VUF-K-8788, a Periphery-Selective Histamine H\textsubscript{1} Antagonist With Anti-pruritic Activities

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ABSTRACT—The pharmacological properties of 7-{3-[4-(2-quinolinylmethyl)-1-piperazinyl]-propoxy}-2,3-dihydro-4\textsubscript{H}-1,4-benzothiazin-3-one (VUF-K-8788) were investigated in vitro and in vivo. VUF-K-8788 inhibited \[^{3}\text{H}\]mepyramine from binding to the cell membrane of lung parenchyma (K\textsubscript{i} value: 5.0 nM) and the histamine-induced contraction of isolated guinea pig ileum (pA\textsubscript{2}: 9.71) without affecting ileal contractions induced by acetylcholine, serotonin, KCl and BaCl\textsubscript{2}. The increase of vascular permeabilities induced by histamine and passive cutaneous anaphylaxis (PCA) in guinea pigs were inhibited by VUF-K-8788 in a dose-dependent fashion (ED\textsubscript{50} : 0.24 and 0.26 mg/kg, p.o., respectively). Moreover, the anti-histaminic effect of VUF-K-8788 was also observed in rats. In experiments on the effects on the central nervous system, VUF-K-8788 at 1 mg/kg, p.o. hardly antagonized the H\textsubscript{1} receptor at all in the cerebral cortex of guinea pigs. VUF-K-8788 inhibited the PCA-induced scratching behavior completely without affecting thiopental-induced sleep in mice. These results suggested that VUF-K-8788 would be useful in the treatment of allergic disorders such as atopic dermatitis and eczema.

Keywords: VUF-K-8788, Antihistaminic, Antiallergic agent, Itch, Central nervous system effect

Histamine is known to mediate allergic and inflammatory responses through histamine H\textsubscript{1}-receptors and to play an important role in atopic asthma (1, 2), allergic rhinitis (3), atopic dermatitis (4, 5), eczema (6), urticaria (7), conjunctivitis (8), etc. Consequently, many histamine H\textsubscript{1}-receptor antagonists have been developed. In the treatment of these affections, classical histamine H\textsubscript{1}-receptor antagonists such as diphenhydramine and chlorpheniramine have been widely used for the treatment of allergic rhinitis and skin diseases (9). However, the inhibitory action of such compounds on muscarine and 5-hydroxytryptamine (serotonin) receptors, besides the histamine receptor, and their permeation through the blood-brain barrier (BBB) have the propensity to cause adverse effects on the central nervous system (CNS) (1). Although ketotifen is a more potent and selective histamine H\textsubscript{1}-receptor antagonist than the classical types, it also produces sedation (10, 11).

Recent success in reducing the side effects of antihistamines such as terfenadine (12), cetirizine (2), astemizole (13) and emedastine (14) has made their use possible at relatively high doses in patients with severe allergic diseases such as asthma. The antagonistic effects of some compounds are weaker than those of classical H\textsubscript{1}-receptor antagonists though (15). Moreover, terfenadine and astemizole adversely affect cardiac activities by prolonging the QT interval (16). Thus, there is still a need to develop new H\textsubscript{1}-receptor antagonists.

In atopic dermatitis and eczema, itch is one of the most important symptoms. It is reported that histamine is a major, but not the only, mediator of itch in humans (17) and mice (18). Although histamine H\textsubscript{1}-receptor antagonists are administered to patients and animals, their anti-pruritic effects are often not strong enough. It was suggested that a new drug with anti-pruritic activity would be a wanted therapeutic treatment for atopic dermatitis, eczema and urticaria (19).

In a series of studies on anti-allergic drugs, we have synthesized a series of compounds with quinoline and/or
piperadine moieties that showed anti-allergic effects (20–23). In this study, we investigated the antihistaminic activities of 7-[3-[4-(2-quinolinylmethyl)-1-piperazine]-propoxy]-2,3-dihydro-4H-1,4-benzothiazin-3-one (VUF-K-8788). The chemical structure is provided.

**Fig. 1.** Chemical structure of 7-[3-[4-(2-quinolinylmethyl)-1-piperazinyl]-propoxy]-2,3-dihydro-4H-1,4-benzothiazin-3-one (VUF-K-8788).

MATERIALS AND METHODS

**Animals**

Male Hartley guinea pigs (4-week-old), male Wistar rats (7-week-old), female BALB/c mice (6-week-old), and male ICR mice (6-week-old) were purchased from Japan SLC, Inc. (Hamamatsu). The animals were fed a standard laboratory diet and water in an air-conditioned room at 23 ± 3°C and relative humidity of 55 ± 15%. When the test compounds were given orally, the animals were deprived of food for 18 h before administration of the test compounds. The experiments were carried out in accordance with the Guidelines for the Care and Use of Laboratory Animals of Kowa Co., Ltd.

**Compounds**

VUF-K-8788 and emedastine were synthesized at Kowa Co., Ltd. Ketotifen, terfenadine, chicken egg albumin (OA), concanavalin A (Con A), prednisolone, platelet activating factor (PAF) (Sigma, St. Louis, MO, USA); histamine dihydrochloride (Wako Pure Chemical, Osaka); leukotriene D_4 (LTD_4) (Cayman, Ann Arbor, MI, USA); dinitrofluorobenzene (Nacalai Tesque, Kyoto); Evans blue dye (Tokyo Kasei, Tokyo); and [^3H]-mepyramine (Amersham Pharmacia Biotech, Tokyo) were purchased from the indicated sources. For the in vitro experiments, the test compounds were dissolved in dimethylsulfoxide and subsequently diluted with Tyrode’s solution. For the in vivo experiments, the test compounds were suspended in a 0.5% carboxymethyl cellulose solution.

[^3H]-Mepyramine binding to guinea pig lung parenchyma membranes in vitro

The method is based on that described previously (20). Briefly, a mixture with a total volume of 1.0 ml containing 0.5 nM [^3H]-mepyramine (specific activity: 21 Ci/mmol), guinea pig lung membrane proteins (370 μg/ml) and the test compound in 50 mM Na-K phosphate buffer (pH 7.5) was incubated at 37°C for 30 min. The reaction was stopped by the addition of 5 ml of ice-cold phosphate buffer and then immediately filtered through Whatman GF/C filters. The filters were washed twice with about 20 ml of cold buffer. The retained radioactivity was determined by a liquid scintillation counter after addition of 5 ml of scintillation liquid. In the saturation experiment, 10^{-4} M (R)-(−)-dimethindene was used to define the nonspecific binding.

**Histamine-induced contraction of guinea pig ileum in vitro**

Male Hartley guinea pigs were killed by a sharp blow to the head, and ileum sections (2 cm) were removed immediately. Each segment was tied to a holder and attached to a transducer by means of a thread. The thread was transferred to 20 ml organ baths maintained at 29°C and continuously aerated with 95% O_2 and 5% CO_2 and washed with Tyrode’s solution. The contraction of ileum was measured isotonically (resting tension, 1.0 g). After 30 min of preincubation with the test compounds at different concentrations (10^{-10} to 10^{-2} M), contraction induced by the cumulative addition of histamine (10^{-3} to 10^{-1} M) was obtained. Interference by VUF-K-8788 (10^{-5} M) of the ileal contraction induced by acetylcholine (10^{-4} M), serotonin (3 × 10^{-6} M), KCl (4 × 10^{-2} M) or BaCl_2 (3 × 10^{-4} M) was also investigated.

**Vascular permeability increase induced by histamine and passive cutaneous anaphylaxis (PCA) in guinea pigs in vivo**

The method was based on that described previously (20). Briefly, male Hartley guinea pigs were passively sensitized by intradermal injection of the anti-OA antiserum on dorsal skin. Two days after sensitization, PCA was elicited by injecting OA (1 mg/kg) and Evans blue dye (50 mg/kg) intravenously, and immediately thereafter, 0.3 μg histamine was injected intradermally into the back in a volume of 100 μl. The vascular permeability increase was assessed by measuring the amount of extravasated dye 30 min after antigen challenge as follows. The blue spots were dissected and were dissolved with 1.4 ml of 1 N KOH solution in a stoppered tube at 37°C overnight and 18.6 ml of a mixture of 0.6 N H_3PO_4 solution and acetone (5:13) was added. After vigorous shaking and centrifugation, the amount of dye in the supernatant was determined colorimetrically at 620 nm. Test compounds were given orally 1 h before antigen challenge.

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Thiopental-induced sleep in mice

The method was based on that described by Lysen et al. (24). Briefly, male Hartley guinea pigs were given a certain dose of the test compound orally. One hour after the administration, the animals were sacrificed by decapitation. The cerebral cortex was dissected and homogenized in 5 ml of 50 mM Na-K phosphate buffer (pH 7.5). Triplicate aliquots of homogenate were mixed with 100 µl of [3H]-mepyramine solution (final concentration 0.5 nM). Incubation was continued for 50 min at 37°C. After addition of 5 ml of ice-cold phosphate buffer, the mixture was filtered (Whatman GF/C filters) and the filters were washed twice with 20 ml of cold buffer. The radioactivity retained on the filters was determined with a scintillation counter. Specific binding was defined as the difference between the total counts in the absence of unlabeled ligand and the counts obtained in the presence of 10 µM mepyramine.

Vascular permeability increase in rats

The method was based on that described by Inagaki et al. (25). Wistar rats were injected with 100 µl of rat anti-OA antiserum intradermally. Two days after passive sensitization, OA (10 mg/kg) and a solution of Evans blue dye (50 mg/kg) were administered intravenously. Immediately after the challenge, histamine (3 µg), Con A (30 µg), LTD4 (0.3 µg) and PAF (0.1 µg) were injected intradermally in a volume of 100 µl at an appropriate distance. Thirty minutes later, the dorsal skin was removed and the amount of permeated Evans blue dye was extracted as described above. VUF-K-8788 was administered orally 1 h before the antigen challenge. Prednisolone, a positive control drug, was administered intraperitoneally 2 h before the antigen challenge.

PCA-induced scratching behavior in mice

The method was based on that described by Inagaki et al. (18). Briefly, mouse monoclonal IgE antibodies against dinitrophenyl residue were prepared by culturing a cell line, EC1. The rostral part of the skin on the back of ICR mice was clipped, and 20 µl of a fivefold diluted IgE preparation was injected intradermally. PCA was elicited by injecting 0.25 mg of dinitrophenylated bovine serum albumin intravenously 24 h after the sensitization. Immediately after the antigen challenge, mice were placed in a chamber to observe their behavior. “Non-sensitized” mice received the antigen challenge without sensitization with IgE. Scratching of the reaction site with the hind paws was assessed for 30 min. The test compounds were administered orally 1 h before the antigen challenge.

Table 1. Effects of VUF-K-8788, emedastine, ketotifen and terfenadine on [3H]-mepyramine-specific binding to cell membranes from guinea pig lung

| Drugs       | Kd value (nM) |
|-------------|---------------|
| VUF-K-8788  | 5.0           |
| Emedastine  | 0.3           |
| Ketotifen   | 0.6           |
| Terfenadine | 660           |

Each value represents the mean for two independent binding assays performed in triplicate. The Kd value of [3H]-mepyramine was 3.30 nM, and the slope of Hill plots was 1.005.
respectively. Emedastine, ketotifen and terfenadine also inhibited histamine-induced contraction in the same way. The calculated pA$_2$ and pD'$_2$ values of these drugs are summarized in Table 2. On the basis of the pA$_2$ value, the inhibitory activity of VUF-K-8788 for H$_1$ receptor is more potent than that of emedastine or terfenadine, but slightly weaker than that of ketotifen. VUF-K-8788 at $10^{-5}$ M did not affect the contraction induced by acetylcholine, serotonin, KCl or BaCl$_2$ (data not shown).

### Table 2. pA$_2$ and pD'$_2$ values of VUF-K-8788, emedastine, ketotifen and terfenadine on histamine-induced contraction of isolated guinea pig ileum

| Drugs        | pA$_2$     | pD'$_2$     |
|--------------|------------|-------------|
| VUF-K-8788   | 9.71 ± 0.17| 7.38 ± 0.16 |
| Emedastine   | 9.42 ± 0.25| 8.67 ± 0.10 |
| Ketotifen    | 9.99 ± 0.15| 8.62 ± 0.03 |
| Terfenadine  | 8.17 ± 0.09| 6.64 ± 0.02 |

Each value represents the mean ± S.E.M. of 5 – 7 experiments.

Fig. 2. Effect of VUF-K-8788 on histamine-induced contraction of isolated guinea pig ileum. Each point indicates the mean of 5 – 7 experiments.

Fig. 3. Effects of VUF-K-8788, emedastine, ketotifen and terfenadine on vascular permeability increase induced by histamine in guinea pigs. Each value represents the mean ± S.E.M. from 8 – 10 animals. *P<0.05, **P<0.01 vs control.
Effect on vascular permeability induced by histamine or PCA in guinea pigs

As shown in Fig. 3, VUF-K-8788, emedastine, ketotifen and terfenadine dose-dependently inhibited cutaneous reactions induced by histamine when administered orally 1 h before histamine injection. As summarized in Table 3, the ED$_{50}$ values of VUF-K-8788, emedastine, ketotifen and terfenadine are 0.24, 0.025, 0.019 and 4.4 mg/kg, respectively. In terms of ED$_{50}$ values, the relative potency of emedastine, ketotifen and terfenadine to VUF-K-8788 was 9.6, 12.6 and 0.055, respectively.

When the drugs were administered orally 1 h before the

| Drugs   | Histamine [A] | PCA | Brain [B] | ID$_{50}$/ED$_{50}$ ratio [B/A] |
|---------|---------------|-----|-----------|-------------------------------|
|         | ED$_{50}$, mg/kg, p.o. (95% C.L.) | ED$_{50}$, mg/kg, p.o. (95% C.L.) | ID$_{50}$, mg/kg, p.o. (95% C.L.) |                  |
| VUF-K-8788 | 0.24 (0.10–0.79) | 0.26 (0.14–0.55) | 18.2 (17.5–18.9) | 75.8 |
| Emedastine | 0.025 (0.015–0.044) | 0.011 (0.006–0.017) | 0.59 (0.55–0.65) | 23.6 |
| Ketotifen | 0.019 (0.013–0.030) | 0.014 (0.007–0.028) | 0.23 (0.21–0.25) | 12.1 |
| Terfenadine | 4.4 (2.2–8.2) | 3.6 (0.89–8.7) | >300 (0.55–0.65) | >68.2 |

Fig. 4. Effects of VUF-K-8788, emedastine, ketotifen and terfenadine on PCA in guinea pigs. Each value represents the mean ± S.E.M. from 8–10 animals. *P<0.05, **P<0.01 vs control.
antigen challenge, PCA was inhibited significantly by VUF-K-8788, emedastine, ketotifen and terfenadine (Fig. 4). The ED$_{50}$ values of VUF-K-8788, emedastine, ketotifen and terfenadine were 0.26, 0.011, 0.014 and 3.6 mg/kg, respectively (Table 3).

**Inhibition of [H]-mepyramine binding to guinea pig cerebral cortex ex vivo**

Oral administration of emedastine and ketotifen produced dose-dependent inhibition of the binding of [H]-mepyramine to H$_1$-receptors in guinea pig cerebrum ex vivo at the dose of 0.1 – 1 mg/kg. VUF-K-8788 hardly inhibited the [H]-mepyramine binding at 1 mg/kg, although it did inhibit it at 10 – 50 mg/kg. Terfenadine did not show an inhibitory effect up to doses of 300 mg/kg (Fig. 5). The ID$_{50}$ values of VUF-K-8788, emedastine and ketotifen were 18.2, 0.59 and 0.23 mg/kg, respectively. The ID$_{50}$ values [B] for [H]-mepyramine binding to H$_1$-receptors were compared with the ED$_{50}$ values [A] for vascular permeability induced by histamine in guinea pigs (Table 3). The ID$_{50}$/ED$_{50}$ ratios [B/A] of VUF-K-8788 (75.8) and terfenadine (>68.2) were much larger than that of emedastine (23.6) or ketotifen (12.1).

**Effects on vascular permeability in rats**

The effects of VUF-K-8788 on vascular permeability induced by PCA, histamine, Con A, LTD$_4$ and PAF were examined (Fig. 6). VUF-K-8788, at doses of 10 and 50 mg/kg, significantly inhibited the vascular permeability induced by PCA, histamine or Con A. On the other hand, VUF-K-8788 did not affect the vascular permeability induced by LTD$_4$ or PAF. In contrast, prednisolone inhibited all of the enhanced permeability.

**Effects on scratching behavior**

The scratching behavior associated with the induction of PCA was observed immediately after the antigenic challenge. The incidence of scratching peaked in the first 10 min and decreased thereafter. The number of scratching events was 83 ± 12 in control mice. The effects of VUF-K-8788 and terfenadine on scratching were examined. The results are shown in Fig. 7. VUF-K-8788 inhibited the scratching behavior in a dose-dependent manner, and at a dose of 50 mg/kg, p.o., it suppressed the behavior to the level found in non-sensitized animals. Terfenadine suppressed the scratching behavior to only 55% of the control at 100 mg/kg.

**Effect on thiopental-induced sleep in mice**

The injection of thiopental (40 mg/kg, i.v.) induces sleep in mice. Sleeping time in control mice was 6.9 ± 0.6 min. When VUF-K-8788, emedastine, or terfenadine was administered at 100 mg/kg, there was no significant difference from the control (Fig. 8). On the other hand, the sleeping time was prolonged significantly by ketotifen at a dose of 30 mg/kg, p.o.

**DISCUSSION**

Classical histamine H$_1$-receptor antagonists easily penetrate the BBB to block histamine H$_1$-receptors in the CNS and interact with various receptors such as serotonin, cholinergic, $\alpha$-adrenergic and dopaminergic receptors, causing adverse effects on the CNS, especially sedation (10, 26, 27). The adverse effects have severely limited the use of this medication. Although the newer H$_1$-receptor antagonists such as ketotifen and terfenadine display affinity for the H$_1$-receptor with less interaction with other receptors and fewer side effects on the CNS, it was reported that they still caused sleep probably because of an affinity for cholinergic and serotonin receptors at high doses (28, 29). The newer H$_1$-receptor antagonists are often prescribed for atopic dermatitis and eczema. However, the anti-pruritic effect of these antagonists is not complete (17). New drugs with less CNS-side effect, but showing anti-pruritic properties should be developed (19).

In the present study, the antihistaminic effect of VUF-K-8788 was investigated both in vitro and in vivo. In the in vitro experiments, VUF-K-8788 clearly showed high affinity to H$_1$ receptors and a potent inhibitory effect on the histamine-induced contraction of isolated guinea pig ileum, without affecting ileal contractions induced by acetylcholine, serotonin, KCl and BaCl$_2$. These results indicate that
A Novel H₁ Antagonist VUF-K-8788

VUF-K-8788 is a potent and selective H₁-receptor antagonist. In the in vivo experiments, VUF-K-8788 inhibited the increase in vascular permeability induced by histamine or PCA in guinea pigs in a dose-dependent fashion. It is clear that the H₁-receptor antagonistic action of VUF-K-8788 in vitro contributed to antiallergic and antihistaminic actions in vivo.

Allergic patients in various clinical studies who took antihistamines complained of adverse effects, such as somnolence, because the antihistamines occupied histamine H₁-receptors in the CNS (30, 31). To examine the adverse effects of the test drugs on the CNS, we investigated the inhibition of [³H]-mepyramine binding to histamine H₁-receptors in the cerebral cortex of guinea pigs ex vivo. VUF-K-8788 little inhibited the [³H]-mepyramine binding to histamine H₁-receptors in guinea pig cerebral cortex at a dose of 1 mg/kg, p.o., although it inhibited histamine-induced vascular permeability and PCA at 0.1–1 mg/kg, p.o. The risk of the compounds interfering with the CNS was evaluated based on the potency ratio between the inhibitory effect on vascular permeability induced by histamine in guinea pigs (ED₅₀) and the ex vivo displacement

Fig. 6. Effects of VUF-K-8788 and prednisolone on PCA, and histamine-, ConA-, leukotriene D₄ (LTD₄)-, and platelet activating factor (PAF)-induced cutaneous reactions in rats. Cutaneous reactions were caused by injecting 3 × 10⁻⁵ g/ml of histamine, 3 × 10⁻⁵ g/ml of Con A, 3 × 10⁻⁵ g/ml of LTD₄ and 1 × 10⁻⁵ g/ml of PAF in a volume of 100 μl. Each value represents the mean ± S.E.M. of 7 or 8 rats. *P<0.05, **P<0.01 vs control.
of [3H]-mepyramine binding to H₁ receptors in guinea pig cerebrum (ID₅₀). The ID₅₀/ED₅₀ ratio of VUF-K-8788 was greater than that of emedastine or ketotifen, although it was equal to or less than that of terfenadine. These results suggest that VUF-K-8788 would have less adverse effects on the CNS than the applied anti-histaminic agents, such as emedastine or ketotifen.

PCA and ConA activate mast cells to release histamine that increases vascular permeability (32, 33). PCA-, Con A- and chemical mediators (histamine, LTD₄, PAF)-induced skin reaction systems are useful to evaluate anti-allergic effects in vivo (25). In this study, VUF-K-8788 inhibited the vascular permeability increase induced by PCA, Con A and histamine in rats in a dose-dependent manner, but not that induced by LTD₄ and PAF. This finally suggests that VUF-K-8788 suppresses the increase of vascular permeability through histamine H₁-receptor antagonism.

In our study, we observed some difference between the effective doses of VUF-K-8788 in guinea pigs and rats. The difference might be attributed to the applied doses of histamine (0.3 μg/site vs 3 μg/site), to the affinity of the compound for the receptors of guinea pigs and of rats, or to pharmacokinetics. Martin and Römer also mentioned a difference in the effective dose of ketotifen between species, the dose in guinea pigs being much lower than that in rats (29). Moreover, Barnett and Kreutner compared the effective doses for several antihistamines (ketotifen, terfenadine, astemizole, etc.) in guinea pigs, rats, mice and humans (34), and they concluded that the active doses were smaller in guinea pigs than in the others. Our results in guinea pigs are consistent with the above reports.

Scratching provoked by itching is one of the most aggravating factors in atopic dermatitis and eczema. It has been reported that histamine, serotonin, tryptase, chymase, kinins, prostaglandins, neuropeptides, acetylcholine, cytokines and opioids can induce itch or potentiate histamine release when injected into atopic skin (35). Antihistamines, anti-leukotrienes, opioid antagonists, topical cromolyn, NSAIDs and immunomodulators (i.e., glucocorticoids, cyclosporin A and tacrolimus) have been reported to be helpful in some cases of atopic dermatitis (36). Although immunomodulators may offer symptomatic relief for some patients with atopic dermatitis, the ultimate goal in the management of this disease is the avoidance of pruritus (35). With the recent development of new animal models, a reproducible itch-scratch behavioral response to pruritogenic stimuli has been elicited (18, 37). Kuraishi et al. reported that the itch-scratch behavioral response in ICR mice was induced by subcutaneous injection of pruritogenic agents, compound 48/80 or substance P (37). Sugimoto
et al. also showed that scratching behavior in BALB/c mice was caused by rostral back injection with compound 48/80 or histamine (38). They suggested that mast cell-derived mediators participate in the scratching behavior. In our experiments, VUF-K-8788 markedly inhibited the scratching behavior induced by PCA in a dose-dependent manner and suppressed it to the level of non-sensitized animals without affecting thiopental-induced sleep. On the other hand, terfenadine showed only partial inhibition of scratching behavior. In the same experimental condition, Inagaki et al. indicated that scratching behavior induced by PCA in ICR mice was not inhibited completely by terfenadine in spite of abolishment of the vascular permeability induced by PCA (18). These authors suggested that in addition to H1 antagonism, another mechanism(s), such as H3 antagonism, would be necessary to inhibit the scratching behavior completely, as the co-administration of terfenadine and ranitidine, H2 antagonist, synergistically suppressed the scratching behavior. The precise mechanism including effects of VUF-K-8788 on H2 receptor and on mast cells should be investigated further. In our preliminary study, VUF-K-8788 inhibited histamine release from cultured mast cells in a concentration dependent manner (10-6 – 10-4 M). One part of the anti-pruritic mechanism might be attributed to the inhibition of the release of the mast cell-derived mediators. Although the anti-pruritic mechanism of VUF-K-8788 is not clear yet, VUF-K-8788 seems to be a promising candidate for the treatment of atopic dermatitis and eczema, as there is currently no drug that potently inhibits the itching relating behavior without affecting the CNS (38 – 40).

In conclusion, VUF-K-8788 was shown to be a potent and selective histamine H1-receptor antagonist without anti-cholinergic or anti-serotonin activity. After systemic administration in guinea pigs, VUF-K-8788 hardly antagonized the CNS H1 receptor at the dose in which VUF-K-8788 showed anti-histaminergic effect. Moreover, VUF-K-8788 inhibited the scratching behavior without affecting thiopental-induced sleep in mice. These results suggested that VUF-K-8788 would be useful in the treatment of allergic disorders such as atopic dermatitis and eczema.

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