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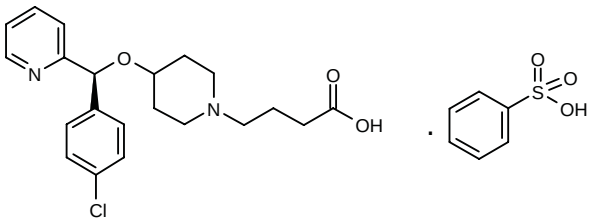
CCC: 0377-8282/98

Betotastine Besilate

Antihistamine
Antiallergic

TAU-284

(+)-(*S*)-4-[4-[1-(4-Chlorophenyl)-1-(2-pyridyl)methoxy]piperidin-1-yl]butanoic acid monobenzenesulfonate



$C_{21}H_{25}ClN_2O_3.C_6H_6O_3S$; Mol wt: 547.06

CAS: 190786-44-8
CAS: 190786-43-7 (as free base)
CAS: 125602-71-3 (as free base undefined isomer)

EN: 193910

Synthesis

The reaction of 4-[1-(4-chlorophenyl)-1-(2-pyridyl)-methoxy]piperidine (I) with ethyl 4-bromobutyrate (II) by means of K_2CO_3 in refluxing acetone gives the corresponding condensation product (III), which is then hydrolyzed with NaOH in ethanol/water yielding compound (IV) whose stereochemistry is not reported (1). Scheme 1.

Introduction

Histamine H_1 antagonists are the most widely used medications in the treatment of allergic rhinitis and other allergic diseases.

Their onset of action is rapid, and they reduce sneezing, pruritus and rhinorrhea, but not congestion. These agents began to be widely used in the mid- to late 1940s. They quickly became established in the treatment of various allergic disorders, particularly rhinitis, conjunctivitis and urticaria. The problem of sedation limited the use of classic antihistamines, however, and the search for H_1 antagonists that are devoid of sedative side effects has thus been a goal within the pharmaceutical industry. Several nonsedating antihistamines have have been launched in recent years and others are under development, as shown in Table I.

In the search for new nonsedating antihistamines, scientists at Ube synthesized a novel series of piperidine and piperazine derivatives and selected one compound, TAU-284 (betotastine besilate), for further evaluation.

Pharmacological Actions

The antiallergic activity of betotastine besilate was evaluated in comparison to that of other compounds in various rat models of allergy. Betotastine besilate inhibited histamine release from rat peritoneal mast cells and inhibited LTB_4 and 5-HETE production in peritoneal cells at high concentrations (1 mM). Following oral administration at doses ranging from 0.1-30 mg/kg p.o., betotastine inhibited the homologous passive cutaneous anaphylaxis (PCA) reaction in a dose-dependent fashion (ID_{30} = 0.38 mg/kg p.o.), an effect which lasted for more than 8 h. This effect was significant at a dose of 1 mg/kg, and was superior to that of ketotifen, terfenadine, cetirizine and epinastine. No tolerance developed following administration to rats for 8 days (2).

The compound also dose-dependently inhibited histamine-induced allergic skin reactions in rats (ID_{30} = 0.10 mg/kg), with the effect lasting for more than 4 h postdosing. This effect was significant at doses of 0.1 and 1.0 mg/kg, and was again superior to that of the above reference compounds. Oral betotastine (30 mg/kg) suppressed to decrease in histamine content in pleural cells in a rat model of concanavalin A-induced pleurisy. Taken together, these results indicate that betotastine besilate is a potent and long-acting antiallergic agent whose activity is due to histamine antagonism (2).

The antiallergic activity of betotastine was also evaluated in several guinea pig models of bronchoconstriction (2-4). Like the reference compounds ketotifen, terfenadine and cetirizine, betotastine besilate dose-dependently prevented severe asthmatic reactions induced in guinea pigs by histamine inhalation or antigen exposure (ED_{50} = 0.01 and 0.3 mg/kg p.o., respectively). The compound also inhibited antigen-induced airway hyperresponsiveness in acutely sensitized guinea pigs at doses of 1 mg/kg p.o. or higher (3).

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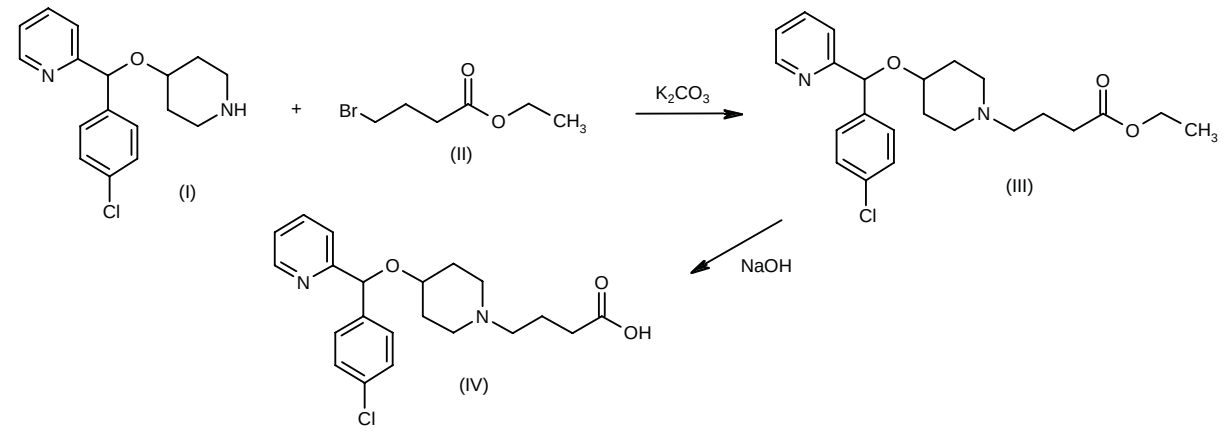
Scheme 1: Synthesis of Betotastine



Anaphylactic bronchoconstriction induced by anti-benzylpenicilloyl bovine gamma-globulin (BPO.BGG) serum or by histamine was inhibited in a dose-dependent fashion following oral administration of the title compound (ID_{50} = 0.21 and 0.11 mg/kg, respectively). It also inhibited PAF-induced bronchoconstriction at doses above 0.1 mg/kg p.o. (ID_{50} = 1.5 mg/kg p.o.), indicating that in addition to its antihistaminic activity, betotastine also acts as a PAF antagonist (4).

In a similar set of experiments in guinea pigs, title compound was also found to inhibit leukotriene D_4 (LTD_4), blocking LTD_4-induced contractions in tracheal smooth muscle and ileum at doses above 30 and 3 μM, respectively. Oral betotastine also dose-dependently inhibited BPO.BGG serum-induced anaphylactic shock (ID_{25} = 0.2 mg/kg p.o.) and histamine-induced systemic shock (ID_{50} = 0.06 mg/kg p.o.); in the latter case, shock was inhibited for 0.5-12 h following oral administration at doses of 0.3 or 1.0 mg/kg p.o. At oral doses above 0.01 mg/kg, betotastine inhibited histamine-induced cutaneous vascular permeability enhancement in a dose-dependent manner (ID_{40} = 0.04 mg/kg) (5).

The antiallergic activity of betotastine besilate was further demonstrated in anesthetized dogs. Title compound inhibited histamine-induced bronchoconstriction in a dose-dependent manner (ED_{50} = 3.2 μg/kg i.v.), with much more potent activity than terfenadine (ED_{50} = 46.0 μg/kg) in this model. Intraduodenal administration of betotastine inhibited bronchoconstriction by approximately 70% and 90% at the respective doses of 10 and 30 μg/kg, with effects lasting 4-5 h after dosing (6).

Betotastine besilate inhibited antigen-induced eosinophil infiltration, a characteristic of allergic inflammatory diseases, in the airway and peripheral blood in ovalbumin-sensitized mice. On the third day after ovalbumin challenge, betotastine (10 mg/kg p.o., b.i.d.) inhibited the increase in eosinophil numbers in bronchoalveolar lavage fluid; it inhibited this increase in peripheral blood on days 1-3 after challenge (7).

The efficacy of betotastine besilate was further established in other animal models of allergic rhinitis. Oral compound (1, 3 or 10 mg/kg) inhibited increase in dye leakage during and after nasal antigen challenge in actively sensitized rats, and inhibited the increase in intranasal pressure resulting from the topical application of histamine in nonsensitized guinea pigs. In actively sensitized guinea pigs, the compound significantly inhibited both phases of the biphasic increase in nasal airway resistance (at 0.5 and 4 h after challenge) (8).

Based on the well-known central effects of many antihistamines, a study was performed in mice and cats to evaluate the CNS effects of the title compound. At doses of 100-1000 mg/kg p.o., betotastine did not produce any marked changes in global behavior, although it did suppress huddling at the highest dose and caused slight mydriasis at doses above 300 mg/kg. Neither spontaneous motor activity nor hexobarbital-induced anesthesia was affected significantly by betotastine at doses up to 300 mg/kg p.o. In cats, betotastine reduced total sleep duration at 10 mg/kg p.o. but not at 30 or 100 mg/kg p.o. Thus, the compound appears to have a low sedative side effect liability (9, 10).

Pharmacokinetics and Metabolism

The pharmacokinetic profile of betotastine besilate was studied in rats and dogs following administration of single oral doses of the ^{14}C-labeled compound. Blood levels of radioactivity in male rats increased within 30 min of drug administration to reach a C_{max} of 0.2 μg eq./ml, and decreased thereafter with a $t_{1/2(1\text{-}8\ h)}$ of 3 h. Maximum levels of radioactivity in tissues were reached by 30 min after oral dosing, with highest levels in liver, followed by kidney, small intestine, stomach, gallbladder, pancreas and adrenal gland. The major component identified in urine

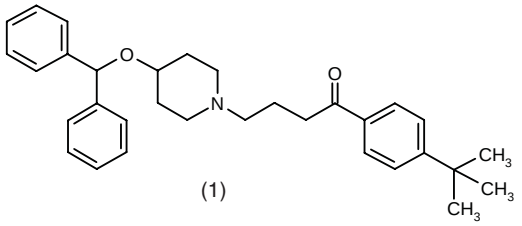
Table I: Nonsedating antihistamines launched (year) and in clinical trials.

Launched

1. Ebastine
   Ebastel
   Almirall; Rhône-Poulenc Rorer (1990)
2. Emedastine fumarate
   Daren, Remicut
   Kanebo; Kowa (1993)
3. Epinastine HCl
   Alesion
   Boehringer Ingelheim; Sankyo (1994)
4. Fexofenadine HCl
   Allegra
   Sepracor; Hoechst Marion Roussel (1996)
5. Levocabastine HCl
   Livostin
   Janssen (1991)
6. Mizolastine[2]
   Mizollen
   Synthélabo (1998)

Clinical Trials

7. Betotastine besilate
   Tanabe Seiyaku; Ube
8. Decarboethoxyloratadine
   Sepracor; Schering-Plough
9. DF-1111301[1]
   Dompe
10. Efletirizine
    UCB
11. HSR-609
    Hokuriku Seiyaku
12. Norastemizole
    Sepracor
13. Rupatadine fumarate[1]
    Uriach



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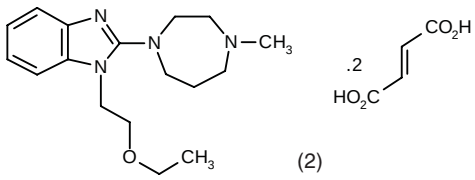

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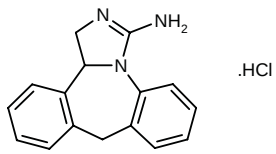

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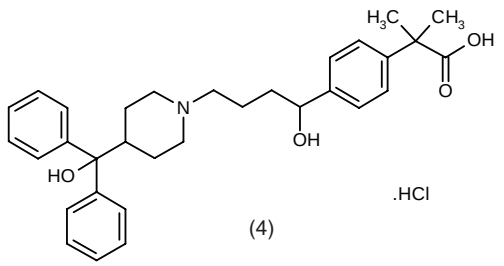

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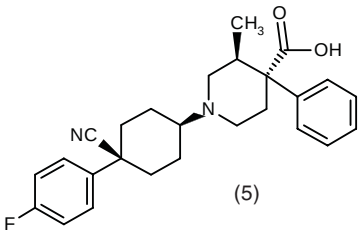

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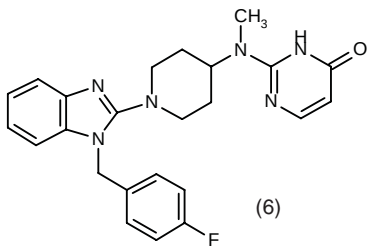

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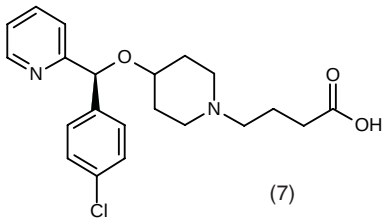

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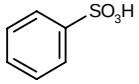

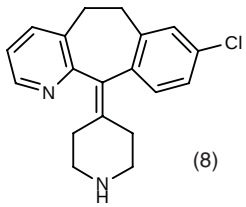

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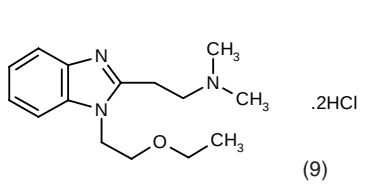
Table I: Continued.



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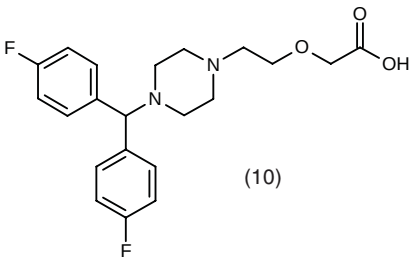

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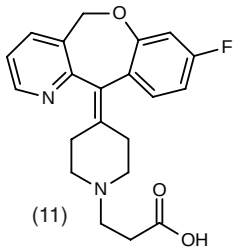

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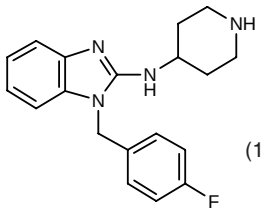

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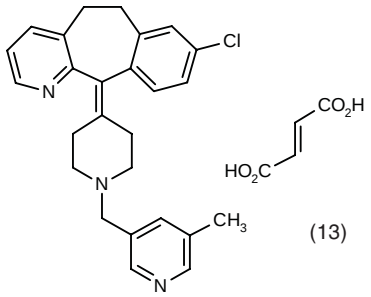

(13)

[1]Also PAF antagonist. [2]Also PAF antagonist and leukotriene antagonist. Source: Prous Science Ensemble database.

and bile was unchanged betotastine besilate; a β-oxidative metabolite was also detected in rat urine, and a taurine-conjugated metabolite of the unchanged drug as well as 5 other metabolites were detected in rat bile. No metabolites were identified in rat or dog plasma or in dog urine. Excretion of dosed radioactivity was 39.7 and 61.6% in urine and feces, respectively, within 120 h of oral administration in male rats. Biliary excretion accounted for 40.6% of the dose administered, and most appeared to be subjected to enterohepatic circulation (11).

Multiple-dose pharmacokinetic studies were also performed in rats and dogs. Steady state was reached on day 16 in male rats administered ^{14}C-labeled betotastine besilate orally for 21 days. Levels of radioactivity in blood decreased more slowly than in the single-dose study. Radioactivity levels were highest in liver and kidney following the 21-day dosing period, and were low in cerebrum, eyeballs, fat, seminal vesicles and testis; levels were moderate in other tissues. Tissue levels of radioactivity increased after each dose. Drug transfer to blood cells also increased with repeat dosing, and the majority of the radioactivity in blood was associated with a globin fraction. Total fecal and urinary excretion of radioactivity during each 24-h period after drug administration was nearly constant. In pregnant female rats administered betotastine besilate on day 18 of pregnancy, levels of radioactivity in the fetal liver 30 min after dosing were nearly equivalent to those in maternal plasma, whereas levels in fetal tissue were 1/3-1/10 those in maternal plasma. Radioactivity in the milk and lactating female rats peaked (0.40 μg eq./ml) at 1 h postdosing; at 48 h after drug administration, radioactivity had dropped below the limits of detection. However, at each determination point, levels in milk were higher than those in plasma (12).

Toxicity

General pharmacology studies of betotastine besilate indicated that the compound had a low potential to induce arrhythmogenicity. In the isolated and perfused guinea pig heart, betotastine decreased contractility by about 30% at a dose of 1000 μg/heart. It was also found to have a low potential to cause adverse effects in the gastrointestinal, renal and respiratory systems following oral or intraduodenal administration in rats, with adverse effects observed only at very high doses (10).

Oral toxicity studies were performed in rats administered the compound at doses ranging from 30-1000 mg/kg/day for 4 weeks and from 20-600 mg/kg/day for 26 weeks. The nontoxic dose level was estimated to be 100 mg/kg/day in the former and 20 mg/kg/day in the latter study. Drug-related toxicities at higher doses included inhibition of body weight gain, mydriasis, decrease in food intake, lower urinary pH, increase in hepatic drug-metabolizing enzyme activity, increase in liver weight, hypertrophy of centrilobular hepatic cells and hyperplasia of urinary epithelium; all these signs decreased or disappeared completely during the recovery period, and there were no treatment-related deaths (13).

Four- and 26-week toxicity studies were also performed in dogs. In this species, the no-toxic effect levels were estimated to be 60 mg/kg/day x 4 weeks or 30 mg/kg/day x 26 weeks. Adverse effects observed at higher doses included vomiting and salivation, which resolved during the recovery period (14).

Based on the results of reproductive toxicity studies in rats and rabbits, the nontoxic dose level was determined

to be 100 mg/kg p.o. in dams for general toxicity and for reproductive function and in offspring (15).

Clinical Studies

Tanabe Seiyaku and Ube have filed for approval to market betotastine besilate in Japan for the treatment of allergic rhinitis and urticaria (16, 17).

Manufacturers

Tanabe Seiyaku Co., Ltd. (JP) and Ube Industries, Ltd. (JP).

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