Bioorganic & Medicinal Chemistry Letters, Vol.1, No.8, pp. 387-390, 1991
Printed in Great Britain

0960-894X/91 $3.00 + .00

OPTICAL ISOMERS OF THE H1 ANTIHISTAMINE TERFENADINE: SYNTHESIS AND ACTIVITY

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(*Received* 9 *July* 1991)

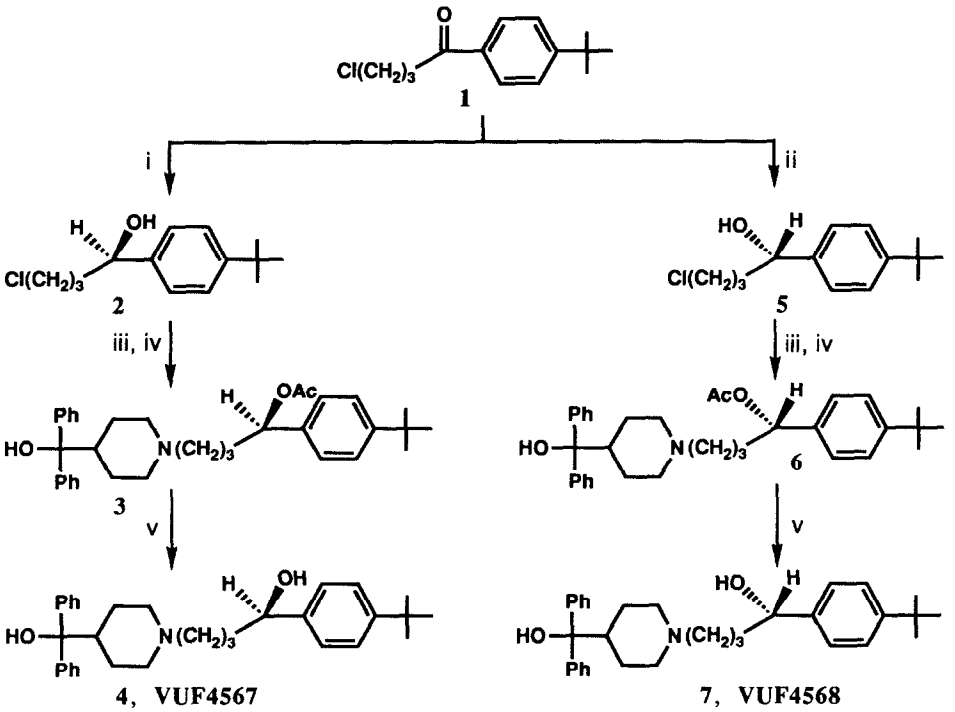
Abstract: The optical isomers of the H_1 antagonist terfenadine, VUF4567 and VUF4568, were synthesized in excellent enantiomer excess. No significant difference in their affinity for histamine receptors in both central (guinea-pig cerebellum) and peripheral (guinea-pig ileum) tissue was found between the R and S isomers.

It is well-known that some chiral H_1 antihistamine drugs show pronounced stereoselective activity. For example, the S isomer of chlorpheniramine was reported to be about 100 times more potent than the R isomer[1] and more recently the R isomer of rocastine was found to be more than 300 times more potent than its S enantiomer.[2]

Terfenadine, a newly developed histamine H_1-receptor antagonist, is chemically the racemic mixture of α-[4-(1,1-dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol. The *in vivo* selectivity of terfenadine on peripheral H_1-receptors promotes this drug to be one of the most frequently prescribed H_1 antihistamines for the treatment of allergic rhinitis, allergic dermatological conditions and other histamine-mediated disorders.[3] Recently, however, there have been increasing concerns on the adverse effects of terfenadine, especially those on cardiovascular system related to *torsades de pointes*,[4,5] a form of polymorphic ventricular tachycardia. It is therefore of great importance and extreme necessity to investigate whether the optical isomers of terfenadine exhibit different cardiotoxicity as well as H_1 antihistaminic activity.

To our knowledge, so far there have been no reports on resolution or asymmetric synthesis of terfenadine enantiomers in literature although a pharmacological study on the optical isomers of terfenadine was carried out without indicating the optical purities of the compounds.[6] The original method employed for the synthesis of terfenadine includes an alkylation of α,α-diphenyl-4-piperidinemethanol with 4-chloro-1-[4-(1,1-dimethylethyl)-phenyl]-1-butanone and a reduction of the ketone function in the side chain.[7] The alkylation step, as originally reported, gave only a very poor yield. A modification on this step by the phase-transfer technique has been reported.[8] In this communication we describe a high-yield and stereoselective synthesis of R and S enantiomers of terfenadine and a preliminary investigation on the antihistamine activities of the isomers on the isolated guinea-

pig ileum and their affinities for H_1 receptors of the guinea-pig cerebellums.



i. (+)-B-chlorodiisopinocampheylborane / THF, -25°C, 7 h; ii. (-)-B-chlorodiisopinocampheylborane / THF, -25°C, 7 h; iii. CH_3COCl / Et_3N / Et_2O, rt, 2 h; iv. α,α-diphenyl-4-piperidinemethanol / K_2CO_3 / NaI / $CH_3COC_2H_5$, refluxing overnight; v $LiAlH_4$ / Et_2O, rt, 6 h.

Figure 1. Synthesis of R and S isomers of terfenadine

As outlined in Figure 1, 4-chloro-1-[4-(1,1-dimethylethyl)phenyl]-1-butanone (**1**; 2.38 g, 10 mmol) was treated with (+)-*B*-chlorodiisopinocampheylborane (Aldrich, 3.53 g, 11 mmol) in THF (10 ml) at -25°C. A similar workup as described in the literature[9] afforded alcohol **2** in 53% yield. Further purification by a silica gel column eluted with ether / petroleumether (40-60°) 1:2 and rescrystallization from petroleumether (40-60°) gave chemically pure (*R*)-4-chloro-1-[4-(1,1-dimethylethyl)phenyl]-1-butanol (mp 50-51°C; $[\alpha]_D^{25}$+32.3° (*c* 1, $CHCl_3$)). The ^{31}P NMR spectrum of the derivatized alcohol with (4*R*,5*R*)-(+)-2-chloro-4,5-dimethyl-1,3,2-dioxa-phospholane-2-oxide (Aldrich) indicated an enantiomer excess (e.e.) of 100% based on the ratio of peak intensities at 14.03 and 14.15 ppm, which is believed to be accurate to ±1%.[10] The absolute configuration of alcohol **2** is based on analogy with the examples in reference 9. This alcohol was then converted to compound **3** by the acetylation with acetyl chloride in dry ether and the subsequent condensation with α,α-diphenyl-4-piperidine-methanol (1 equivalent) in butanone-2 in the presence of K_2CO_3 and NaI. Purification by a silica gel

column (ethyl acetate / petroleumether (40-60°) 1:1 saturated with NH_3) furnished a thick colourless oil (65% yield calculated on alcohol **2**; $[\alpha]_D^{25}$+26.1° (*c* 1, $CHCl_3$)). Reduction of compound **3** with $LiAlH_4$ in dry ether at room temperature for 6 hours afforded VUF4567 (**4**) (the R isomer of terfenadine) in 91% yield (mp 147-147.5°C (acetone); $[\alpha]_D^{25}$+40.6° (*c* 1, $CHCl_3$), 100% e.e. (based on ^{31}P NMR spectrum of the derivative with the "Anderson-Shapiro" reagent[10])). The S isomer of terfenadine, VUF4568 (**7**) ($[\alpha]_D^{25}$-40.6°, *c* 1, $CHCl_3$), was synthesized similarly as described for the R isomer by starting with (*S*)-4-chloro-1-[4-(1,1-dimethylethyl)-phenyl]-1-butanol (**5**) ($[\alpha]_D^{25}$-32.1°, *c* 1, $CHCl_3$) which was obtained by the reduction of ketone **1** with (-)-*B*-chlorodiisopinocampheylborane in 62% yield.

Both isomers were tested for their antihistamine activity measured as inhibition of histamine-induced contraction of the isolated guinea-pig ileum and their binding affinity for the H_1 receptors of the guinea-pig cerebellum in comparison with terfenadine itself. The method used for the functional study is derived from that reported by Cheng *et al.*[11] Thus, a piece of the ileum (about 2 cm length) isolated from guinea pigs was trimmed, tied at both ends and mounted in a 20 ml organ bath containing Krebs-buffer (37°C, constantly bubbled with 95% O_2 - 5% CO_2). The first three dose-response experiments were performed by adding histamine cumulatively to the organ bath (from $1x10^{-8}$ to $1x10^{-5}$ 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 ($3x10^{-8}$, $1x10^{-7}$, $3x10^{-7}$ and $1x10^{-6}$ M) of each antagonist were used for each test following adequate washing and restoration of a stable baseline after the previous lower concentration experiment. Five independent tests for each compound gave the pA_2 values, the negative logarithm of the molar antagonist concentration in the presence of which twice the original agonist concentration is needed for the original effect, as follows (means with the lowest and highest values found, n = 5): 7.72 (7.63-7.79, VUF4567); 7.61 (7.47-7.75, VUF 4568) and 7.65 (7.44-7.76, terfenadine).

The method for the binding assay was based on that reported by Leurs *et al*[12] using ^3H-mepyramine as the radioligand. Thus cerebellums of male guinea-pigs (350-450 g) were homogenized in Na/K phosphate buffer (50 mM, pH 7.5). 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 approximately 1 nM ^3H-mepyramine was incubated with increasing concentrations of non-labelled terfenadine in Na/K phosphate buffer (50 mM, pH 7.5) at 37°C for 30 min. Three experiments for each concentration gave the pKd values, the negative logarithm of the equilibrium dissociation constant, as follows (means ± S.E., n = 3): 6.67 ± 0.11 (VUF4567); 6.42 ± 0.09 (VUF4568); 6.52 ± 0.05 (terfenadine).

In conclusion, we have developed a convenient and high-yield synthetic method for the preparation of optically pure isomers of terfenadine. The similar range of activities on both guinea-pig ileum and cerebellum among the R, S isomers and terfenadine might be explained by the assumption that the chiral center in the molecule is far away from the moiety which is responsible for the affinity of the compounds to H_1-receptors. The difference between the pA_2 and pKd values is probably due to the time-dependence of the compounds for binding to the H_1-receptors[13]. Similar difference between pA_2 and Ki values, the inhibition constants, of terfenadine has previously been reported by other researchers[14]. A more detailed pharmacological evaluation of

the optical isomers of terfenadine will be reported elsewhere soon.

Acknowledgements

We thank Mr. O. P. Zuiderveld for his assistance in pharmacological tests of the compounds.

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