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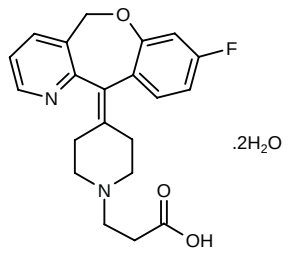
CCC: 0377-8282/98

HSR-609

Antiallergic Agent

3-[4-(8-Fluoro-5,11-dihydrobenz[*b*]oxepino[4,3-*b*]pyridin-11-ylidene)piperidin-1-yl]propionic acid dihydrate



$C_{21}H_{21}FN_2O_3.2H_2O$ Mol wt: 404.43

CAS: 188199-97-5
CAS: 161522-25-4 (anhydrous)

EN: 200676

Synthesis

HSR-609 is obtained as shown in Scheme 1 (1). Tricyclic compound (II), derived from (I) by known methods, is converted to piperidine derivative (III) by Grignard reaction and dehydration. The reaction of (III) with $ClCO_2Et$ and KOH affords (IV). Michael reaction and hydrolysis of (IV) give HSR-609.

Description

White to light red crystalline powder, m.p. approx. 145 °C (decomp., after drying).

Introduction

The incidence of allergic diseases such as urticaria, pruritic dermatitis, rhinitis, conjunctivitis and bronchial asthma has increased in recent years. Although basic antiallergic agents with antihistaminic action have been widely used for the treatment of allergic diseases, the use of these drugs when operating dangerous machines and vehicles has been restricted because of their central adverse effects of drowsiness and malaise. The nonsedative antiallergic agents terfenadine and astemizole are free from these adverse effects but have other cardiovascular adverse effects such as palpitations and arrhythmia due to Q-T prolongation. HSR-609, a new nonsedative antiallergic agent with high selectivity for the H_1 receptor, was synthesized by Hokuriku Seiyaku Co., Ltd.

Researchers at Hokuriku Laboratories observed that most antiallergic agents having antihistaminic effects as their main action, which had been developed up to the present, had chemical structures with a basic moiety. Since it is known that these basic compounds easily penetrate into the central nervous system and are metabolized exclusively due to their high lipophilic characteristics, it was thought that the defects of basic antiallergic agents could be eliminated by converting their chemical structures to those of amphoteric compounds (compounds having both a basic and acidic moiety in their molecules). Based on this hypothesis, a classical basic antihistamine, cyproheptadine, was selected as a lead compound and conversion of its chemical structure to compounds having amphoteric moieties was begun. As a result, we obtained a compound which had the following characteristics: 1) less penetrable into the central nervous system; 2) more selective for the H_1 receptor; and 3) less susceptible to metabolic conversion. Thus, the deficiencies of conventional basic antiallergic agents were eliminated. Modifications of the chemical structure of this compound were then carried out in order to enhance potency and prolong duration of action, leading to the discovery of HSR-609 (2).

Pharmacological Actions

Oral pretreatment with HSR-609 inhibited the passive cutaneous anaphylaxis reaction evoked by intravenous injection of dinitrophenylated Ascaris extract (DNP-As) in rats topically sensitized with anti-DNP-As rat serum. The effective dose which produced 50% inhibition (ED_{50}) was 0.31 mg/kg p.o. This efficacy was more potent than those of basic antiallergic agents such as ketotifen fumarate, azelastine hydrochloride, oxatomide and terfenadine. Oral pretreatment with HSR-609 at doses of 0.2 and 2 mg/kg inhibited the increase of dye leakage in nasal perfusate evoked by nasal perfusion of DNP-As in anesthetized rats systemically sensitized with anti-DNP-As rat serum. Oral pretreatment with HSR-609 inhibited the bronchoconstriction evoked by intravenous injection of benzylpenicilloyl bovine serum albumin (BPO-BSA) in anesthetized guinea pigs passively sensitized with anti-BPO-BGG (bovine gamma globulin) guinea pig serum. The ED_{50} of HSR-609 was 0.10 mg/kg p.o. (3).

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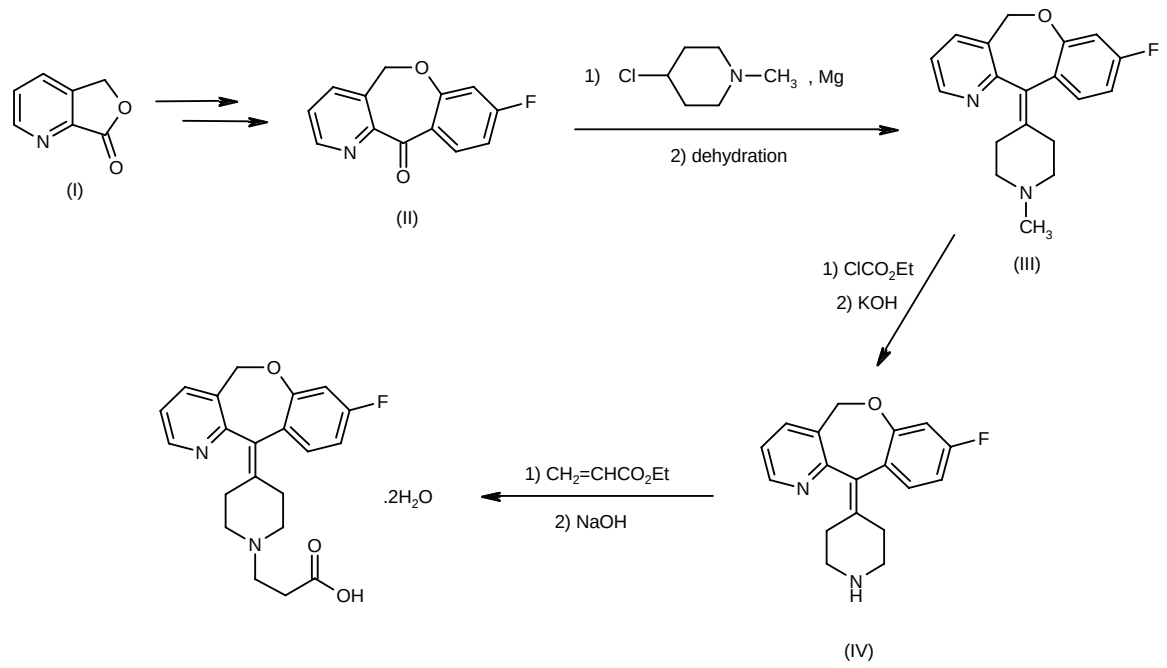
Scheme 1: Synthesis of HSR-609



HSR-609 inhibited the cutaneous reaction induced by intradermal injection of histamine in various species (ED_{50}: mice, 0.021 mg/kg; rats, 0.081 mg/kg; guinea pigs, 0.067 mg/kg; and dogs, minimum effective dose was 0.02 mg/kg). It was confirmed that the antihistaminic action of HSR-609 lasted over 24 hours after oral administration in guinea pigs and dogs (3).

HSR-609 inhibited the contraction of isolated guinea pig trachea induced by the cumulative application of histamine. HSR-609 competitively antagonized the histamine H_1 (H_1) receptor at low concentrations (pK_B: 7.65) and insurmountably at high concentrations (pD_2': 6.71), similar to basic antiallergic agents such as ketotifen fumarate, azelastine hydrochloride, oxatomide and terfenadine (4). Since HSR-609 exhibited slow but reversible dissociation from the H_1 receptor, the long-lasting activity of HSR-609 seemed to be due to this strong binding to the H_1 receptor.

Oral treatment with HSR-609 (10 mg/kg) inhibited eosinophil accumulation into airway cavity elicited by repeated inhalation of ovalbumin in BALB/c mice (Fig. 1) (5). Terfenadine did not affect the leukocyte accumulation even at a dose of 100 mg/kg. Oral treatment with HSR-609 (1 and 10 mg/kg) also inhibited eosinophil accumulation into nasal cavity elicited by the repeated inhalation of ovalbumin and nasal perfusion in Brown-Norway rats. Furthermore, oral treatment with HSR-609 (1, 3 and 10 mg/kg) was shown to inhibit eosinophil accumulation into peritoneal cavity elicited by the intraperitoneal injection of conalbumin-stimulated D10G4.1 cells in AKR/J mice (5).

HSR-609 (1-100 mg/kg p.o.) did not affect general behavior, spontaneous locomotor activities, convulsions, algesthesia, body temperature, spontaneous electroencephalogram (EEG) or barbiturate-induced anesthesia in animal studies (6, 7). This may be due to its low penetration into the central nervous system and its high selectivity for the H_1 receptor (4, 6, 8).

In receptor binding experiments using membrane fractions of rat brain, terfenadine inhibited the binding of [^{3}H]-QNB, [^{3}H]-prazosin, [^{3}H]-spiperone and [^{3}H]-ketanserin to muscarinic, α_1, D_2 and 5-HT_2 receptors, respectively, whereas HSR-609 did not even at a concentration of 10 μM. Thus, HSR-609 was considered to have higher H_1 selectivity than terfenadine (4, 8). Epinastine hydrochloride and ebastine were also less selective than HSR-609 in these experiments (Fig. 2).

HSR-609 at doses up to 10 mg/kg i.v. did not affect the Q-T interval on the electrocardiogram (ECG) in anesthetized dogs and guinea pigs. However, terfenadine and ebastine at doses of 3 and 10 mg/kg i.v., respectively, prolonged the Q-T interval in guinea pigs (Fig. 3). Furthermore, Hey et al. have also reported that terfenadine, ebastine and astemizole prolonged the Q-T interval in guinea pigs (9).

Clinical Studies

Results of phase I clinical studies have confirmed that HSR-609 is well tolerated in healthy male volunteers at single doses up to 40 mg and at multiple doses of 20 mg/day for 7 days.

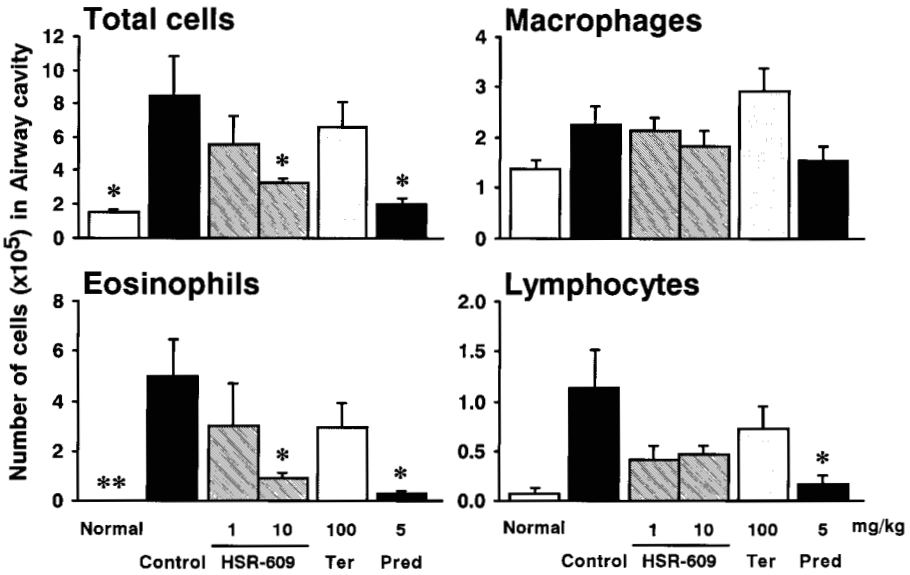


Fig. 1. Effects on antigen (OA)-induced leukocyte accumulation into airway cavity in mice. HSR-609, terfenadine (Ter) and prednisolone (Pred) were orally administered once a day for 10 days. Each value represents the mean ± S.E.M. (n = 5-7). * $p < 0.05$, ** $p < 0.01$ (*vs.* control group).

Pharmacokinetic studies after single doses have revealed that maximum serum concentrations of HSR-609 are reached at 1.0-1.4 h after dosing and decline thereafter with a half-life of 2.73-3.73 h. Within 48 h, 72.2-77.0% of the total dose of HSR-609 was excreted in urine as unchanged drug (10), indicating that HSR-609 is less susceptible to metabolic conversion. In addition, pharmacokinetic parameters and urinary excretion were not influenced by food intake or repeated dosing.

The histamine-induced skin test of HSR-609 was performed with placebo and terfenadine in healthy male volunteers. Inhibition of wheal induced by intradermal injection of histamine began 2 h after administration of HSR-609 at doses of 10 and 20 mg, and at 4 h after administration of 5 mg. Wheal inhibition with all doses lasted for 24 h. The inhibition rates of HSR-609 5, 10 and 20 mg were 67-81, 84-93 and 93-97%, respectively,

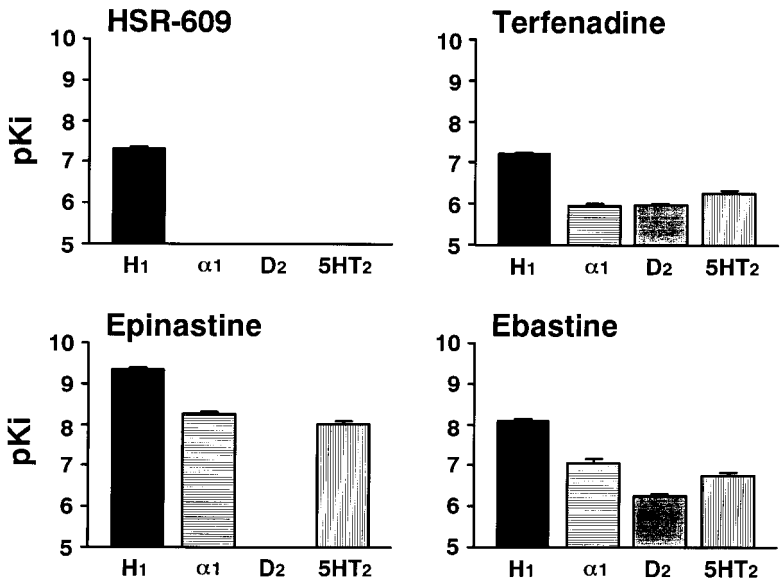


Fig. 2. Affinity for various receptors. Each value represents the mean ± S.E.M. (n = 3-4).

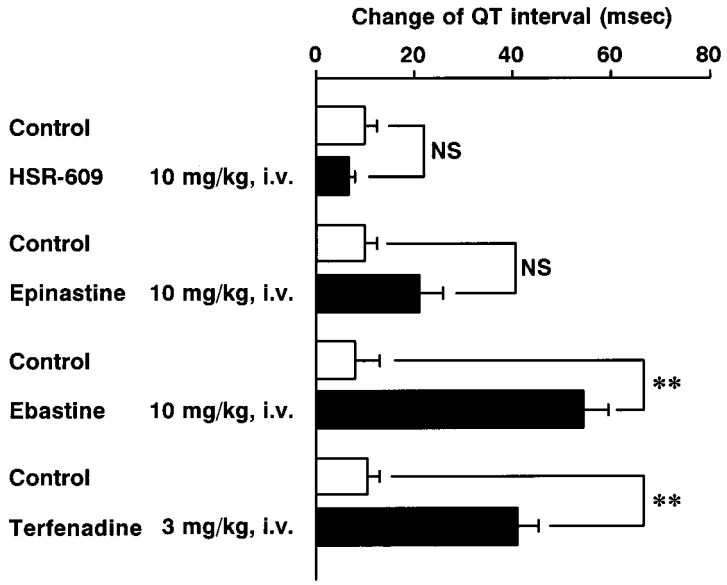


Fig. 3. Effects on Q-T intervals in anesthetized guinea pig ECG. HSR-609, terfenadine, epinastine hydrochloride (epinastine) and ebastine were intravenously administered. Each value represents the mean ± S.E.M. (n = 5). NS: $p > 0.05$, $^{**}p < 0.01$ (*vs.* control group treated with each diluent).

during 4-12 h after administration, and 47, 69 and 63%, respectively, 24 h after administration. On the other hand, the inhibition rate of terfenadine (60 mg) was 60-87% during 4-12 h after administration. Eight hours after administration, there was a statistically significant difference in inhibition between HSR-609 10 mg (92%) or 20 mg (94%) and terfenadine (65%). HSR-609 inhibited the histamine-induced flare in a similar manner as the wheal. These results show that HSR-609 has potent and long-lasting antihistaminic activity compared with terfenadine in humans.

Subjective and objective symptoms were not elicited by any treatments. There was no difference among HSR-609, terfenadine and placebo in the continuous number addition tests. It was suggested that HSR-609, like terfenadine, has no sedative action.

Conclusions

As described above, HSR-609 is a new nonsedative antiallergic agent. Because of its low penetration into the central nervous system, antieosinophilia action, high selectivity for the H_1 receptor, sustained duration of action and less susceptibility to metabolic conversion, HSR-609 is expected to be a useful drug for the treatment of allergic diseases such as urticaria, pruritic dermatitis, rhinitis, conjunctivitis and bronchial asthma.

Manufacturer

Hokuriku Seiyaku Co., Ltd. (JP).

References

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