Eur J Med Chem (1993) 28, 165–173

Structure–activity relationships within a series of analogues of the histamine H_1-antagonist terfenadine

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(Received 24 March 1992; accepted 9 September 1992)

Summary — A number of terfenadine derivatives including terfenadine enantiomers were synthesized and tested for histamine H_1-receptor affinity. No significant differences in H_1 activity were found between terfenadine enantiomers. Qualitative structure–activity relationship studies identified the α,α-diphenyl-4-piperidinomethanol moiety as the pharmacophore for the H_1 activity of this group of compounds. The major role of the phenylbutanol moiety in terfenadine seems to be preventing the compound from crossing the blood–brain barrier.

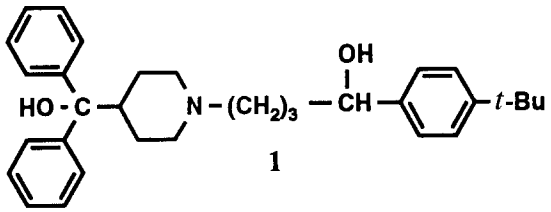
histamine H_1-antagonists / structure–activity relationships / terfenadine / terfenadine analogues / terfenadine enantiomers

Introduction

Although it has been more than 50 years since the discovery of the first histamine H_1-receptor antagonist, the precise structural requirements for H_1-receptor affinity are still unclear. At present, many different structural types of compounds are known to exhibit H_1-antagonistic activity [1]. Further structure–activity relationship (SAR) information on H_1-antagonists will undoubtedly contribute to our understanding of the drug–receptor interaction at the histamine H_1-site.

Terfenadine **1** is the first so-called non-sedative H_1-receptor antagonist. The marked decrease of side effects correlated to the central nervous system (CNS) led to the widespread therapeutic application of terfenadine in the treatment of allergic rhinitis, allergic dermatological conditions and other histamine-mediated disorders [2]. The original SAR study on terfenadine indicated that: 1) varying the diphenylmethanol group, to diphenylmethylene or diphenylmethyl, results in reduced activity; 2) butanol compounds are preferred over the lower alkanols; 3) *tert*-butyl substitution at the phenylbutanol moiety yields more-active compounds as compared to halo-, alkoxy- or *tert*-amino-derivatives [3]. Much later, it was suggested that the α,α-diphenyl-4-piperidinomethanol moiety in terfenadine was related to its H_1-receptor blocking activity [4]. Most studies on the optical isomers of terfenadine showed that both enantiomers exhibited similar activity and toxicity profiles [5–7], though a more than 12-fold difference between the enantiomers in antagonizing histamine-induced guinea-pig ileum contraction was found in one report [8]; this report was a poster presentation with incomplete information. The metabolic studies of the terfenadine enantiomers on animal and human subjects are somehow contradictory. While the animal studies revealed that the *R*-enantiomer of an orally administered racemic terfenadine was preferentially oxidized to form the *R*-enantiomer of the carboxylic acid metabolite [9], the human studies seem to suggest that racemic terfenadine does not undergo any stereoselective isomeric interconversion in man after oral administration [7]. Recently, a different series of compounds bearing the α,α-diaryl-4-piperidinomethanol moiety was evaluated for anti-allergic activity, among which AHR-5333 (**2**) was shown to be more potent than terfenadine [10].

In this paper we present the synthesis and antihistamine activity of the terfenadine enantiomers and a group of related compounds (fig 1). Structure–activity relationships regarding both α,α-diphenyl-4-piperidinomethanol and phenylbutanol moieties are discussed. Although a few compounds in this series, namely **3**, **6**, **8** and **9**, had already been synthesized for various purposes [11, 12], a comparative SAR study concerning H_1-receptor activity has never been reported.



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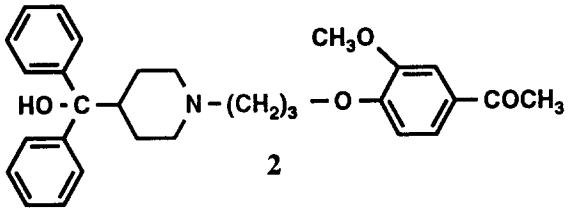

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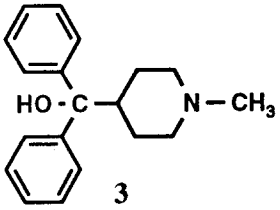

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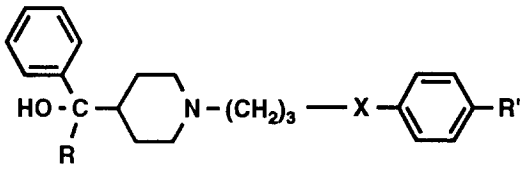


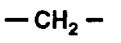
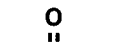
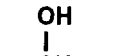
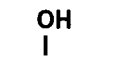
	R	X	R'
4	Ph		*t*-Bu
5	Ph		*t*-Bu
6	Ph		*t*-Bu
7	Ph		*t*-Bu
8	Ph		H
9	Ph		H
10	H		*t*-Bu

Fig 1. Structures of terfenadine **1** and some analogues.

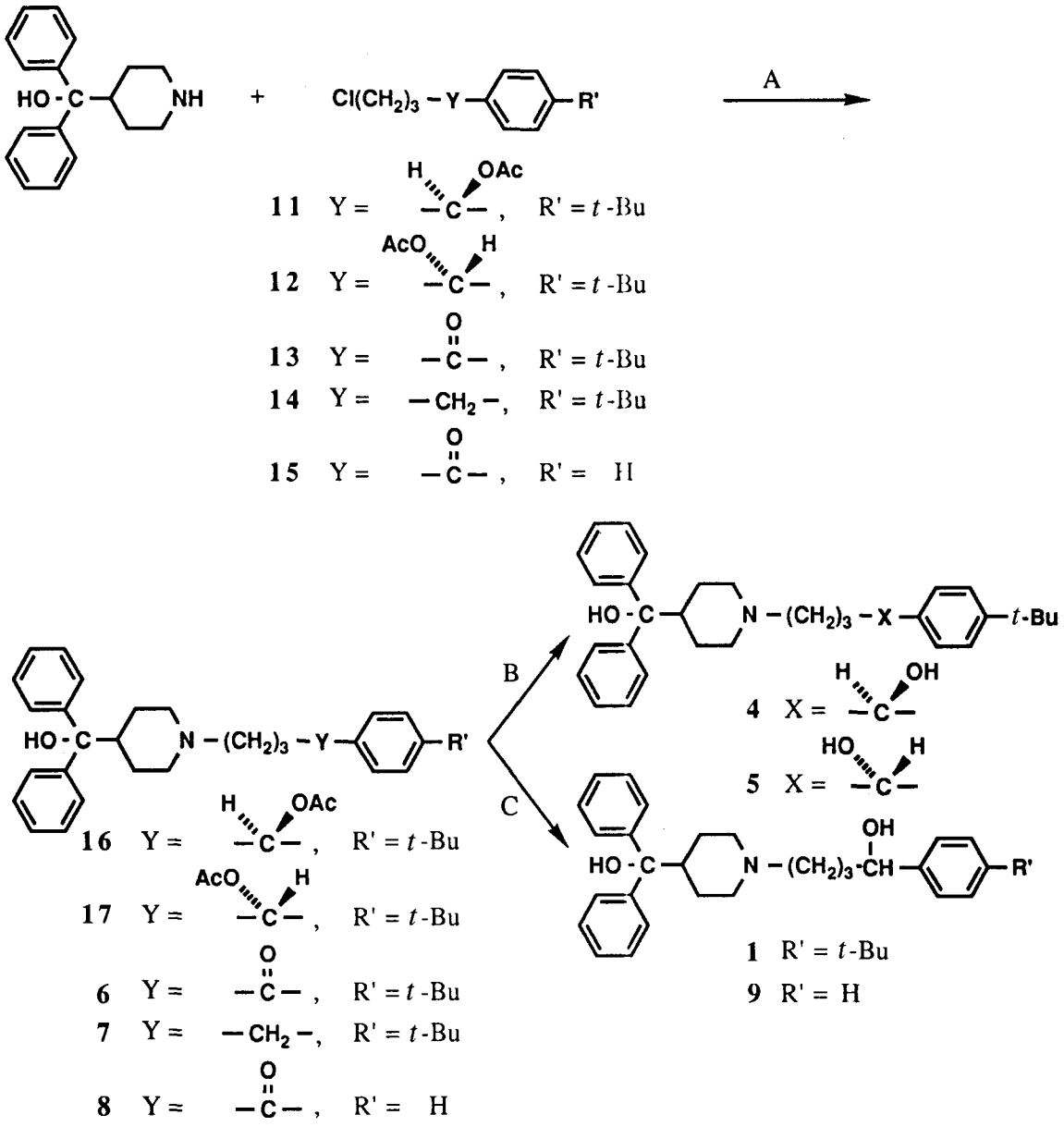
Chemistry

The synthesis of compounds **3–10** was rather straightforward. As illustrated in scheme 1, α,α-diphenyl-4-piperidinomethanol was alkylated with the appropriate chloroalkanes **11–15** in the presence of potassium carbonate to yield the tertiary amines **6–8**, **16** and **17**. Reduction of esters **16** and **17** with lithium aluminum hydride afforded the terfenadine enantiomers **4** and **5**, whilst reduction of the ketones **6** and **8** with sodium borohydride gave terfenadine **1** and its des-*tert*-butyl analogue **9**. It was found that alkylation of α,α-diphenyl-4-piperidinomethanol with crude alkyl iodide obtained from halide exchange of the corresponding chloride with sodium iodide in dry acetone gave much better yield than a 'one-pot' reaction with alkyl chloride in the presence of potassium iodide. For instance, the alkylation of α,α-diphenyl-4-piperidinomethanol with the crude product of the halide exchange between **13** and sodium iodide gave a yield of 75%, much higher than that with chloride **13** in the presence of potassium iodide (yield: 20–25% [4]). ^{1}H-NMR analysis of the crude iodide indicated that it contains at least 70% 4-iodo-1-(4-*tert*-butylphenyl)-1-butanone based on the integration ratio between a triplet at 3.54 ppm (the chloride) and a triplet at 3.18 ppm (the iodide). This was further confirmed by a gas chromatography analysis of the sample showing the area ratio of 1:2.5 between peaks at retention time of 9.40 and 10.48 min for the chloride and the iodide, respectively.

The enantiomeric purity of the terfenadine optical isomers **4** and **5** was determined by ^{31}P-NMR after derivatization with (4*R*,5*R*)-(+)-2-chloro-4,5-dimethyl-1,3,2-dioxaphospholane-2-oxide [13]. A singlet at 14.04 ppm was found for derivatized **4** and a singlet at 14.16 ppm was found for derivatized **5**. The derivatization of racemic terfenadine **1** with (4*R*,5*R*)-(+)-2-chloro-4,5-dimethyl-1,3,2-dioxaphospholane-2-oxide showed 2 singlets at 14.04 and 14.16 ppm, respectively. The intensity ratio of these 2 singlets was 48:52. Taking into account the accuracy of NMR spectrometry, it is fair to say the enantiomer excess of **4** and **5** is at least more than 95%.

The des-phenyl terfenadine analogue **10** was synthesized in a similar way (scheme 2). 4-Benzoylpiperidine was alkylated with chloride **13**. The obtained ketone **18** was then reduced to the corresponding alcohol **10** with sodium borohydride. *N*-Methyl azacyclonol **3** was obtained by reductive methylation of α,α-diphenyl-4-piperidinomethanol with formaldehyde and sodium borohydride.

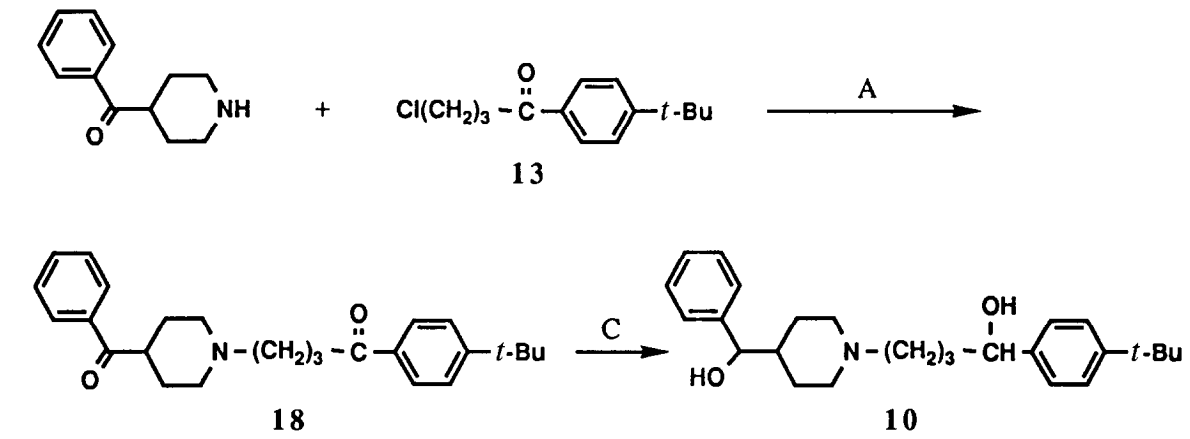
The synthesis of enantiomeric esters **11** and **12** is outlined in scheme 3. The chlorobutanone **13** was stereoselectively reduced to *R*-(+)-alcohol **19** with (+)-*B*-chlorodiisopinocampheylborane or S-(–)-alcohol



Scheme 1. Synthesis of terfenadine **1** and some derivatives. A: NaI/K_2CO_3/acetone. B: $LiAlH_4$/ether. C: $NaBH_4$/methanol.

20 with (–)-*B*-chlorodiisopinocampheylborane [14]. These alcohols were then quantitatively converted into esters **11** and **12** with acetyl chloride in dry ether in the presence of triethylamine. The enantiomeric excess (more than 95%) of the alcohols was determined with the same technique as described for terfenadine enantiomers. The absolute configuration of alcohols **19** and **20** is based on analogy with the examples in [14].

Chlorobutylbenzene **14** was obtained almost quantitatively by reduction of ketone **13** with sodium borohydride in trifluoroacetic acid [15]. This is one of the few successful examples of reducing monoaryl ketones to alkanes wilh sodium borohydride in carboxylic acids [16, 17]. The electron-donating property of *tert*-butyl on the phenyl ring of **14** may contribute to the facility of the reduction by stabilizing the carbocation formed during the proposed deoxygenation process [17].



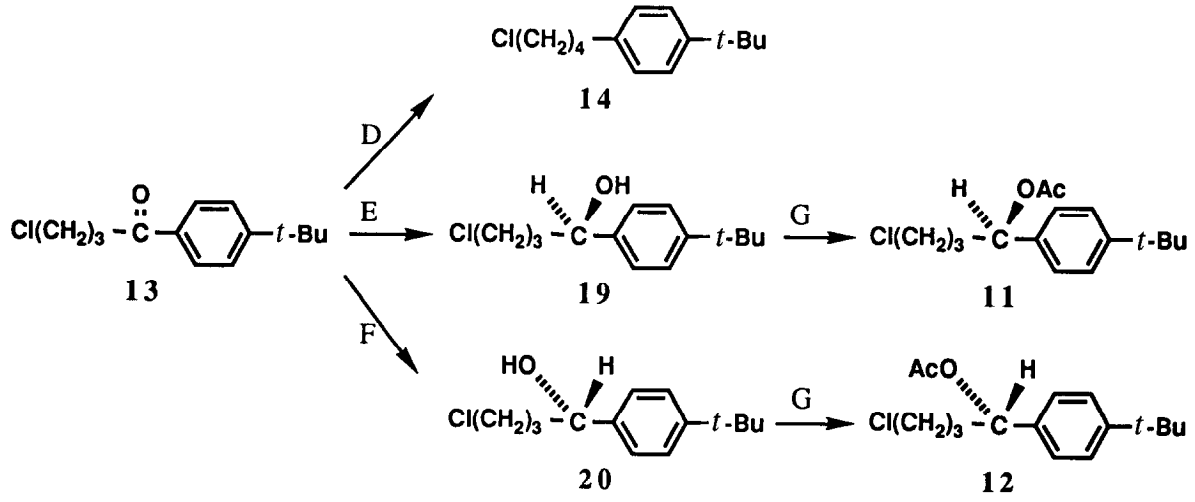
Scheme 2. Synthesis of des-phenyl terfenadine **10**. A: NaI/K_2CO_3/acetone. B: $NaBH_4$/methanol.

Pharmacology

Compounds **3–10** were tested for histamine H_1-receptor activity by both functional and binding assays. In the functional assay the anti-histamine activities of the compounds were determined as the inhibition of histamine-induced contraction in guinea-pig ileum [18]. Table I lists the pA_2-values calculated from a Schild analysis. The slopes of the Schild plots were not significantly different from unity which is consistent with competitive antagonism, except for **10**, whose the Schild slope was significantly lower than unity.

In the binding assay, the histamine H_1-receptor affinities of the compounds were measured as the inhibition of [^{3}H]-mepyramine binding to guinea-pig cerebellum membranes [19]. The negative logarithm of the equilibrium dissociation constants (pK_d) are presented in table I. The potency order of the compounds in the binding assay is consistent with that in functional assay.

The pK_d-values obtained from the binding studies are not equivalent to the pA_2-values obtained from the functional studies. This could suggest different affinities of the compounds for guinea-pig central and peripheral histamine H_1-receptors, respectively. It is,



Scheme 3. Synthesis of chloroalkane **11**, **12** and **14**. D: $NaBH_4/CF_3COOH$. E: (+)-B-chlorodiisopinocampheylborane/THF, –25°C. F: (–)-B-chlorodiisopinocampheylborane/THF, –25°C. G: $CH_3COCl/Et_3N/Et_2O$.

Table I. Histamine H_1-receptor activity of terfenadine derivatives.

Compd	*Functional assay* [a]			*Binding assay* [b]	
	$pA_2 \pm SD$	*Slope*	*n*	$pK_d \pm SD$	*n*
3	7.52 ± 0.01	0.91	3	6.95 ± 0.36	3
4	7.72 ± 0.09	0.99	5	7.06 ± 0.10	3
5	7.61 ± 0.14	0.98	5	6.81 ± 0.08	3
6	7.48 ± 0.29	1.13	3	6.78 ± 0.18	2
7	7.73 ± 0.16	1.14	3	6.49 ± 0.18	2
8	8.28 ± 0.23	1.00	3	7.40 ± 0.08	2
9	8.35 ± 0.25	1.01	3	7.42 ± 0.28	2
10	7.22 ± 0.09	0.63	3	6.00 ± 0.08	3
Terfenadine	7.65 ± 0.11	1.01	5	6.88 ± 0.03	3

[a]Measured as inhibition of histamine-induced contraction in guinea pig ileum; *n* indicates the number of independent tests in each of which 4 different concentrations of the indicated compound were used; [b]measured as inhibition of [^{3}H]-mepyramine binding to guinea pig cerebellum membranes; *n* indicates the number of independent experiments which were performed in triplicate.

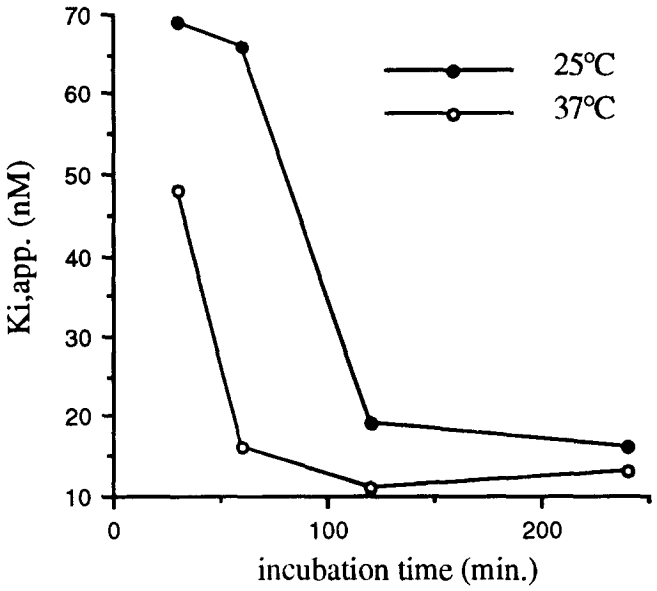


Fig 2. Effect of incubation time on the apparent equilibrium inhibition constants ($K_{i,app}$ values) of terfenadine in guinea pig cerebellum membranes. $K_{i,app}$ (nM) was plotted *versus* incubation time (min). Data are the means of a triplicate determination.

however, known that drug–receptor binding equilibria are theoretically only achieved at incubation times 4-times longer than the half-time ($t_{1/2}$) of drug–receptor dissociation [19]. When a drug dissociates very slowly, a binding equilibrium can practically not be achieved because of degradation of the tissue. It is known the $t_{1/2}$ of terfenadine is 220 ± 40 min [19]. Thus the affinity of the compounds determined in this study are apparent. Indeed, as shown in figure 2, the apparent equilibrium inhibition constants ($K_{i,app}$ values) of terfenadine decreased with prolonged incubation times. At 37°C, the $K_{i,app}$ values decreased from 4.8 x 10^{-8} to 1.6 x 10^{-8} M when the incubation time was prolonged from 30 to 60 min. A $K_{i,app}$ of 1.1 x 10^{-8} M was obtained when the incubation time was 120 min. Similarly, at the incubation temperature of 25°C, the $K_{i,app}$ of terfenadine decreased along with prolongation of incubation time. An incubation time longer than 120 min did not decrease the $K_{i,app}$ of terfenadine further, possibly because of tissue digestion. Thus the difference between pA_2- and pK_d values in table I is mostly the result of different incubation times, rather than of differences in receptor characteristics.

Discussion

Although stereoselectivity has been observed in histamine H_1-antagonists [1, 20, 21], not all chiral H_1-antagonists show stereoselective activity. For example, promethazine and clemastine both possess asymmetric centers but show no stereoselectivity in their interactions with the H_1-receptor [21]. It appears that an asymmetric center close to the side chain nitrogen is of minor importance for stereoselectivity. Therefore, it is not surprising that the terfenadine enantiomers **4** and **5** showed almost no difference in their affinities for both central and peripheral H_1-receptors (table I). In fact, the achiral analogues **6** and **7** of terfenadine exhibited similar activities compared to terfenadine. This result also implies that it is the α,α-diphenyl-4-piperidinomethanol moiety that is responsible for H_1-activity of terfenadine. Indeed, α,α-diphenyl-1-methyl-4-piperidinomethanol **3** showed practically the same activity as terfenadine. Surprisingly, however, the desphenyl analogue **10** of terfenadine exhibited only 2.7-fold weaker activity than terfenadine in the functional assay and 7.6-fold lower affinity in the binding assay. It is possible that the aromatic moiety in the phenylbutanol part of the molecule assumes the role of the phenyl group removed from the diphenylmethanol part in binding to the receptor. As the Schild slope for this compound was significantly smaller than unity, mechanisms other than simple competitive inhibition may also be involved in its action.

In contrast to the observation reported earlier [3], the unsubstituted phenylbutanol derivative **8** as well as its ketone analogue **9** showed higher activities than terfenadine with pA_2 values of 8.28 for **8** and 8.35 for **9**.

It is widely accepted that the sleep-inducing effects of H_1-antagonists are caused by the occupancy of cerebral H_1-receptors [1]. The non-sedating profile of terfenadine proved to be due to its poor penetration through the blood–brain barrier [22]. As α,α-diphenyl-4-piperidinomethanol (azacyclonol) has been shown to be an anti-hallucinatory agent [23, 24], we believe that the poor penetration of terfenadine into the CNS is largely due to the introduction of the *p-tert*-butylphenylbutanol moiety. Nevertheless, an additional explanation is needed for the inability of terfenadine to readily pass the blood–brain barrier, because its lipophilicity index (log $P_{\text{octanol/water}}$ = 5.26 [19]) should allow this drug to cross the blood–brain barrier. Recently, in a study on centrally acting H_2-antagonists, Young *et al* [25] found a significant correlation between the logarithms of the equilibrium brain/blood concentration ratios in the rat and the partition parameter, Δlog *P*, defined as log $P_{\text{octanol/water}}$ − log $P_{\text{cyclohexane/water}}$ which suggests that brain penetration might be related to the overall hydrogen-bonding ability of the compound. Whether this concept is valid for H_1-antagonists remains to be elucidated.

In conclusion, we have developed a convenient and high-yield synthetic method for the preparation of terfenadine enantiomers and related alkyl piperidine derivatives. The reduction of **13** to **14** serves as one of a few successful examples in reducing monoaryl ketone to the corresponding alkanes with acyloxyborohydrides. The similar range of activity in both guinea-pig ileum and cerebellum for the enantiomers is because the chiral center is located relatively far from the α,α-diphenyl-4-piperidinomethanol moiety which is responsible for H_1 activity of the compound. The SAR comparison among a group of terfenadine analogues revealed that the major contribution of phenylbutanol substitution may be to prevent the compound from penetrating into the CNS. The differences between the pA_2 and pK_d values presented in table I are due to the different incubation times of the experiments.

Experimental protocols

Chemistry

All compounds were checked for their structures by ^{1}H-NMR and MS. The ^{1}H-NMR spectra were recorded on a Bruker AC 200 spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane and coupling constants are in Hz. Mass spectral data were registered on a Finnigan MAT 90 mass spectrometer with electron impact (EI) ionization, ion source temperature 200°C, source pressure 2.2 x 10^{-6} Torr. Melting points were determined on a Mettler FP5 melting point apparatus. Specific rotations were measured on a Perkin–Elmer 241 MC polarimeter. Thin-layer chromatography was performed on a Kiesegel 60 F254 (Merck) thin-layer chromatography (TLC) aluminum sheets.

Enantiomeric excesses of **4**, **5**, **19** and **20** were determined by the ^{31}P-NMR technique [13]. A Bruker WM 250 spectrometer was used for this purpose. All shifts obtained are reported by using external phosphoric acid as reference standard, δ = 0.0. Starting materials α,α-diphenyl-4-piperidinomethanol and **13** were purchased from Janssen Chimica, Tilburg, The Netherlands.

R-(+)-1-{4-Acetoxy-4-[4-(1,1-dimethylethyl)phenyl]butyl}-α,α-diphenyl-4-piperidinomethanol **16**

To a solution of 1.41 g (5 mmol) of **11** in 250 ml dry acetone was added 0.75 g (5 mmol) of sodium iodide (dried at 150°C overnight). The solution was refluxed for 6 h. After evaporating to dryness, the residue was extracted with petroleum ether (40–60°C) (100 ml x 3). The combined petroleum ether layer was dried with sodium sulfate and evaporated to dryness. The residue was then dissolved in 300 ml of butanone-2. To this solution was added 1.34 g (5 mmol) of α,α-diphenyl-4-piperidinomethanol and 0.69 g (5 mmol) of potassium carbonate. After refluxing overnight, the mixture was evaporated to dryness and the residue was taken up with dichloromethane. A slightly brown oil was obtained after evaporating the solvent. Purification by silica gel column chromatography (ethyl acetate/petroleum ether 40–60°C, 1/1) furnished the title compound as a thick colorless oil. Yield: 70.1%, $[\alpha]_D^{25}$ + 26.1° (*c* = 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.35 (s, 9H, CH_3), 1.49 (m, 4H, piperidine $C_{3',5'}$-H), 1.65–1.98 (m, 6H, piperidine $C_{2',6'}$-H_{ax} and $NCH_2CH_2CH_2$), 2.10 (s, 3H, $COCH_3$), 2.30 (t, 2H, *J* = 7.0 Hz, NCH_2-), 2.45 (m, 1H, piperidine C_4-H), 2.90 (br d, 2H, *J* = 12 Hz, piperidine $C_{2',6'}$-H_{eq}), 5.72 (t, 1H, *J* = 7.0 Hz, -*CH*$OCOCH_3$), 7.12–7.49 (m, 14H, aromatic H); MS *m/e*: 513 (M^+); Anal for $C_{34}H_{43}NO_3$ (C, H).

Compounds **6–8** and **17** were prepared by the reaction of α,α-diphenyl-4-piperidinomethanol with chlorides **12–15** in the same way as described for **16**. The characteristics of **6–8** are listed in tables II and III, while the physical properties of **17** were identical to those of **16** except that specific rotation for **17** was $[\alpha]_D^{25}$ –26.1° (*c* = 1, $CHCl_3$). In the mass spectrum, the molecular ion of all compounds appeared as a moderate peak. The fragment ion generated after the β-fission in the alkyl chain constituted the base peak in all spectra except for **3** and **6**. The processes common to all compounds are: 1) loss of H_2O from the base fragment ion; 2) loss of C_6H_5· from the base fragment ion; 3) $M^{+\cdot}$ undergoes fission of the C–C bond at the α-position to the methanol group; 4) $M^{+\cdot}$ undergoes McLafferty rearrangement which constituted a strong peak in the compounds containing the ketone function.

R-(+)-1-{4-[4-(1,1-Dimethylethyl)phenyl]-4-hydroxybutyl}-α,α-diphenyl-4-piperidinomethanol **4**

To a solution of 1.54 g (3 mmol) of **16** in 100 ml dry ether under nitrogen was added portionwise 0.12 g (3 mmol) of lithium aluminum hydride. The mixture was stirred at room temperature for 6 h. After the reaction was completed, 50 ml of water were added to the reaction mixture and the ether layer was separated. The water layer was filtered and the white solid was washed with dichloromethane. The combined organic solution was dried and evaporated to dryness. The residue was crystallized from acetone affording the title compound as white crystals. Yield: 91%, $[\alpha]_D^{25}$ +40.6° (*c* = 1, $CHCl_3$), 100% *ee* based on ^{31}P-NMR (δ = 14.03 ppm). For other physical data see tables II and III.

Compound **5** was prepared by the reduction of **17** with lithium aluminum hydride in the same way as described for **4**. Specific rotation for **5** was $[\alpha]_D^{25}$ –40.6° (*c* = 1, $CHCl_3$).

Table II. Characteristics of terfenadine derivatives.

Compd	*Formula*	*mp °C (solvent)*	*Yield (%)* [a]	*TLC (R_f)* [b]	*^{1}H-NMR ($CDCl_3$) (δ)*
3	$C_{19}H_{23}NO$ Anal (C, H)	134.0–134.7 (acetone)	94	0.097	1.49–1.70 (m, 4H, piperidine $C_{3',5'}$–H), 1.94 (m, 2H, piperidine $C_{2',6'}$–H_{ax}), 2.24 (s, 3H, CH_3), 2.41 (m, 1H, piperidine C_4–H), 2.88 (br d, 2H, J = 12 Hz, piperidine $C_{2',6'}$–H_{eq}), 7.13–7.51 (m, 10H, aromatic H)
4	$C_{32}H_{41}NO_2$ Anal (C, H)	143.2–144.1 (acetone)	91	0.174	1.29 (s, 9H, CH_3), 1.51–1.63 (m, 4H, piperidine $C_{3',5'}$–H), 1.81–2.17 (m, 4H, piperidine $C_{2',6'}$–H_{ax} and $CH_2CH_2CH_2$), 2.38–2.43 (m, 5H, piperidine C_4–H and $CH_2CH_2CH_2$), 2.98 and 3.14 (two d, 2H, J = 11.5 Hz, piperidine $C_{2',6'}$–H_{eq}) 3.46 (br s, 1H, CHOH), 4.59 (m, 1H, CH_2CHOH), 7.13–7.50 (m, 14H, aromatic H)
5	$C_{32}H_{41}NO_2$ Anal (C, H)	143.2–144.1 (acetone)	97	0.174	The same as above
6	$C_{32}H_{39}NO_2$ Anal (C, H)	73.1–74.0 (acetone)	75	0.458	1.25 (s, 9H, CH_3), 1.36 (m, 4H, piperidine $C_{3',5'}$–H), 1.76–1.93 (m, 4H, piperidine $C_{2',6'}$–H_{ax} and –$CH_2CH_2CH_2$–), 2.31 (m, 3H, NCH_2 and piperidine C_4–H), 2.86 (m, 4H, CH_2CO and piperidine $C_{2',6'}$–H_{eq}), 7.03–7.83 (m, 14H, aromatic H)
7	$C_{32}H_{41}NO$ Anal (C, H)	126.2–127.0 (acetone)	54	0.778	1.29 (s, 9H, CH_3), 1.47–1.64 (m, 8H, piperidine $C_{3',5'}$–H and –$(CH_2)_2$–), 1.94 (m, 2H, piperidine $C_{2',6'}$–H_{ax}), 2.33 (t, 2H, J = 7 Hz, NCH_2), 2.47 (m, 1H, piperidine C_4–H), 2.59 (t, 2H, J = 7 Hz, CH_2Ph), 2.97 (*br* d, 2H, J = 11 Hz, piperidine $C_{2',6'}$–H_{eq}), 7.09–7.51 (m, 14H, aromatic H)
8	$C_{28}H_{31}NO_2$ Anal (C, H)	85.9-86.3 (methanol)	52	0.271	1.20–1.52 (m, 4H, piperidine $C_{3',5'}$–H), 1.77–1.98 (m, 4H, piperidine $C_{2',6'}$–H_{ax} and –$CH_2CH_2CH_2$), 2.31 (m, 3H, NCH_2 and piperidine C_4–H), 2.89 (m, 4H, CH_2CO and piperidine $C_{2',6'}$–H_{eq}), 7.05–7.9 (m, 15H, aromatic H)
9	$C_{28}H_{33}NO_2$ Anal (C, H)	63.8–65.6 (acetone)	96	0.153	1.44–1.62 (m, 4H, piperidine $C_{3',5'}$–H), 1.74–2.15 (m, 4H, piperidine $C_{2',6'}$–H_{ax} and –$CH_2CH_2CH_2$), 2.34–2.51 (m, 5H, piperidine C_4–H and $CH_2CH_2CH_2$), 2.94 and 3.12 (two d, 2H, J = 11 Hz, piperidine $C_{2',6'}$–H_{eq}), 3.43 (br d, 1H, J = 7 Hz, CHOH), 4.60 (m, 1H, CH_2CHOH), 7.11–7.67 (m, 15H, aromatic H)
10	$C_{26}H_{37}NO_2$ Anal (C, H)	93.7–94.3 (acetone)	98	0.056	1.31 (s, 9H, CH_3), 1.55–1.70 (m, 5H, piperidine $C_{3',4',5'}$–H), 1.76–2.17 (m, 6H, piperidine $C_{2',6'}$-H_{ax} and –CH_2CH_2CH(OH)Ph), 2.39 (t, 2H, J = 6.7 Hz, NCH_2), 2.85–3.18 (m, 2H, piperidine $C_{2',6'}$–H_{eq}), 4.34 (d, 1H, J = 7.2 Hz, PhCH(OH)–piperidine), 4.60 (m, 1H, –CH_2CH_2CH(OH)Ph), 7.30 (m, 9H, phenyl H)

[a]Data indicate the yield of the last step of the reaction to give the indicated compound; [b]eluent: ethyl acetate/petroleum ether (40–60°C) saturated with NH_3.

Table III. Electron impact mass spectra[a] of terfenadine derivatives **3–10**.

	Compound No							
	3	***4***	***5***	***6***	***7***	***8***	***9***	***10***
M^+	281 (18)	471 (30)	471 (27)	469 (6)	455 (16)	413 (6)	415 (27)	395 (27)
a	–	293 (8)	293 (6)	293 (100)	–	293 (63)	293 (7)	217 (7)
b	–	280 (100)	280 (100)	280 (90)	280 (100)	280 (100)	280 (100)	204 (100)
c	262 (6)	262 (13)	262 (9)	262 (9)	262 (7)	262 (13)	262 (14)	186 (5)
d	204 (8)	203 (7)	203 (6)	203 (24)	203 (1)	203 (1)	203 (1)	–
e	183 (31)	183 (10)	183 (4)	183 (25)	183 (6)	183 (18)	183 (10)	–
f	–	147 (4)	147 (5)	–	–	147 (29)	147 (6)	147 (7)
g	105 (34)	105 (10)	105 (29)	105 (37)	105 (16)	105 (73)	105 (37)	105 (7)
h	98 (100)	98 (3)	98 (6)	–	98 (7)	–	98 (6)	98 (5)

[a]Data presented as *m/z* (relative intensity %).

1-(4-Hydroxy-4-phenylbutyl)-α,α-diphenyl-4-piperidinomethanol **9**

Compound **9** was prepared by reduction of **8** with sodium borohydride in methanol. A similar work-up procedure was described in [4] and afforded **9** as a white crystalline. Yield: 96%. See tables II and III for the characteristics of **9**.

4-(4-Benzoylpiperidin-1-yl)-1-[4-(1,1-dimethylethyl)phenyl]-1-butanone ***18***

A solution of 4.77 g (20 mmol) of **13** and 3.0 g (20 mmol) of sodium iodide in 250 ml dry acetone was refluxed for 3 h. After removing the insoluble salts, 4.51 g (20 mmol) of 4-benzoylpiperidine hydrochloride and 5.52 g (40 mmol) of potassium carbonate were added to the filtrate. The mixture was then refluxed overnight. After removing the insoluble materials, the acetone solution was evaporated to dryness. The oily residue was put on a silica gel column (ethyl acetate/petroleum ether 40–60°C, 1/2) affording the title compound as white crystals. Yield: 40.8%, mp: 84.2–85.0°C. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (s, 9H, CH_3), 1.83 (m, 4H, piperidine $C_{3',5'}$–H), 1.91–2.17 (m, 4H, piperidine $C_{2',6'}$–H_{ax} and $-CH_2CH_2CH_2-$), 2.44 (t, 2H, J = 7.0 Hz, NCH_2-), 3.00 (m, 4H, piperidine $C_{2',6'}$–H_{eq} and $-CH_2CO-$), 3.23 (m, 1H, piperidine C_4–H), 7.41–7.95 (m, 9H, aromatic H); MS *m/e*: 391 (M^+); Anal for $C_{26}H_{33}NO_2$ (C, H).

1-{4-Hydroxy-4-[4-(1,1-dimethylethyl)phenyl]butyl}-α-phenyl-4-piperidinomethanol ***10***

To a solution of 2.0 g (5.1 mmol) of **18** in 300 ml of methanol was added portionwise 0.4 g (10 mmol) of sodium borohydride. The mixture was stirred at room temperature for 2 h. After evaporating to dryness, water was added to the residue and the mixture was extracted with dichloromethane. Removing the solvent afforded the title compound as a white crystalline which was further purified by recrystallization from acetone. Yield: 98%. See tables II and III for physical data.

R-(+)-4-Chloro-1-[4-(1,1-dimethylethyl)phenyl]-1-butanol ***19***

A solution of 2.38 g (10 mmol) of **13** in 10 ml tetrahydrofuran saturated with nitrogen was added to a solution of 3.8 g (12 mmol) of (+)diisopinocampheylchloroborane in 20 ml tetrahydrofuran at –25°C. After stirring at 25°C for 7 h, the temperature was raised to room temperature and the mixture was evaporated to dryness. The residue was dissolved in ether and 2.6 g (25 mmol) of diethanolamine was added to the solution. The mixture was then stirred for 2 h and filtered. The precipitate was washed well with petroleum ether (40–60°C). The combined organic solution was evaporated to remove organic solvents. The remaining oil was distilled under reduced pressure. The colorless distillate was further purified by a silica gel column (ether/petroleum ether, 1/2) affording the title compound as colorless crystals. Yield: 53%, mp: 50–51°C; $[\alpha]_D^{25}$ +2.3° (c = 1, $CHCl_3$), 100% *ee* based on ^{31}P-NMR (d = 14.05 ppm); ^{1}H-NMR ($CDCl_3$) δ: 1.35 (s, 9H, CH_3), 1.60 (br s, 1H, –OH), 1.78–2.02 (m, 4H, $-CH_2CH_2-$), 3.58 (t, 2H, J = 7.0 Hz, $ClCH_2-$), 4.70 (t, 1H, J = 7.0 Hz, $-CH_2CH(OH)-$), 7.25–7.37 (m, 4H, phenyl H); MS *m/e*: 231 (M^+); Anal for $C_{14}H_{21}ClO$ (C, H).

Alcohol **20** was prepared by the reduction of **13** with (–)diisopinocampheylchloro borane in the way similar to that described for **19**. It exhibited physical properties identical to those of **19** except for $[\alpha]_D^{25}$ with its value of –32.1° (c = 1, $CHCl_3$).

R-(+)-4-Chloro-1-[4-(1,1-dimethylethyl)phenyl]-1-butanol acetate ***11***

To a solution of 1.25 g (5.2 mmol) of **19** and 0.79 g (7.8 mmol) of triethylamine in 100 ml dry ether was added carefully 0.41 g (5.2 mmol) of acetyl chloride. The mixture was stirred at room temperature for 2 h. Water was then added to the mixture and the ether layer was separated, dried with sodium sulfate and evaporated to dryness to afford the title compound as a light yellow oil which was used for the subsequent reaction without further purification. Yield: 100%, $[\alpha]_D^{25}$ +59.8 (c = 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 1.32 (s, 9H, CH_3), 1.70–1.98 (m, 4H, $-CH_2CH_2-$), 2.08 (s, 3H, $-COCH_3$), 3.52 (t, 2H, J = 7.1 Hz, $ClCH_2-$), 5.75 (t, 1H, J = 7.0 Hz, Ac*OCH*Ph), 7.22–7.38 (m, 4H, phenyl H).

Compound **12** was prepared by acetylation in a way similar to that described above. $[\alpha]_D^{25}$ –58.3°(c = 1, $CHCl_3$).

1-Chloro-4-[4-(1,1-dimethylethyl)phenyl]butane ***14***

To 50 ml of trifluoroacetic acid stirred at 0°C under nitrogen was added 4.56 g (0.12 mol) of sodium borohydride over 30 min. To this mixture at 15°C was added dropwise over 30 min a solution of 4.77 g (0.02 mol) of **13** in 50 ml of dichloromethane. After stirring at room temperature overnight, the mixture was diluted by adding 100 ml of water and neutralized with 10% aqueous sodium hydoxide solution at 0°C. The dichloromethane layer was separated and the water layer was extracted twice with petroleum ether (40–60°C). The combined organic solution was dried with sodium sulfate and evaporated to dryness to afford the title compound as a colorless oil which was used for the subsequent reaction without further purification. Yield: 99%. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.31 (s, 9H, CH_3), 1.80 (m, 4H, $-CH_2CH_2-$), 2.62 (t, 2H, $PhCH_2-$, J = 7.0 Hz), 3.55 (t, 2H, $ClCH_2-$, J = 6.5 Hz), 7.10–7.35 (m, 4H, aromatic H); MS *m/e*: 224 (M^+, 14.7%), 209 (M^+-CH_3, 100%).

Pharmacology

Inhibition of histamine-induced contraction of guinea pig ileum

A piece of ileum (about 2 cm long) isolated from guinea pigs was trimmed, tied at both ends and mounted in a 20 ml organ bath containing Krebs buffer (NaCl 117.5 mM, KCl 5.6 mM, $CaCl_2$ 2.5 mM, NaH_2PO_4 1.28 mM, $MgSO_4$ 1.18 mM, $NaHCO_3$ 25 mM and glucose 5.5 mM, pH 7.4). The buffer was constantly bubbled with 95% O_2–5% CO_2 at 37°C. The first 3 dose–response experiments were performed by adding histamine cumulatively to the organ bath (from 1×10^{-8} to 1×10^{-5} M). After adequate washing, the ileal strip was incubated with the antagonist for 50 min. The dose–response experiment was then conducted again. Four different concentrations (3×10^{-8}, 1×10^{-7}, 3×10^{-7} and 1×10^{-6} M) of each antagonist were used for each test following adequate washing and restoration of a stable baseline after the previous lower concentration experiment.

Inhibition of [^{3}H]mepyramine binding to guinea pig cerebellum membranes

Cerebella of guinea pigs were homogenized in 50 mM Na/K phosphate buffer (KH_2PO_4 7.25 mM, Na_2HPO_4 42.75 mM and NaCl 0.15 M, pH 7.4). After the first centrifugation at 260 *g* for 1 min, the supernatant was centrifuged at 20 000 *g* for 30 min. The pellet was subsequently washed twice and resuspended in the phosphate buffer.

In the displacement experiment the membrane suspension of guinea pig cerebellum (200 μg of protein/ml) was incubated with increasing concentrations of the antagonist for 30 min at 37°C in 50 mM Na/K phosphate buffer (pH 7.4). Incubation

volume was 0.5 ml and [^{3}H]-mepyramine concentration was 1 nM. The reaction was stopped by the addition of 4 ml of ice-cold Na/K phosphate buffer (pH 7.4 at 0°C), followed by immediate filtration under reduced pressure onto Whatman GF/C filters. The filters were washed twice with 4 ml of cold buffer. The retained radioactivity was counted with a Packard liquid scintillation counter after addition of 5 ml of scintillation fluid to the filters. Each experiment was performed in triplicate.

Acknowledgments

The authors thank BLM van Baar for measuring the mass spectra and FJJ de Kanter for measuring the ^{31}P-NMR spectra.

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