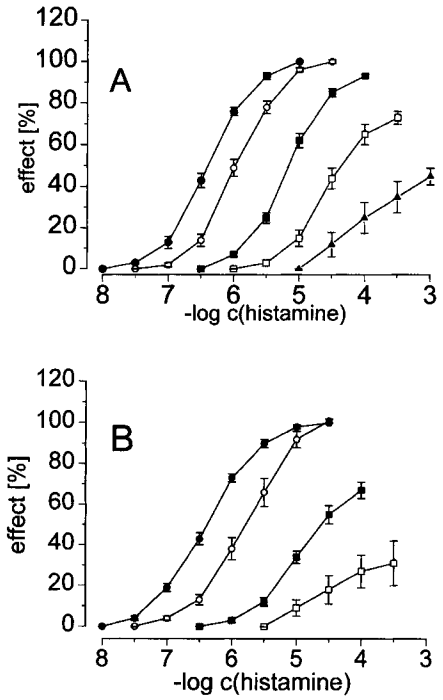


Figure 1. Concentration-effect curves of histamine at the isolated guinea-pig ileum (H_1-receptor). Responses are expressed as a percentage of the maximal response to histamine in the control curves (●). (**A**) Contraction evoked in the absence (●, $n = 8$) and presence of **29d** [M]: 10^{-8} (○, $n = 4$), $10^{-7.5}$ (■, $n = 8$), 10^{-7} (□, $n = 8$) and $10^{-6.5}$ (▲, $n = 4$). (**B**) Contraction evoked in the absence (●, $n = 12$) and presence of **32** [M]: 10^{-8} (○, $n = 11$), $10^{-7.5}$ (■, $n = 8$) and 10^{-7} (□, $n = 4$).

Table 1. Preparative and analytical data of the nitroethenediamines **29a–d, 30–32** and ureas **33a–d, 34**.

no.	yield [%]	m.p. [°C] (Et_2O)	formula[a] (mol. mass)	$^+$FAB-MS *m/z* [%]
29a	30	82–83	$C_{32}H_{46}N_8O_3S_2 \cdot 0.5\ H_2O$ (663.9)	655 ($[M+H]^+$, 4), 167 (100)[b]
29b	39	73–74	$C_{32}H_{45}ClN_8O_3S_2$ (689.5)	689 ($[M+H]^+$, 4), 201 (100)[b]
29c	9	hygr.[d]	$C_{32}H_{45}FN_8O_3S_2$ (672.9)	673 ($[M+H]^+$, 2), 185 (100)[b]
29d	12	88–89	$C_{33}H_{48}N_8O_3S_2$ (668.9)	669 ($[M+H]^+$, 1), 181 (100)[b]
30	25	116–118	$C_{36}H_{46}N_8O_2S_2 \cdot 1.5\ H_2O$ (713.8)	687 ($[M+H]^+$, 7), 42 (100)[c]
31	20	129–131	$C_{36}H_{48}N_8O_2S_2 \cdot 0.5\ H_2O$ (697.8)	689 ($[M+H]^+$, 7), 155 (100)[c]
32	22	126–127	$C_{33}H_{40}N_8O_2S_2$ (644.7)	645 ($[M+H]^+$, 4), 155 (100)[c]
33a	22	hygr.[d]	$C_{31}H_{45}N_7O_2S_2 \cdot 0.5\ H_2O$ (620.8)	612 ($[M+H]^+$, 4), 167 (100)[b]
33b	10	71–72	$C_{31}H_{44}ClN_7O_2S_2$ (646.2)	646 ($[M+H]^+$, 4), 201 (100)[c]
33c	17	hygr.[d]	$C_{31}H_{44}FN_7O_2S_2$ (629.7)	630 ($[M+H]^+$, 1), 185 (100)[c]
33d	7	hygr.[d]	$C_{32}H_{47}N_7O_2S_2$ (625.9)	626 ($[M+H]^+$, 2), 181 (100)[c]
34	16	103–104	$C_{35}H_{45}N_7OS_2 \cdot 0.5\ CH_3OH$ (659.7)	644 ($[M+H]^+$, 40), 155 (100)[c]

[a] elemental analyses of all compounds were within 0.4 % of the calculated values;
[b] (DMSO/ m-nitrobenzylalcohol); [c] (DMSO/glycerol); [d] hygroscopic foam

Table 2. ^{1}H-NMR data of the nitroethenediamines **29a–d**, **30–32** and the ureas **33a–d**, **34**.

no.	^{1}H-NMR ($CDCl_3$), [ppm][a]
29a	1.27 (m, 6H, -$(CH_2)_3$-), 1.44 (m, 2H, -$CH_2(CH_2)_3CH_2$-), 1.57 (m, 2H, -$CH_2(CH_2)_3CH_2$-), 2.25 (s, 3H, NCH_3), 2.34–2.39 (m, 2H, $OCH_2CH_2NCH_2$), 2.67 (t, J = 5.8 Hz, 2H, OCH_2CH_2N), 2.77 (m, 2H, CH_2CH_2S), 3.09 (m, 2H, CH_2NH), 3.26 (m, 2H, CH_2NH), 3.55–3.59 (m, 4H, OCH_2CH_2N, SCH_2Thia), 5.36 (s, 1H, Ar_2CH), 6.07 (br. s, part of 1H, Gua-H[b], 1.conformer), 6.34 (s, 1H, Thia-5-H and part of 1H, Gua-H[b], 2.conformer), 6.57 (s, 1H, $CHNO_2$), 6.60 (br. s, 3H, Gua-H[b]), 7.20–7.34 (m, 10 H, aromatic H), 10.13 (br. s, 1H, NH[b]), 10.37 (br. s, 1H, NH[b])
29b	1.28 (m, 6H, -$(CH_2)_3$-), 1.44 (m, 2H, -$CH_2(CH_2)_3CH_2$-), 1.59 (m, 2H, -$CH_2(CH_2)_3CH_2$-), 2.23 (s, 3H, NCH_3), 2.32–2.37 (m, 2H, $OCH_2CH_2NCH_2$), 2.65 (t, J = 5.6 Hz, 2H, OCH_2CH_2N), 2.81 (m, 2H, CH_2CH_2S), 3.08 (m, 2H, CH_2NH), 3.28 (m, 2H, CH_2NH), 3.55 (t, J = 5.8 Hz, 2H, OCH_2CH_2N), 3.60 (s, 2H, SCH_2Thia), 5.34 (s, 1H, ArAr'CH), 5.76 and 5.86 (2 br. s, 1H, Gua-H[b], 2 conformers), 6.35 (s, 1H, Thia-5-H), 6.48 (br. s, 3H, Gua-H[b]), 6.57 (s, 1H, $CHNO_2$), 7.26–7.31 (m, 9H, aromatic H), 10.14 (br. s, 1H, NH[b]), 10.37 (br. s, 1H, NH[b])
29c	1.27 (m, 6H, -$(CH_2)_3$-), 1.43 (m, 2H, -$CH_2(CH_2)_3CH_2$-), 1.59 (m, 2H, -$CH_2(CH_2)_3CH_2$-), 2.23 (s, 3H, NCH_3), 2.32–2.37 (m, 2H, $OCH_2CH_2NCH_2$), 2.64 (t, J = 5.9 Hz, 2H, OCH_2CH_2N), 2.78 (m, 2H, CH_2CH_2S), 3.10 (m, 2H, CH_2NH), 3.28 (m, 2H, CH_2NH), 3.54 (t, J = 6.0 Hz, 2H, OCH_2CH_2N), 3.60 (s, 2H, SCH_2Thia), 5.34 (s, 1H, ArAr'CH), 5.99 and 6.13 (2 br. s, 1H, Gua-H[b], 2 conformers), 6.34 (s, 1H, Thia-5-H), 6.57 (s, 4H, $CHNO_2$, 3 Gua-H[b]),6.98 (t, J = 8.7 Hz, 2H, 4-F-Ph-3-H and -5-H), 7.23–7.32 (m, 7H, aromatic H), 10.14 (br. s, 1H, NH[b]), 10.39 (br. s, 1H, NH[b])
29d	1.28 (m, 6H, -$(CH_2)_3$-), 1.46 (m, 2H, -$CH_2(CH_2)_3CH_2$-), 1.59 (m, 2H, -$CH_2(CH_2)_3CH_2$-), 2.27 (s, 3H, NCH_3), 2.30 (s, 3H, Ph-CH_3), 2.37–2.42 (m, 2H, $OCH_2CH_2NCH_2$), 2.68 (t, J = 5.8 Hz, 2H, OCH_2CH_2N), 2.79 (t, J = 6.0 Hz, 2H, CH_2CH_2S), 3.10 (m, 2H, CH_2NH), 3.27 (m, 2H, CH_2NH), 3.55–3.61 (m, 4H, OCH_2CH_2N, SCH_2Thia), 5.33 (s, 1H, ArAr'CH), 5.99 and 6.20 (2 br. s, 1H, Gua-H[b], 2 conformers), 6.35 (s, 1H, Thia-5-H), 6.57 (s, 4H, $CHNO_2$, 3 Gua-H[b]), 7.11 (d, J = 7.9 Hz, 2H, 4- CH_3-Ph-3-H and -5-H), 7.21 (d, J = 8.1 Hz, 2H, 4- CH_3-Ph-2-H and-6-H), 7.24–7.34 (m, 5H, aromatic H), 10.14 (br. s, 1H, NH[b]), 10.40 (br. s, 1H, NH[b])
30	1.26 (m, 6H, -$(CH_2)_3$-), 1.42 (m, 2H, -$CH_2(CH_2)_3CH_2$-), 1.58 (m, 2H, -$CH_2(CH_2)_3CH_2$-), 2.08-2.17 (m, 4H, 4 Pip-H), 2.21–2.26 (m, 2H, $PipNCH_2$), 2.31–2.38 (m, 2H, 2 Pip-H), 2.54–2.56 (m, 2H, 2 Pip-H), 2.78 (m, 2H, CH_2CH_2S), 3.09 (m, 2H, CH_2NH), 3.27 (m, 2H, CH_2NH), 3.59 (br. s, 2H, SCH_2Thia), 5.89 and 6.03 (2 br. s, 1H, Gua-H[b], 2 conformers), 6.33 (s, 1H, Thia-5-H), 6.56 (s, 4H, $CHNO_2$, 3 Gua-H[b]), 6.90 (s, 2H, -CH=CH-), 7.17–7.30 (m, 8H, aromatic H), 10.13 (br. s, 1H, NH[b]), 10.33 (br. s, 1H, NH[b])
31	1.30 (m, 6H, -$(CH_2)_3$-), 1.47 (m, 2H, -$CH_2(CH_2)_3CH_2$-), 1.61 (m, 2H, -$CH_2(CH_2)_3CH_2$-), 2.15–2.17 (m, 2H, 2 Pip-H), 2.27–2.32 (m, 2H, $PipNCH_2$), 2.40–2.43 (m, 4H, 4 Pip-H), 2.65–2.68 (m, 2H, 2 Pip-H), 2.77–2.85 (m, 4H, CH_2CH_2S, Ph-CH_2CH_2-Ph), 3.10 (m, 2H, CH_2NH), 3.30 (m, 2H, CH_2NH), 3.41–3.51 (m, 2H, Ph-CH_2CH_2-Ph), 3.61 (br. s, 2H, SCH_2Thia), 5.74 (br. s, 1H, Gua-H[b]), 6.35 (s, 1H, Thia-5-H), 6.48 (br. s, 3H, Gua-H[b]), 6.57 (br. s, 1H, $CHNO_2$), 7.07–7.12 (m, 8H, aromatic H), 10.14 (br. s, 1H, NH[b]), 10.36 (br. s, 1H, NH[b])
32	1.58–1.68 (m, 4H, -$(CH_2)_2$-), 2.11 (m, 4H, 4 Pip-H), 2.27–2.32 (m, 4H, 2 Pip-H, $PipNCH_2$), 2.52 (m, 2H, 2 Pip-H), 2.77 (m, 2H, CH_2CH_2S), 3.11 (m, 2H, CH_2NH), 3.26 (m, 2H, CH_2NH), 3.58 (br. s, 2H, SCH_2Thia), 5.96 (br. s, 1H, Gua-H[b]), 6.31 (s, 1H, Thia-5-H), 6.56 (s, 4H, $CHNO_2$, 3 Gua-H[b]), 6.90 (s, 2H, -CH=CH-), 7.17 (d, J = 7.0 Hz, 2H, aromatic H), 7.23 (d, J = 7.0 Hz, 2H, aromatic H), 7.28–7.33 (m, 4H, aromatic H), 10.14 (br. s, 1H, NH[b]), 10.36 (br. s, 1H, NH[b])
33a	1.25 (m, 6H, -$(CH_2)_3$-), 1.41 (m, 4H, -$CH_2(CH_2)_3CH_2$-), 2.23 (s, 3H, NCH_3), 2.32–2.37 (m, 2H, $OCH_2CH_2NCH_2$), 2.60–2.68 (m, 4H, OCH_2CH_2N, CH_2CH_2S), 3.06 (q, J = 6.0 Hz, 2H, CH_2NH[c]), 3.29 (q, J = 5.9 Hz, 2H, CH_2NH[d]), 3.55–3.59 (m, 4H, OCH_2CH_2N, SCH_2Thia), 5.10 (t, 1H, NHCO[b]), 5.36 (s, 1H, Ar_2CH), 5.43 (t, J = 5.6 Hz, 1H, NHCO[b]), 6.35 (s, 1H, Thia-5-H), 6.52 (br. s, 3H, Gua-H[b]), 7.22–7.35 (m, 10 H, aromatic H)
33b	1.24 (m, 6H, -$(CH_2)_3$-), 1.42 (m, 4H, -$CH_2(CH_2)_3CH_2$-), 2.29 (s, 3H, NCH_3), 2.39–2.44 (m, 2H, $OCH_2CH_2NCH_2$), 2.65 (q, J = 5.8 Hz, 4H, OCH_2CH_2N, CH_2CH_2S), 3.07 (q, J = 6.4 Hz, 2H, CH_2NH[e]), 3.30 (q, J = 6.0 Hz, 2H, CH_2NH[f]), 3.55 (t, J = 5.9 Hz, 2H, OCH_2CH_2N), 3.62 (s, 2H, SCH_2Thia), 4.82 (t, 1H, NHCO[b]), 5.18 (t, 1H, NHCO[b]), 5.33 (s, 1H, ArAr'CH), 6.36 (s, 1H, Thia-5-H), 6.67 (s, 3H, Gua-H[b]), 7.26–7.30 (m, 9H, aromatic H)
33c	1.26 (m, 6H, -$(CH_2)_3$-), 1.43 (m, 4H, -$CH_2(CH_2)_3CH_2$-), 2.23 (s, 3H, NCH_3), 2.32–2.37 (m, 2H, $OCH_2CH_2NCH_2$), 2.63–2.67 (m, 4H, OCH_2CH_2N, CH_2CH_2S), 3.08 (q, J = 6.4 Hz, 2H, CH_2NH[g]), 3.31 (q, J = 6.0 Hz, 2H, CH_2NH[h]), 3.55 (t, J = 5.9 Hz, 4H, OCH_2CH_2N), 3.61 (s, 2H, SCH_2Thia), 4.86 (t, J = 5.5 Hz, 1H, NHCO[b]), 5.22 (t, J = 5.6 Hz, 1H, NHCO[b]), 5.35 (s, 1H, ArAr'CH), 6.37 (s, 4H, Thia-5-H, 3 Gua-H[b]), 6.98 (t, J = 8.7 Hz, 2H, 4-F-Ph-3-H and-5-H), 7.24–7.32 (m, 7H, aromatic H)
33d	1.26 (m, 6H, -$(CH_2)_3$-), 1.42–1.44 (m, 4H, -$CH_2(CH_2)_3CH_2$-), 2.26 (s, 3H, NCH_3), 2.30 (s, 3H, Ph-CH_3), 2.35–2.40 (m, 2H, $OCH_2CH_2NCH_2$), 2.61–2.70 (m, 4H, OCH_2CH_2N, CH_2CH_2S), 3.08 (q, J = 6.2 Hz, 2H, CH_2NH[i]), 3.30 (q, J = 5.8 Hz, 2H, CH_2NH[j]), 3.55–3.60 (m, 4H, OCH_2CH_2N, SCH_2Thia), 5.04 (t, 1H, NHCO[b]), 5.34 (s, 1H, ArAr'CH), 5.38 (t, 1H, NHCO[b]), 6.36 (s, 1H, Thia-5-H), 6.48 (s, 4H, Gua-H[b]), 7.01 (d, J = 7.9 Hz, 2H, 4- CH_3-Ph-3-H and-5-H), 7.11 (d, J = 7.9 Hz, 2H, 4-CH_3-Ph-2-H and-6-H), 7.23–7.34 (m, 5H, aromatic H)
34	1.23–1.25 (m, 6H, -$(CH_2)_3$-), 1.42 (m, 4H, -$CH_2(CH_2)_3CH_2$-), 2.09–2.17 (m, 4H, 4 Pip-H), 2.22–2.27 (m, 2H, $PipNCH_2$), 2.31–2.39 (m, 2H, 2 Pip-H), 2.55–2.57 (m, 2H, 2 Pip-H), 2.65 (t, J = 6.2 Hz, 2H, CH_2CH_2S), 3.06 (q, J = 6.4 Hz, 2H, CH_2NH[k]), 3.31 (q, J = 6.0 Hz, 2H, CH_2NH[l]), 3.60 (s, 2H, SCH_2Thia), 4.79 (t, 1H, NHCO[b]), 5.13 (t, J = 5.6 Hz, 1H, NHCO[b]), 6.37 (s, 3H, Thia-5-H, 2 Gua-H[b]), 6.90 (s, 2H, -CH=CH-), 7.17–7.22 (t, J = 6.9 Hz, 2H, aromatic H), 7.24–7.33 (m, 6H, aromatic H)

[a] abbreviations: Ar, Ar' = aryl, Gua = guanidino, Ph = phenyl, Pip = piperidyl, Thia = thiazolyl; [b] exchangeable with D_2O; [c–l] after H-D exchange with D_2O: [c] t, J = 6.8 Hz, [d] t, J = 6.2 Hz, [e] t,J = 6.7 Hz, [f] t, J = 6.1 Hz, [g] t, J = 6.9 Hz, [h] t, J = 6.3 Hz, [i] t, J = 6.6 Hz, [j] t, J = 6.1 Hz, [k] t, J = 6.9 Hz, [l] t, J = 6.3 Hz.

receptor) are shown as examples. The H_1- and H_2-receptor antagonist activity of the compounds is described by pK_B values.

In the diphenhydramine series the H_1-receptor affinity was determined for at least three different antagonist concentrations. Regression analysis (*Schild* plot[24]) afforded straight lines with slopes significantly different from unity ($p < 0.05$). Therefore, calculated pA_2 values cannot be regarded as an estimation of the receptor affinity. The results of the *Schild* regression analyses confirm the existence of a mixed competitive-noncompetitive mechanism of the compounds provided that the experiments were carried out under equilibrium conditions[25, 26]. Equilibrium states for the determination of the H_1-receptor affinity of these compounds were obtained after prolonged incubation times. Especially the cyproheptadine derivatives **31**, **32**, and **34** required 30 min at concentration of 10^{-8} M, whereas the other test compounds were incubated for 15 min as a rule. The results are summarized in Table 3.

Considering the nitroethenediamines with the diphenhydramine element the 4-chloro and 4-methyl substitution (**29b, d**) provide the highest H_1-receptor antagonist activity with pK_B values of 8.71 and 8.61, respectively (for comparison: diphenhydramine $pA_2 = 8.14$[27]). The 4-fluoro-substituted compound **29c**, however, shows the highest H_2-receptor antagonist potency ($pK_B = 7.92$) and exceeds the potency of tiotidine ($pA_2 = 7.8$[28]) as the only one among all presented compounds. The cyproheptadine derivatives **30–32** display H_1-receptor antagonist activity comparable to the diphenhydramines, but they do not achieve the antagonist potency of cyproheptadine itself ($pA_2 = 8.76$[23]). Shortening of the alkyl spacer from 7 to 4 methylene groups results in a significant enhancement ($p < 0.05$) of the H_1-receptor antagonist activity from 8.38 (**30**) to 8.68 (**32**). At the same time the affinity to H_2-receptors is significantly decreased (7.15 (**30**) *vs.* 6.86 (**32**), $p > 0.05$), although it should be taken into account that the number of experiments ($n = 3$) is small. As a result compound **32** displays a difference between H_1- and H_2-receptor affinity of about 1.8 log units. The incorporation of the 10,11-dihydro derivative of cyproheptadine (**31**) induces a further slight decrease in the H_2-receptor antagonist potency. The use of urea as a polar group apparently leads to less active H_1- and H_2-receptor antagonists (Table 3). The differences towards the nitroethenediamines are partly minor and not significant, partly they come up to 0.5 log units (e.g. H_1: **29b–33b**; H_2: **29a–33a**, **30–34**). Within the urea series the 4-methyl group (**33d**) affords the most pronounced H_1-receptor antagonist activity, while the 4-fluoro substitution is again of advantage for the H_2-receptor affinity (**33c**: $pK_B = 7.56$). Comparing the two investigated H_1-receptor antagonist moieties, diphenhydramine and its *para*-substituted analogues, provide the more potent compounds at both histamine receptor subtypes. Although the cyproheptadine derivatives **30–32** and **34** achieve very good H_1-receptor antagonist activities, this rather rigid structure element has a negative effect on affinity to H_2-receptors. Furthermore, the nitroethenediamine function should be preferred as the polar group towards urea. Thus, both **29c** and **29d** can be regarded

Table 3. *Histamine H_1- and H_2-receptor antagonism of the nitroethenediamines* **29a–d**, **30–32** *and the ureas* **33a–d**, **34**.

	H_1-receptor antagonism (guinea-pig ileum)			H_2-receptor antagonism (guinea-pig right atrium)		
compd.	$pK_B \pm$ s.e.m. (n[a])	antagonist conc. [M]	rel. E_{max}[b] [%] (conc. [M])	$pK_B \pm$ s.e.m. (n)[a]	antagonist conc. [M]	rel. E_{max}[b] [%] (conc. [M])
29a	7.92 ± 0.04 (16)	$10^{-7.5} - 10^{-6.5}$	–[c]	7.50 ± 0.11 (3)	$10^{-7.5} - 10^{-6.5}$	77 ($10^{-6.5}$) 38 (10^{-6})
29b	8.71 ± 0.11 (12)	$10^{-7.5} - 10^{-6.5}$	84 ± 2 ($10^{-6.5}$)	7.26 ± 0.07 (2)	$10^{-7} - 10^{-6.5}$	73 ($10^{-6.5}$)
29c	8.26 ± 0.08 (12)	$10^{-7.5} - 10^{-6.5}$	83 ± 2 ($10^{-6.5}$)	7.92 ± 0.04 (2)	$10^{-7.5}$	–[c]
29d	8.61 ± 0.06 (24)	$10^{-8} - 10^{-6.5}$	75 ± 1 (10^{-7}) 45 ± 4 ($10^{-6.5}$)	7.62 ± 0.00 (2)	$10^{-7.5}$	–[c]
30	8.38 ± 0.06 (24)	$10^{-7.5} - 10^{-7}$	48 ± 3 (10^{-7})	7.15 ± 0.08 (3)	$10^{-7} - 10^{-6.5}$	88 ($10^{-6.5}$)
31	7.93 ± 0.05 (20)	$10^{-8} - 10^{-7}$	79 ± 2 (10^{-7}) 30 ± 5 ($10^{-6.5}$)	6.79 ± 0.14 (4)	$10^{-6.5} - 10^{-6}$	81 ± 3 (10^{-6})
32	8.68 ± 0.09 (19)	$10^{-8} - 10^{-7.5}$	63 ± 3 ($10^{-7.5}$) 34 ± 9 (10^{-7})	6.86 ± 0.07 (3)	$10^{-6.5} - 10^{-6}$	83 (10^{-6})
33a	8.22 ± 0.04 (12)	$10^{-7.5} - 10^{-6.5}$	73 ± 6 ($10^{-6.5}$)	7.02 ± 0.06 (4)	10^{-6}	–[c]
33b	8.11 ± 0.07 (15)	$10^{-7.5} - 10^{-6.5}$	68 ± 3 ($10^{-6.5}$)	7.21 ± 0.14 (2)	$10^{-7.5} - 10^{-7}$	–[c]
33c	7.97 ± 0.03 (24)	$10^{-7.5} - 10^{-6.5}$	72 ± 2 ($10^{-6.5}$)	7.56 ± 0.12 (2)	$10^{-7.5} - 10^{-7}$	–[c]
33d	8.31 ± 0.10 (12)	$10^{-7.5} - 10^{-6.5}$	58 ± 6 ($10^{-6.5}$)	7.40 ± 0.16 (2)	$10^{-7.5} - 10^{-7}$	–[c]
34	8.15 ± 0.06 (27)	$10^{-8} - 10^{-7}$	68 ± 3 (10^{-7})	6.61 ± 0.04 (3)	$10^{-6.5} - 10^{-6}$	–[c]

[a] number of experiments; [b] calculated in relation to the mean E_{max} (= 100 %) of the histamine control curves; [c] rel. E_{max} 90 %.

as the compounds with the highest combined H_1-/H_2-receptor antagonism not only in the diphenhydramine series, but also in comparison to all other substances.

Finally, the H_1- and H_2-receptor antagonist activity obtained *in vitro* show that these two antagonist features are very effectively combined by the concept presented.

Acknowledgement

The authors are grateful to Dr. S. Elz for his continuous support of pharmacological investigations. This study was granted by the Fonds der Chemischen Industrie.

Experimental Part

Chemistry. Mp (uncorrected): digital melting point apparatus Elektrothermal IA 9200.– Elemental analyses: Perkin-Elmer Elementaranalysator 240B, 240C, and Vario EL.– ^{1}H-NMR: Bruker AC 300 (300 MHz), TMS as internal reference, for abbreviations see footnotes of Table 2, *: exchangeable with D_2O.– $^+$FAB-MS: Finnigan MAT CH5DF (Xenon); EI-MS: Finnigan MAT CH7A (170 °C, 70 eV), elemental analyses of novel compounds agreed with the calculated values within ± 0.4 %.– Preparative chromatography: flash chromatography using silica gel 60 (Merck, 0.063–0.2 mm), column height 150 mm, column width 50 or 60 mm, nitrogen pressure 1 bar; Chromatotron 7924T (Harrison Research) using glass rotors with 2 or 4 mm layers of silica gel PF_{254} containing gypsum (Merck). All compounds of the substituted diphenhydramine series were prepared as racemates without separating the enantiomers.

N,N-Dimethyl-2-(diphenylmethoxy)ethanamines **3b–d**

The diphenylmethanols **1b–d** (15 mmol, obtained by reduction of the corresponding benzophenones with $LiAlH_4$) were dissolved in 25 ml absol. toluene and dropped into an ice-cooled suspension of NaH (0.66 g, 16.50 mmol, 60 % dispersion in mineral oil) under nitrogen atmosphere. The reaction mixture was heated up to 90 °C and after 30 min a 33 % (*m/m*) solution of **2** in absol. toluene (7.33 g, 22.50 mmol) was added dropwise. The mixture was stirred further 5 h under reflux. The cooled solution was then treated with water, the toluene phase separated and washed with water again. After removing the solvent the residue was redissolved in Et_2O and treated with 2N HCl. The acid phase was alkalized and extracted with Et_2O. The ethereal solution was dried (Na_2SO_4) and evaporated. Yield 3.13 g (72 %) **3b**, 3.28 g (68 %) **3c**, 2.34 g (58 %) **3d**; **3b**: $C_{17}H_{20}ClNO$ (289.8).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.26 (s, 6H, $N(CH_3)_2$), 2.58 (t, *J* = 6.0 Hz, 2H, OCH_2CH_2N), 3.54 (t, *J* = 6.0 Hz, 2H, OCH_2CH_2N), 5.33 (s, 1H, ArAr'CH), 7.15–7.18 (m, 1H, Ph-4-H), 7.23–7.32 (m, 8H, aromatic H).– $^+$FAB-MS (DMSO/glycerol); *m/z* (%) = 290 ($[M+H]^+$, 11), 288 ($[M-H]^+$, 4), 58 (100).

5-(1-Methyl-4-piperidyl)-5H-dibenzo[a,d]cyclohepten-5-ol (**7**) *and 10,11-Dihydro-5-(1-methyl-4-piperidyl)-5H-dibenzo[a,d]cyclohepten-5-ol* (**8**)

The carbinols **7**, **8** were prepared as described in ref.[13] from 4-(1-methylpiperidyl)magnesium chloride **6** (obtained from Mg° turnings (1.26 g, 52.00 mmol) and 1 equiv. 4-chloro-1-methylpiperidine in absol. THF) and 0.8 equiv. of the ketones **4** and **5**, respectively. THF was used as solvent and the reaction time was 6–7 h at 70 °C. The Grignard adduct was hydrolyzed with 10 % NH_4Cl. The product was taken up in toluene, extracted with 5N HCl, and subsequently the acid phase was alkalized. Further extraction with toluene, drying (Na_2SO_4) and distillation of the solvent afforded the carbinols **7, 8**. Yield 9.65 g (76 %) **7**, 6.90 g (54 %) **8**; **7**: $C_{21}H_{23}NO$ (305.3).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.75 (d, *J* = 13.1 Hz, 2H, 2 Pip-H), 1.32 (dq, J_d = 3.7 Hz, J_q = 12.4 Hz, 2H, 2 Pip-H), 1.63 (dt, J_d = 2.5 Hz, J_t = 11.8 Hz, 2H, 2 Pip-H), 1.86 (s, 1H, OH*), 2.15 (s, 3H, NCH_3), 2.52 (tt, *J* = 3.7/12.1 Hz, 1H, CH), 2.69 (d, *J* = 11.2 Hz, 2H, 2 Pip-H), 6.95 (s, 2H, -CH=CH-), 7.25 (dd, *J* = 1.2/7.3 Hz, 2H, aromatic H), 7.32 (dd, *J* = 1.6/7.6 Hz, 2H, aromatic H), 7.40 (dt, J_d = 1.6 Hz, J_t = 7.5 Hz, 2H, aromatic H), 7.92 (d, *J* = 8.0 Hz, 2H, aromatic H).– $^+$FAB-MS (DMSO/glycerol); *m/z* (%) = 306 ($[M+H]^+$, 30), 304 ($[M-H]^+$, 20), 288 ($[M+H]^+ - H_2O$, 16), 44 (100). **8**: $C_{21}H_{25}NO$ (307.3).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.21 (d, *J* = 12.5 Hz, 2H, 2 Pip-H), 1.55 (dq, J_d = 3.3 Hz, J_q = 12.2 Hz, 2H, 2 Pip-H), 1.73 (dt, J_t = 11.6 Hz, 2H, 2 Pip-H), 2.16 (s, 3H, NCH_3), 2.31 (s, 1H, OH*), 2.41 (tt, *J* = 3.4/11.7 Hz, 1H, CH), 2.79 (d, *J* = 11.3 Hz, 2H, 2 Pip-H), 2.92–3.04 (m, 2H, Ph-CH_2CH_2-Ph), 3.42–3.53 (m, 2H, Ph-CH_2CH_2-Ph), 7.09–7.23 (m, 6H, aromatic H), 7.84 (dd, *J* = 1.8/7.5 Hz, 2H, aromatic H).– $^+$FAB-MS (DMSO/glycerol); *m/z* (%) = 308 ($[M+H]^+$, 68), 290 ($[M+H]^+ - H_2O$, 25), 44 (100).

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)-1-methylpiperidine (**9**) *and 4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-methylpiperidine* (**10**)

The carbinols **7**, **8** were dehydrated by heating them in 60 ml of a mixture of anhydrous acetic acid and concd. HCl (2.5:1) for at least 2 h at 120 °C (control by TLC!). Afterwards the reaction mixture was poured into water, rendered strongly alkaline and extracted with toluene. After drying and evaporation of the solvent the crude products were purified by flash chromatography (eluent: EtOAc/CH_3OH/NEt_3 92/6/2 (*V/V*)). Yield 7.54 g (83 %) **9**, 4.87 g (75 %) **10**; **9**: $C_{21}H_{21}N$ (287.3).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.09–2.21 (m, 4H, 4 Pip-H), 2.23 (s, 3H, NCH_3), 2.31–2.40 (m, 2H, 2 Pip-H), 2.47–2.54 (m, 2H, 2 Pip-H), 6.91 (s, 2H, -CH=CH-), 7.18–7.25 (m, 4H, aromatic H), 7.29–7.34 (m, 4H, aromatic H).– $^+$FAB-MS (DMSO/glycerol); *m/z* (%) = 288 ($[M+H]^+$, 63), 44 (100). **10**: $C_{21}H_{23}N$ (289.3).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.09–2.27 (m, 2H, 2 Pip-H), 2.27 (s, 3H, NCH_3), 2.39–2.44 (m, 4H, 4 Pip-H), 2.58–2.65 (m, 2H, 2 Pip-H), 2.76–2.88 (m, 2H, Ph-CH_2CH_2-Ph), 3.35–3.47 (m, 2H, Ph-CH_2CH_2-Ph), 7.05–7.13 (m, 8H, aromatic H).– $^+$FAB-MS (DMSO/glycerol); *m/z* (%) = 290 ($[M+H]^+$, 86), 44 (100).

N-Methyl-2-(diphenylmethoxy)ethanamines **11a–d**

To a solution of 5–10 mmol of the diphenhydramines **3a–d** in 15–30 ml absol. 1,2-dichloroethane a small amount of Na_2CO_3 was added. The mixture was cooled to 0 °C and after dropwise addition of 2 equiv. of 1-chloroethylchloroformate it was first kept at 0 °C for 10 min and then refluxed for 2 h. The cooled mixture was filtered and the solvent evaporated. The oily residue was gradually treated with stirring with 20–30 ml absol. CH_3OH at ambient temperature and afterwards heated at 50 °C for 2 h. To the 1-chlorocarbamate of **3d** CH_3OH was added at 0 °C and the mixture cautiously warmed up to only room temperature. After removing the CH_3OH the hydrochlorides of **11a–d** were obtained. In order to get the free bases the salts were dissolved in water, alkalized with NaOH and the basic solution extracted with *n*-hexane. The solvent was removed and the crude products purified by chromatography (Chromatotron, eluent: EtOAc/CH_3OH 98/2 (*V/V*), NH_3 atmosphere). Yield 85 % **11a**, 86 % **11b**, 72 % **11c**, 46 % **11d**; **11c**: $C_{16}H_{18}FNO$ (259.3).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.98 (br. s, 1H, NH*), 2.44 (s, 3H, NCH_3), 2.80 (t, *J* = 5.1 Hz, 2H, OCH_2CH_2N), 3.57 (t, *J* = 5.1 Hz, 2H, OCH_2CH_2N), 5.35 (s, 1H, ArAr'CH), 7.00 (t, *J* = 8.7 Hz, 2H, 4-F-Ph-3-H and -5-H), 7.23–7.31 (m, 7H, aromatic H).– $^+$FAB-MS (DMSO/glycerol); *m/z* (%) = 260 ($[M+H]^+$, 11), 185 (100).

4-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)piperidine (**12**) *and 4-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)piperidine* (**13**)

The tricyclic compounds **9, 10** were demethylated according to the procedure described for **11a–d**. In contrast to the diphenhydramines, the methanolysis of the intermediate 1-chloro-carbamates has already finished after 15 min at ambient temperature, followed by 15 min at 50 °C. Purification was carried out by Chromatotron (eluent: CH_2Cl_2/CH_3OH 98/2 (*V/V*), NH_3 atmosphere) for **12** and by flash chromatography (eluent: CH_2Cl_2/CH_3OH/NEt_3 92/6/2 (*V/V*)) for **13**. Yield 76 % **12**, 77 % **13**; **12**: $C_{20}H_{19}N$ (273.3).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.70 (br. s, 1H, NH*), 2.04–2.12 (m, 2H, 2 Pip-H), 2.22–2.30 (m, 2H, 2 Pip-H), 2.61–2.69 (m, 2H, 2 Pip-H), 2.85–2.93 (m, 2H, 2 Pip-H), 6.91 (s, 2H, -CH=CH-), 7.18-7.24 (m, 4H, aromatic H), 7.29–7.33 (m, 4H, aromatic H).– EI-MS; *m/z* (%) = 273 ($M^{+\cdot}$,100). **13**: $C_{20}H_{21}N$ (275.3).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.35–2.39 (m, 4H, 4 Pip-H), 2.59 (br. s, 1H, NH*), 2.69–2.77 (m, 2H, 2 Pip-H), 2.79–2.88 (m, 2H, Ph-CH_2CH_2-Ph), 2.97–3.04 (m, 2H, 2 Pip-H), 3.35–3.47 (m, 2H, Ph-CH_2CH_2-Ph), 7.05–7.13 (m, 8H, aromatic H).– EI-MS; *m/z* (%) = 275 ($M^{+\cdot}$,100).

7-Aminoheptanonitriles **14a–d** *and 7-Piperidinoheptanonitriles* **15, 16**

Solutions of 10 mmol of the respective secondary amines **11a–d** and **12, 13** in 30 ml absol. CH_3CN were stirred together with 3 equiv. of K_2CO_3 and 1 equiv. of 7-bromoheptanonitrile at 90 °C during 5–6 h. After returning to ambient temperature water was added, followed by extraction with toluene. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The 7-amino- and 7-piperidinoheptanonitriles were pure enough for the following reaction. Yield 83 % **14a**, 84 % **14b**, 83 % **14c**, 84 % **14d**; 99 % **15**, 92 % **16**; **14d**: $C_{24}H_{32}N_2O$ (364.6).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.26–1.34 (m, 2H, $NCH_2CH_2(CH_2)_4CN$), 1.38–1.52 (m, 4H, $-(CH_2)_2-$), 1.57–1.67 (quint, J = 7.2 Hz, 2H, CH_2CH_2CN), 2.26 (s, 3H, NCH_3), 2.31 (s, 3H, Ph-CH_3), 2.34–2.40 (m, 4H, $NCH_2(CH_2)_4CH_2CN$), 2.66 (t, J = 6.0 Hz, 2H, OCH_2CH_2N), 3.55 (t, J = 6.0 Hz, OCH_2CH_2N), 5.34 (s, 1H, ArAr'CH), 7.11 (d, J = 8.0 Hz, 2H, 4-CH_3-Ph-3-H and -5-H), 7.21–7.36 (m, 7H, aromatic H).– $^+$FAB-MS (DMSO/glycerol); *m/z* (%) = 365 ($[M+H]^+$, 6), 363 ($[M-H]^+$, 7), 181 (100). **16**: $C_{27}H_{32}N_2$ (384.6).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.33–1.41 (m, 2H, $PipNCH_2CH_2$), 1.43–1.53 (m, 4H, $-(CH_2)_2-$), 1.62–1.67 (m, 2H, CH_2CH_2CN), 2.13–2.19 (m, 2H, 2 Pip-H), 2.28–2.34 (m, 4H, $PipNCH_2$, CH_2CN), 2.39–2.43 (m, 4H, 4 Pip-H), 2.62–2.69 (m, 2H, 2 Pip-H), 2.77–2.85 (m, 2H, Ph-CH_2CH_2-Ph), 3.37–3.45 (m, 2H, Ph-CH_2CH_2-Ph), 7.06–7.13 (m, 8H, aromatic H).– EI-MS; *m/z* (%) = 384 ($M^{+\cdot}$, 17), 288 (100).

4-[4-(5H-Dibenzo[a,d]cycloheptен-5-ylidene)piperidino]butanonitrile **(17)**

Equimolar amounts of **12** (2.48 g, 9.10 mmol) and 4-chlorobutanonitrile in 20 ml of absol. CH_3CN/DMF 1/1 together with 3 equiv. Na_2CO_3 and a small amount KI were refluxed for 5–6 h. The product **17** was isolated as described for **14a–d** and **15, 16** and purified by flash chromatography (eluent: EtOAc/CH_3OH/NEt_3 94/4/2 (*V/V*)). Yield 2.48 g (80 %) **17**; $C_{24}H_{24}N_2$ (340.5).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.78 (quint, J = 7.0 Hz, 2H, CH_2CH_2CN), 2.06–2.18 (m, 4H, 4 Pip-H), 2.28–2.34 (m, 2H, 2 Pip-H), 2.36–2.42 (m, 4H, $PipNCH_2CH_2CH_2CN$), 2.49–2.54 (m, 2H, 2 Pip-H), 6.91 (s, 2H, -CH=CH-), 7.18 (d, J = 7.3 Hz, 2H, aromatic H), 7.24 (d, J = 7.9 Hz, 2H, aromatic H), 7.30–7.34 (m, 4H, aromatic H).– EI-MS; *m/z* (%) = 340 ($M^{+\cdot}$, 59), 286 (100).

1,7-Heptanamines **18a–d**, *7-Piperidinoheptanamines* **19, 20** *and 4-Piperidinobutanamine* **21**

Under a nitrogen atmosphere 5 mmol of the respective nitrile **14a–d** or **15–17** dissolved in 30 ml absol. THF were dropped to an ice-cooled suspension of 2 equiv. of $LiAlH_4$ in 30 ml absolute Et_2O under vigorous stirring and subsequently maintained at ambient temperature for further 2 h. Then the reaction mixture was cooled in an ice-bath and consecutively hydrolyzed with Et_2O saturated with water and by dropwise addition of 10 % NaOH. After stirring for 30 min the precipitate was filtered off with suction, thoroughly treated with Et_2O and the mixture filtered again. The combined filtrates were dried (Na_2SO_4) and the solvent was removed. The obtained oily residues of **18a–d** and **21** were purified by Chromatotron (eluent: CH_2Cl_2/CH_3OH 95/5 (*V/V*) for **18a–d** and CH_2Cl_2/CH_3OH 90/10 (*V/V*) for **21**, NH_3 atmosphere). Flash chromatography (eluent: CH_2Cl_2/CH_3OH/NEt_3 90/8/2 (*V/V*)) was used for the purification of **19, 20**. Yield 55 % **18a**, 55 % **18b**, 49 % **18c**, 63 % **18d**; 81 % **19**, 70 % **20**, 62 % **21**; **18d**: $C_{24}H_{36}N_2O$ (368.6).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.25–1.29 (m, 6H, $-(CH_2)_3-$), 1.42–1.44 (m, 4H, $-CH_2(CH_2)_3CH_2-$), 2.25 (s, 3H, NCH_3), 2.31 (s, 3H, Ph-CH_3), 2.33–2.39 (m, 2H, $NCH_2(CH_2)_6NH_2$), 2.64–2.68 (m, 4H, OCH_2CH_2N, CH_2NH_2), 3.57 (t, J = 6.2 Hz, 2H, OCH_2CH_2N), 5.33 (s, 1H, ArAr'CH), 7.11 (d, J = 8.0 Hz, 2H, 4-CH_3-Ph-3-H and -5-H), 7.22 (d, J = 7.7 Hz, 2H, 4-CH_3-Ph-2-H and -6-H), 7.27–7.36 (m, 5H, aromatic H).– $^+$FAB-MS (DMSO/glycerol); *m/z* (%) = 369 ($[M+H]^+$, 4), 367 ($[M-H]^+$, 2), 181 (100). **20**: $C_{27}H_{36}N_2$ (388.6).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.30 (m, 6H, $-(CH_2)_3-$), 1.43–1.48 (m, 4H, $NCH_2CH_2(CH_2)_3CH_2CH_2NH_2$), 1.64 (br. s, 2H, NH_2*), 2.12–2.19 (m, 2H, 2 Pip-H), 2.30 (t, J = 7.8 Hz, 2H, $PipNCH_2$), 2.40 (m, 4H, 4 Pip-H), 2.65–2.69 (m, 4H, 2 Pip-H, CH_2NH_2), 2.77–2.87 (m, 2H, Ph-CH_2CH_2-Ph), 3.35–3.45 (m, 2H, Ph-CH_2CH_2-Ph), 7.08–7.12 (m, 8H, aromatic H).– $^+$FAB-MS (DMSO/glycerol); *m/z* (%) = 389 ($[M+H]^+$, 100). **21**: $C_{24}H_{28}N_2$ (344.5).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.37–1.51 (m, 6H, $-(CH_2)_2-$, NH_2*), 2.08–2.19 (m, 4H, 4 Pip-H), 2.26–2.39 (m, 4H, 2 Pip-H, $PipNCH_2$), 2.52–2.59 (m, 2H, 2 Pip-H), 2.67 (t, J = 6.7 Hz, 2H, CH_2NH_2), 6.91 (s, 2H, -CH=CH-), 7.18–7.26 (m, 4H, aromatic H), 7.29–7.34 (m, 4H, aromatic H).– EI-MS; *m/z* (%) = 344 ($M^{+\cdot}$, 28), 286 (100).

Nitroethenediamines **29a–d, 30–32**

Equimolar amounts (1.5–2.5 mmol) of 1,1-bis(methylthio)-2-nitroethene and the primary amines **18a–d, 19–21** in 30 ml absol. CH_3CN were refluxed for 3–4 h[16]. Afterwards, the strongly concentrated solutions of the ketene-*N,S*-acetals **22a, b** were stirred without purification with 1.5 equiv. of the free base of **28** at 85 °C for 4 h. Differing from this procedure the intermediates **22c, d** were treated with **28** (free base) in 5 ml absol. EtOH at 50 °C overnight. The solutions of the ketene-*N,S*-acetals **23–25** were evaporated to dryness and directly converted into the nitroethenediamines **30–32** by reaction with 1.2 equiv. of the dihydrochloride of **28** in 5 ml absol. CH_3OH in the presence of 3 equiv. of NEt_3 at 75 °C for 18–20 h. After removing the solvent all products were isolated by Chromatotron using two eluents consecutively for the purification of each compound (eluent: EtOAc/CH_3OH 95/5 and CH_2Cl_2/CH_3OH 98/2 (*V/V*) for **29a–d**; eluent: CH_2Cl_2/CH_3OH 95/5 and CH_2Cl_2/CH_3OH 98/2 (*V/V*) for **30–32**). For preparative and analytical data see Table 1 and 2.

Ureas **33a–d** *and* **34**

Preparation according to ref.[17]: solutions of 1–3 mmol of the primary amines **18a–d** and **19** in 3 ml absol. THF were added dropwise to an ice-cooled solution of 1 equiv. of 1,1'-carbonyldiimidazole in 10 ml absol. THF during 30 min and afterwards stirred at 0 °C. After the reaction had finished (control by TLC), 1.1 equiv. of **28** (free base) in 5 ml absol. DMF were added at 0 °C and the mixture subsequently stirred at ambient temperature for 24 h. The reaction mixture was quenched in water and after 30 min extracted with CH_2Cl_2 for several times. The combined organic layers were washed with NaCl solution (semi-satd.), dried (Na_2SO_4), and evaporated to dryness. The crude products were purified by Chromatotron as described for the nitroethene-diamines. Preparative and analytical data are summarized in Table 1 and 2.

Pharmacology

Histamine H_1-receptor Antagonist Activity on the Isolated Guinea-Pig Ileum

The experiments were carried out according to the procedure given in ref.[19]. The cumulative concentration-response curves for histamine were recorded starting with 10^{-8} M histamine and geometrically increasing until maximal contraction was obtained. Incubation time depends on the antagonist tested. The cyproheptadine derivatives **31, 32,** and **34** were incubated for 30 min. For all other compounds 15 min were sufficient for equilibration.

Histamine H_2-receptor Antagonist Activity on the Isolated Spontaneously Beating Guinea-Pig Right Atrium

The inhibition of the histamine induced increase in heart rate was determined as described in detail in [19, 20].

Expression of Results

Results are given as means ± s.e.m.; pK_B values are calculated from the expression $pK_B = -\log c_A + \log (CR - 1)$ where c_A is the concentration of the antagonist used and CR is the ratio of the EC_{50} of the agonist in the presence to that in the absence of antagonist[21].

References

☆ Dedicated to Professor Dr. Dr. E. Mutschler on the occasion of his 65th birthday.

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Received: October 11, 1995 [FP065]