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Research Article

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Effective Treatment for Itching Caused by Atopic Dermatitis

Masanori Somei,[1*] Hiizu Somei,[1] Kazuko Somei,[1] & Yoshio Tanaka[2]

[1]*SOMEIYAKKO Kenkyusho, 56-7 Matsuhidai, Matsudo, Chiba 270-2214, Japan*
[2]*Prof. of Pharmacology, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan*

[*]Corresponding author: Masanori Somei SOMEIYAKKO Kenkyusho, 56-7 Matsuhidai, Matsudo, Chiba 270-2214, Japan.

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Abstract

1-Hydroxy-N-acyltryptamine (VED#2) and N-acyltryptamine (VED#1) are low molecular weight organic compounds, and they can instantly eliminate itching caused by atopic dermatitis. They are effective medicine candidates that are safe, inexpensive with no side effects. They are molecules that any synthetic chemist can easily synthesize. So far, they have helped more than 1,000 people suffering from the disease.

The number of patients with atopic dermatitis continues to increase year by year. In 2025, it is estimated that there are 100 million patients worldwide. Patients suffer from itching every day. Sleep is particularly disturbed at night, which interferes with daytime work and research.

Keywords: Itching, Atopic dermatitis, 1-Hydroxyindoles, 1-Hydroxy-N-acyltryptamine, N-Acyltryptamine, Vasodilator, alpha2-blocker, VED

Introduction

Even now, the physiological mechanism, cause, and action of itching remain unknown [1]. In case that histamine is the cause, it can be cured with antihistamines. Many treatment drugs have been developed and are in use, such as steroids, Corectim, Moizerto and Dupilumab, an antibody drugs. Genetically modified drug discovery research is being actively conducted to suppress itching by targeting causative substances such as interleukin 4, 13, and 31,and new drugs are being developed almost every year. However, an effective drug without side effects has yet to be discovered, and patients continue to suffer every day [1-4].

The authors are organic chemists, and suffer from atopic dermatitis, like many others, continued to receive treatments from dermatologists, but the prescribed medicines were hardly effective, and we suffered every day for years. We calmly observed, analyzed, and discussed the cause of their itching from the view point of organic chemists for a long time. And came up with the hypothesis that the itching could be cured by synthesizing a substance that functions to eliminate active oxygen, improve blood flow, prevent blood coagulation, block α2 receptor and dilate blood vessels, simultaneously.

Fortunately, one of the authors is a synthetic organic chemist and can create compounds as they wish. However, what kind of compound should he synthesize as a target compound to stop itching? He was undecided about the direction of his research.

The authors thought that in order to minimize the side effects of the target molecule, it would be necessary to produce it from a substance that exists in the human body. Many substances are known to act as active oxygen scavengers in the body, including vitamins, carotenoids, polyphenols, glutathione, superoxide dismutase, and so on. As a vasodilator, an α2 blocker, yohimbine has long been known as a folk medicine.

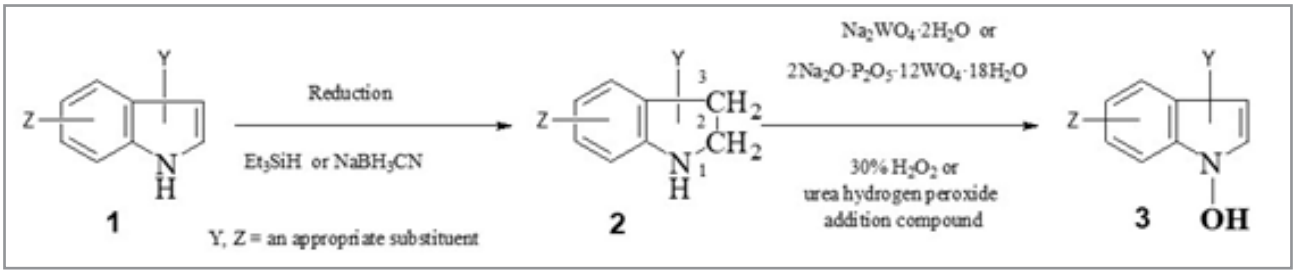
We decided to try a completely new idea that deviated from conventional wisdom, focusing on the essential amino acid tryptophan. Tryptophan has a unique structure called an indole skeleton in its molecule, and is a component of many alkaloids, and is useful to society as a folk medicine and pharmacologically active substance. Furthermore, tryptophan is converted into substances such as serotonin, melatonin, NMN (β-nicotinamide mononucleotide) and so on during metabolic processes in the human body, fulfilling essential functions for the human body [5-6]. We have expected that tryptophan derivatives may have some of these functions.

It is well known that indole skeleton, the mother nucleus of the molecular structure, is easily oxidized by air (oxygen). Therefore, the author determined that it was the ideal mother nucleus to act as an active oxygen scavenger. The author also hypothesized that the substance "X" that is produced after reacting with active oxygen plays an important role in the body by improving blood flow and dilating blood vessels [7].

The chemical structure of the compound "X" was assumed to be that of a 1-hydroxyindole compound.1-Hydroxyindoles are a fictitious group of compounds that nobody had ever seen before; they have never been isolated as natural products, and no method for their synthesis [8-10].

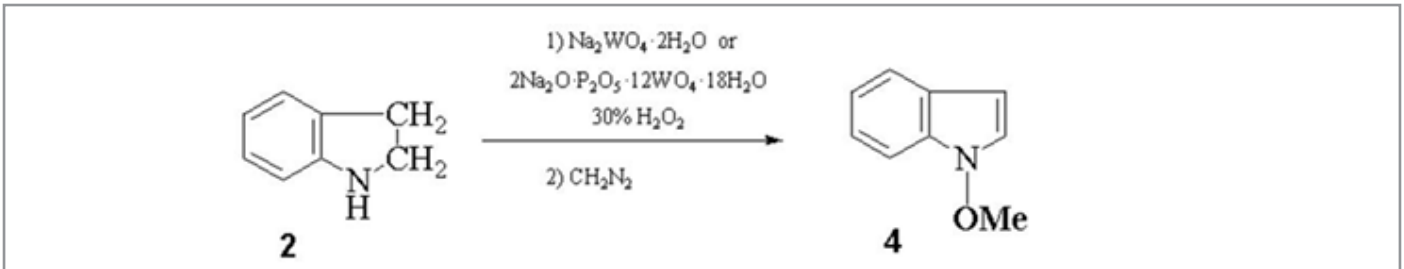
The first step in research began to find a synthetic method for the unprecedented 1-hydroxyindole. As a result of 30 years of repeated challenges and failures, we were fortunate enough to develop a unique synthetic method for synthesizing the desired 1-hydroxyindole compound group, as shown in Scheme 1 [11-13].

Scheme 1 General Synthetic Method for 1-hydroxyindole



The first step is the reduction of indole (1), converting to 2,3-dihydroindole (2), then oxidize 2 by reacting with 30% H2O2 aqueous solution using Na2WO4 · 2H2O as a catalyst to produce 1-hydroxyindole (3). In the case of Y = Z = H, the compound 3 obtained was extremely unstable, and rapidly decomposed in air to tar. It was found that this instability was the reason why the discovery of a synthetic method was prevented [10].

Table 1 General Synthetic Method for 1-hydroxyindole



Entry	Oxidizing Reagent (mol eq.)		Solvent	Reaction Temp. (°C)	Yield (%) of 4	Yield (%) of 2
1	$Na_2WO_4·2H_2O$ (0.1)	30% H_2O_2 (1)	MeOH-H_2O (10:1, v/v)	13	15	21
2	〃	〃 (3)	〃	18	35	5
3	〃	〃 (10)	〃	17	50	0
4	$2Na_2O·P_2O_5·12WO_4·18H_2O$ (0.2)	30% H_2O_2 (1)	〃	14	26	29
5	〃	〃 (3)	〃	15	41	11
6	〃	〃 (10)	〃	15	58	0

We found when the 1-hydroxy group was alkylated or acylated, it became stable and turned into molecules that could be handled normally in the air. Therefore, to develop a general synthetic method for 1-hydroxyindole (3), we adopted a method in which after generating 3, CH2N2 was immediately added to the reaction mixture solution. As a result, 1-hydroxyindole (3)

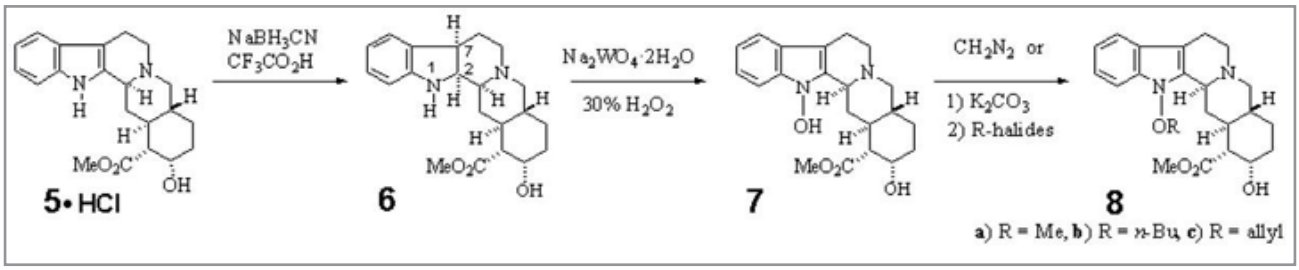
was isolated as stable 1-methoxyindole (4). Some of the reaction conditions examined are shown in Table 1. As a result, the conditions of entries 3 and 6, which gave the highest yield of 4, were determined to be the optimal conditions for the synthesis of 1-hydroxyindole and as a general synthetic method.

Thus, we could establish the original method to obtain previously unknown 1-hydroxyindole compounds which are treasure trove of discovering new biologically active compounds only by first converting any indole compounds into a 2,3-dihydroindole form, and then reacting it with a 30% H2O2 aqueous solution using either Na2WO4·2H2O or 2Na2O· P2O5·12WO4·18H2O as a catalyst [14, 15].

We next focused on yohimbine (5), a well-known herbal medicine and an α2 blocker, which has been used to treat erectile dysfunction (ED, peripheral vasodilator) [16-18]. Yohimbine (5) is known to be sensitive to chemical structural modifications, and its α2 blocker activity is lost simply by changing the hydrogen at the position 1 to a methyl group. But we wondered what happens when the methyl group is changed to a hydroxyl group? We decided to investigate this question.

We applied our 1-hydroxyindole general synthetic method to 5 in order to obtain 1-hydroxyyohimbine (7), the N(1)–OH form, which is expected to be produced when 5 scavenges reactive oxygen species [19]. As shown in Scheme 2, NaBH3CN reduction of yohimbine·hydochloride (5·HCl) produced quantitatively 2α,7α-dihydroyohimbine (6), which was then reacted with 30% H2O2 aqueous solution using Na2WO4·2H2O as a catalyst. The desired novel 1-hydroxyyohimbine (7) was prepared for the first time in 86% yield. The good news was that we found the α2 blocker activity of 7 was maintained without diminishing. Even better, the toxicity of 5 was attenuated in 7. Thus, we could discover that 7 may be a new safe ED treatment medicine [19, 20].

Scheme 2 Synthesis of 1-hydroxyyohimbine Derivatives



The reaction of 7 with CH2N2 afforded the corresponding 1-methoxyyohimbine (8a). In the presence of K2CO3, various alkyl halides (R-halides) reacted with 7 and afforded 1-alkyloxyyohimbines (8b,8c) in excellent yields. Their α2 blocker action were almost equal with that of 7 and the data are summarized in Table 2. Whether they have other useful pharmacological actions remains under investigation.

Table 2: Effect of Yohimbine Derivative on the Contraction Induced by Clonidine in Rat Thoracic Aorta.

Compound	n	Tension (g)		Relaxant response (%)[b]
		80 mM KCl	Clonidine (10^{-7} or 10^{-6} M)[a]	
7	3	1.36 ± 0.12	1.35 ± 0.03	101.9 ± 3.7
8a	3	1.60 ± 0.20	1.09 ± 0.05	98.2 ± 1.8
8b	3	1.46 ± 0.37	0.98 ± 0.11	101.8 ± 1.8
8c	3	1.38 ± 0.24	1.10 ± 0.15	101.5 ± 1.5

a) Clonidine-induced contraction was attained by 10^{-7} M or 10^{-6} M in the presence of N^{G}-nitro-L-arginine methyl ester (L-NAME, 10^{-4} M).

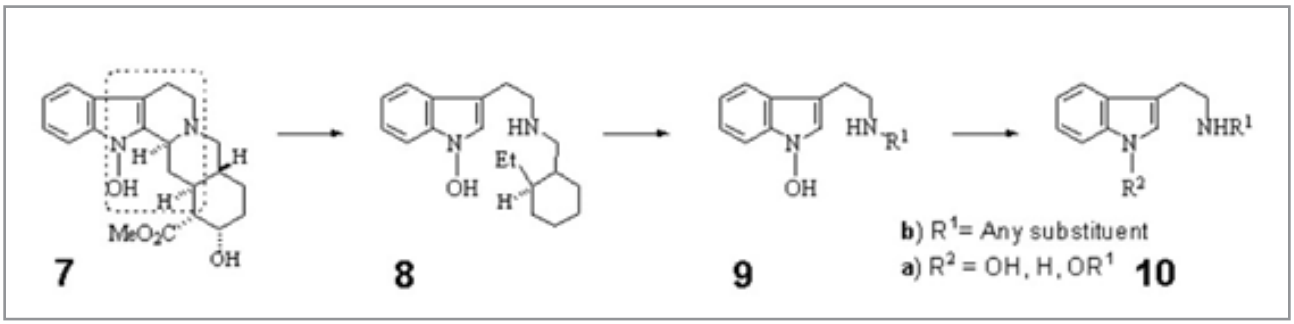
b) Responses to yohimbine derivatives are expressed as % relaxation to the maximum relaxation by 10^{-5} M yohimbine. Results are represented as mean ± S.E.M. of n number of experiments.

Let us now consider the production of 5. Generally speaking, substances derived from natural sources have production drawbacks. As 5 is an alkaloid contained in the bark of an evergreen tree called yohimbe, the amount of 5 contained in plants varies from season to season depending on the weather and growing conditions. Furthermore, various chemical processes are

required to extract the active ingredients from the bark and crystallize them. The handling and purification process require that the health of workers and the environment are taken into consideration. Therefore, the manufacturing costs are inevitably high and vary depending on the season and climate conditions.

In addition, when using plants as raw materials, there is a concern that using large quantities of them could lead to the extinction of the plants. In order to increase the amount of medicines needed to save a large number of patients, it is more advantageous to use chemical synthetic methods that use cheap raw materials that can be supplied steadily throughout the year. With these idea in mind, we compared the author's hypothetical metabolic process of tryptophan with the molecular structure of yohimbine.

Scheme 3 Imaginary Searching Core Structure for α2 Blocker of Yohimbines



In order to find the core structure of the action of yohimbines, we considered it as shown in Scheme 3. Focusing on the structure enclosed by the dotted line in 7, we inferred structure 8, then structure 9, and finally arrived at compound 10. 10 is a tryptamine derivative.

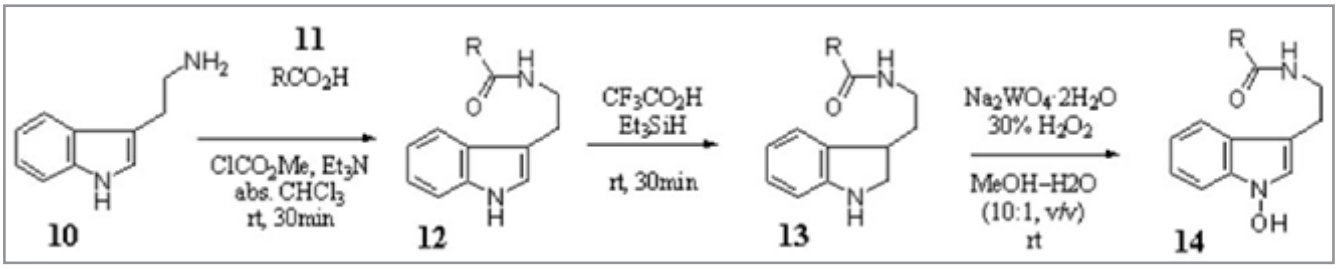
Tryptamine (10: R1,R2 = H) itself exists in the body as a trace biogenic amine, but it is an unstable substance that is extremely difficult to handle. When isolated, it forms colorless crystals, but is oxidized by oxygen in the air, quickly turning into a black, sticky liquid. Due to this instability, its pharmacological tests could not be carried out until now. The author thought this is the reason why the hidden potential in this precious treasure could not be discovered.

In order to make it possible to freely handle this unstable and easily oxidizable tryptamine, the author came up with the idea of creating 1-hydroxytryptamine derivative, which is presumed to be produced as the result of functioning as an antioxidant. Or adding an acyl group to Nb to make it resistant to oxidation. We set up a research policy to synthesize Nb-acyl-1-hydroxytryptamines, which are expected to be formed by oxidation in the body, and to investigate their physical properties and pharmacological actions.

As mentioned earlier, the 1-hydroxyindoles are imaginary compounds and unstable so that they have never been isolated as natural products. It was unclear whether Nb-acyl-1-hydroxytryptamines were stable substances that could be isolated, or whether they were unstable and could not exist in the real world. As shown in Table 3, tryptamine (10) was first converted into the stable Nb-acyltryptamine (12) compounds group using an acid anhydride method with RCO2H (11). Then they were reduced with Et3SiH in the presence of CF3CO2H to obtain the Nb-acyl-2,3-dihydrotryptamine (13) compounds group. Next, the oxidation was carried out with 30% H2O2 aqueous solution using Na2WO4·2H2O as a catalyst, and the desired unprecedented Nb-acyl-1-hydroxytryptamine (14) group compounds were obtained in good yield. Fortunately, all Nb-acyl-1-hydroxytryptamines were stable and crystals. The α2 blocker activity of these compounds was examined. To our surprise, every compound showed the results shown in Table 4. Assuming that the α2 blocker activity of yohimbine is 100%, 14b, 14c, and 14d showed 25.6, 66.2, and 79.0% of those of yohimbine activity, respectively. Surprisingly, even when the N(1) substituent was a hydrogen instead of a hydroxyl group, the compounds showed almost the same α2 blocking effect as the hydroxyl group substituent. Thus 12b, 12c, and 12d demonstrated 26.9%, 70%, and 80.7% of those of yohimbine activity.

Interestingly, the strength of the α2 blocking effect differs depending on the number of carbons in the Nb acyl side chain, increasing as the number of carbons increases from 2 to 7, and reaching its highest strength at 9, reaching about 80% of that of yohimbine.

Table 3: Synthesis of N-acyl (12) and 1-hydroxy-N-acyltryptamines (14)



Carboxylic Acid 11	R	Compound 12	Yield (%)	Compound 13	Yield (%)	Compound 14	Reaction Time (min)	Yield (%)
11a	$-CH_2CH_3$	**12a**	94	**13a**	98	**14a**	15	67
11b	$-(CH_2)_3CH_3$	**12b**	91	**13b**	86	**14b**	15	61
11c	$-(CH_2)_5CH_3$	**12c**	95	**13c**	87	**14c**	30	68
11d	$-(CH_2)_7CH_3$	**12d**	93	**13d**	78	**14d**	30	61

In this way, we were able to discover new α2-blockers, 12 and 14, which have a simple molecular structure rather than a molecule with a complex structure like yohimbine. Compounds 12 and 14 are easy to synthesize, inexpensive, and easy to mass-produce, and meets the requirements for use as a medicine

Table 4: α2-Blocker Effect of Yohimbine Derivatives

Yohimbine: 100%			
14b	25.6 ± 6.0%	**14d**	79.0 ± 13%
12b	26.9 ± 11.4%	**12d**	80.7 ± 2.5%
14c	66.2 ± 13.9%		
12c	70.0 ± 6.9%		

Whenever the author synthesized a new compound, he mixed it with petrolatum to make a cream and applied it to the itchy part of his skin. Then, when he applied the cream containing either 14d or 12d, it was a memorable and astonishing moment. The itching disappeared the moment he applied it [21, 22]. Since then, the safety of 14d and 12d were tested at a public institution. The safety tests on goats and humans were conducted as part of a project to green the Gobi Desert in China. The results were the followings.

Compounds 12 and 14 are vasodilators and can be used to treat erectile dysfunction. Therefore, compounds 12 and 14 were named VED, combining the first letters of the word's vasodilator and erectile dysfunction. Compound 12d was designated VED#1, and compound 14d was designated VED#2.

Safety of VEDs

1. Ames' Test Negative
2. Human skin patch test Safe product
3. Toxicity test (mouse, 2,000 mg/single dose
   - Oral administration toxicity test, 12 mice, 14 days observation Post-necropsy No deaths.
   - No abnormal findings at necropsy.
4. Goats taking (1 mg/day) for 4 years. No abnormalities.
   - Improved reproductive ability, reproducibility confirmed for 4 years. All baby goats born healthy. No abnormalities.
5. Human taking (1 mg/day) for 20 years and 236 days (July 5th, 2024) Good health (no ED), healthy, no abnormalities.

Since the safety was confirmed, we have created a skin care cream containing 12d and named it "Ritayakko VED cream". They are provided to people suffering from itching. Consequently, the cream has cured the itching that dermatologists could not cure, contributing to improving people's quality of life. Below we will introduce only 8 of the 1,000 cases for which we received thank-you letters and e-mails.

Case 1: An Infant: From his Mother

My child's atopic dermatitis was so itchy that even with the medicine prescribed by the dermatologist, he couldn't sleep. He cried all night, so I was suffering every day. I applied "Ritayakko cream", and the itching went away with just one application and he fell asleep. It was like magic, I was amazed. Thank you very much.

Case 2: Another Toddler: From her Mother.

My child suddenly developed a rash and felt very itchy. She was given medicine by the doctor at the clinic, but the itching did not stop. I applied the "Ritayakko cream" I purchased the other day, and the itching went away immediately, so I am very grateful. I will continue to use it in the future.

Case 3: From 45-year-old Clinical Doctor for Atopic Dermatitis.

- My daughter has atopic dermatitis, but the itching did not disappear prescribing steroid and other medicines. I also applied the cream to the rash on her face at night, and the rash improves in the morning. It's amazing that it's good for both atopic dermatitis and rash.

- It's effective for treating age spots.
- Currently, in addition to treating dark spots, I am using it for patients whose skin has thinned due to long-term use of steroids. My impression it is a mysterious topical agent.

Case 4: From 49-year-old Man.

- At the age of 7, I developed atopic dermatitis. Since then, I has received various treatments such as steroids, and other medicines at a dermatologist, but the irritation is so strong that I could not sleep. I have suffered for 40 years.
- Started using the "Ritayakko cream" on August 4, 2016. As soon as I applied the cream, the itching stopped and I stopped scratching. Thanks to it, my wounds began to heal. I can sleep at night and my physical condition has improved.
- September 26. Every time I get itchy, I applies the cream and it goes away immediately. My skin is also getting clearer. Thank you. Thank you.
- November 21. My skin is in great condition. My work is also going well.

Case 5: From 31-year-old Man.

- I had been itching and unable to sleep well for days. I work in the customer service industry, so I was having trouble with the effects of lack of sleep.
- After using the "Ritayakko cream" for 10 days, I am definitely feeling better. When I apply the cream, the itching subsides immediately, so I can sleep at night.
- After two months, I am feeling much better.
- After three months, I am completely better. I am trying to improve my physical condition so that I don't end up in that state again. I am healthy and working hard at serving customers.

Case 6: From 64 Years old Woman.

Recently, the whole family has been using this Recently, the whole family has been using "Ritayakko cream", and it has become like a talisman.

My mother in particular has suffered from allergies and atopic dermatitis for many years, just like me. I wonder if this cream also has the effect of fading blemishes? My mother is surprised that her allergies have disappeared, and more than anything, that her blemishes have faded. I am also surprised at how amazing "Ritayakko cream" is.

As we suffer from skin diseases, this cream is something we cannot do without. We would appreciate your continued support in the future. With gratitude., and it has become like a talisman.

Case 7: From 45 Years Lady.

Her skin on the left leg was abnormal due to atopic dermatitis, with fish-like scales, hardness, and severe itching (Figure 3). After applying "Ritayakko cream" for six months, her skin healed beautifully (Figure 4). The itching and the wounds were cured.

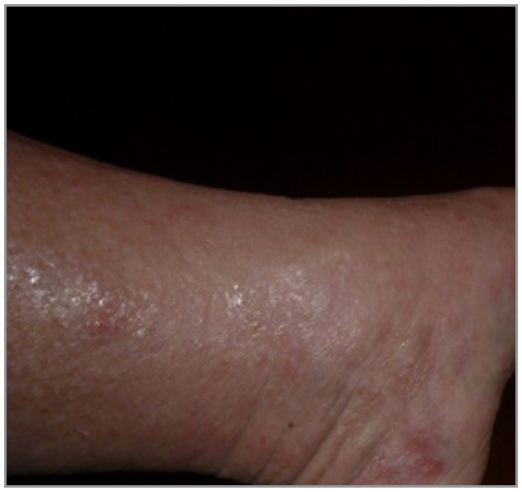


Figure 3 22 August, 2017

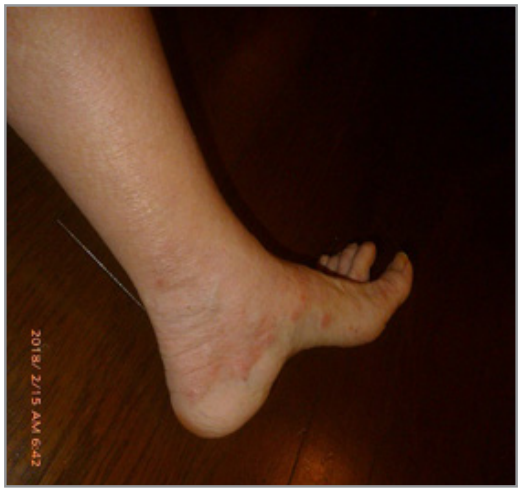


Figure 4 25 February, 2018

Case 8: From 72 Years old Woman.

It's been a month since I started taking your nutritional supplement and applying "Ritayakko cream" to my hands and feet. I'd like to let you know how it's going so far.

I've noticed that my allergies are getting better day by day, especially since I started taking the nutritional VED supplement. I only take it when I feel tired, so I don't take it at the same time every day.

Still, I'm really happy that the effects are so clear, and I hold my hands over them and stare at them. To my surprise, I was completely cured in about 20 days.

I had itchy eczema in various places on my feet, and it was depressing because it didn't go away, but it's all gone now and it's cleared up. My hands have been cured for the first time in 15 years. I've been suffering from it for a long time and I've felt pathetic and sad. I'm finally freed from the depths of despair. I can't believe it.

I want to tell people with allergies all over the world. Everyone says that it's not cured. Until now, I've tried all kinds of things that were said to be good, but I've ended up going back to steroids. And it got worse again - it was a cycle.

Conclusion

The authors have succeeded in developing Nb-acyltryptamine (12d, VED#1) and 1-hydroxy-Nb-acyltryptamine (14d, VED#2) as treating itching caused by atopic dermatitis. These molecules are low-molecular-weight organic compounds with simple chemical structures, as safe, inexpensive, and effective substances that can eliminate the itching caused by atopic dermatitis [20-22].

VEDs are not just an itching remedy. They eliminate active oxygen, improve blood flow, inhibit blood clotting, and potent inhibitor of platelet aggregation [23]. Their ability to increase metabolism helps to remove age spots, heal wounds and repair scars [24]. In addition, they can treat muscle pain, joint pain, lower back pain, and improve hair growth [25, 26]. Quite recently, Korean researchers reported that 1-hydroxy, 1-alkoxy, and 1-acyloxyindole derivatives were suppressor against tumor growth through inhibiting lactate dehydrogenase [27].

We hope that VEDs will relieve the 100 million atopic dermatitis patients around the world from the suffering of itching, as well as resolve problems associated with aging and skin and physical problems, thereby improving the quality of life of many patients [28].

EXPERIMENTAL; Yohimbine α2-blocker Test Method

Animals: Male Wistar rats were used in the present study. Animals were housed under controlled conditions (21–22ºC, relative humidity 50±5%). Food and water were freely available to all animals. This study was performed according to the Guideline for the Care and Use of Laboratory Animals of Toho University School of Pharmaceutical Sciences (which is accredited by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan), and the protocol of this study was approved by the Institutional Animal Care and Use Committee.

Preparation of Rat Thoracic Aortic Rings

Rats were killed by cervical dislocation and exsanguinated from the common carotid arteries. A section of the thoracic aorta between aortic arch and diaphragm was carefully removed and immersed in oxygenated Krebs-HEPES solution of the following composition (in mM): NaCl, 126.9; KCl, 5.9; CaCl2, 2.36; MgCl2, 1.18; HEPES, 10.03 and glucose, 11.8 (pH=7.4). The aorta was cleaned of loosely adhering fat and connective tissues and cut into ring segments about 2 mm in length. In this series of experiments, the endothelium was not removed.

Measurement of Tension Changes

The aortic tissue was then mounted using stainless steel hooks (outer diameter, 200 μm) under the resting tension of 2.0 g in a 5 mL organ bath (UC-5, UFER Medical Instrument, Kyoto, Japan) containing normal Tyrode's solution (mM): NaCl, 158.3; KCl, 4.0; NaHCO3, 10.0; NaH2PO4:, 0.42; CaCl2, 2.0; MgCl2, 1.05 mM, glucose, 5.6), which was continuously gassed with 95% O2–5% CO2 being kept at 37±1ºC (pH=7.4). Tension changes of the muscle preparation were isometrically recorded with a force-displacement transducer (T7-8-240; Orientec, Tokyo, Japan; TB-612T, Nihon Kohden, Tokyo, Japan) connected to a carrier amplifier (AP-600G/AP-621G, Nihon Kohden, Tokyo, Japan; Signal Conditioner: Model MSC-2, Labo Support, Suita-City, Japan). Vascular preparations were equilibrated for 90 min in normal Tyrode's solution, which was exchanged every 20–30 min. Before starting assessment of yohimbine derivatives, aortic preparations were contracted with isotonic high-KCl (80 mM) Tyrode's solution (mM: NaCl, 82.3; KCl, 80.0; CaCl2, 2.0; MgCl2, 1.05; NaH2PO4, 0.42; NaHCO3, 10.0 and glucose, 5.6), in order to confirm the muscle normal contractility. After washing out, experiments were started after a subsequent 30 min equilibration period.

Assessment of Relaxant Potencies of Yohimbine Derivatives

Aortic ring preparations were contracted with an α2-adrenoceptor (α2-AR) agonist clonidine (10-7–10-6 M) in the presence of a NO synthase inhibitor nitro-L-arginine methyl ester (L-NAME, 10-4 M). When the sustained contraction induced by clonidine reached a steady-state level, yohimbine derivatives (10-5 M) were applied to the bath solution. When the relaxant effects of yohimbine derivatives reached their maximum level, yohimbine at 10-5 M was applied. The steady-state tension level before application of each yohimbine derivative and the tension level corresponding to yohimbine-induced maximum relaxation were defined as 0% and 100% relaxation, respectively. Relaxant potency of tested yohimbine derivatives was expressed as percentage relaxation to the maximum response to 10-5 M yohimbine.

Drugs

The following drugs were used in the present study: clonidine hydrochloride (Sigma-Aldrich, St. Louis, MO, USA); yohimbine hydrochloride (Wako Pure Chemical Industries, Ltd., Osaka, Japan); NG-nitro-L-arginine methyl ester hydrochloride (L-NAME) (Dojindo Laboratories, Kumamoto, Japan). Yohimbine derivatives tested in this study were dissolved in pure dimethyl sulfoxide (DMSO) at 10-2 M. Final DMSO concentrations in the bath medium did not exceed 0.1%, which did not affect the vascular responses. Other drugs were dissolved/diluted in/with distilled water. All drugs are expressed in molar concentrations (mol/L, M) in bathing solution.

Statistics

Data are presented as means±S.E.M. and n refers to the number of experiments.

Experimental; Chemical Part

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-420 spectrophotometer, and 1H-NMR spectra with either a JEOL JNM FX100S or JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. MS spectra were recorded on a JEOL SX-102A spectrometer. Column chromatography was performed on silica gel (SiO2, 100-200 mesh, from Kanto Chemical Co. Inc.). Preparative thin-layer chromatography (p-TLC) was performed on Merck Kieselgel GF254 (Type 60)(SiO2).

1-Methoxyindole (4) from 2,3-dihydroindole (2) — General method A (Table 1, Entry 1) : A solution of Na2WO4·2H2O[70] (2.834 g, 8.42 mmol) in H2O (40.0 mL) was added to a solution of 2 (5.015 g, 42.1 mmol) in MeOH (375 mL). 30% H2O2 (47.657 g, 421 mmol) was added to the resultant solution at 0 °C with stirring. After stirring for 15 min at rt (16 °C), K2CO3 (20.456 g, 147 mmol) and a solution of Me2SO4 (7.972 g, 631 mmol) in MeOH (25.0 mL) were added to the reaction mixture.

After stirring for 90 min at rt (16 °C), brine (330 mL) was added and the whole was extracted with CHCl3 (200 mL x 3). The extract was washed with brine, dried over Na2SO4, and evaporated under reduced pressure to leave a black oil, which was column-chromatographed on SiO2 with CHCl3–hexane (1:4, v/v) to give 4 (3.361 g, 15%). 4: colorless oil. Mass and all spectral data are identical with those reported by Acheson et al [29, 30].

General Method B (Table 1, Entry 3): A solution of Na2WO4·2H2O (13.2 mg, 0.04 mmol) in H2O (0.5 mL) was added to a solution of 2 (47.5 mg, 0.39 mmol) in MeOH (4.0 mL). 30% H2O2 (452.5 mg, 4.0 mmol) was added to the resultant solution at 0 °C with stirring. After stirring for 30 min at rt (17 °C), ethereal CH2N2 (excess) was added to the reaction mixture with stirring at rt until the starting material was not detected on tlc monitoring. Brine was added and the whole was extracted with CH2Cl2. The extract was washed with brine, dried over Na2SO4, and evaporated under reduced pressure to leave oil, which was purified by p-TLC on SiO2 with CH2Cl2–hexane (7:3, v/v) as a developing solvent. Extraction of a band having a Rf value of 0.92–0.79 with CH2Cl2 afforded 4 (29.6 mg, 50%).

Entry 6: In the same procedure for Entry 3, 2Na2O·P2O5·12WO4·18H2O (23.8 mg, 0.007 mmol), 2 (50.3 mg, 0.42 mmol), 30% H2O2 (479.2 mg, 4.22 mmol) were used. And the same work-up as Entry 3 afforded 4 (35.9 mg, 58%).

2α,7α-Dihydroyohimbine (6) from yohimbine (5·HCl) — General Procedure: NaBH3CN (36.4 mg, 0.55 mmol) was added to a solution of 5·HCl (107.6mg, 0.28 mmol) in CF3CO2H (2.0 mL) at 0°C. The mixture was stirred at rt for 3 h. After evaporation of the solvent, the whole was made alkaline with initially aq. 8% and then 0.8% NaOH under ice cooling, and extracted with CHCl3. The extract was washed with brine, dried over Na2SO4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO2 with AcOEt–CHCl3–MeOH–28% aq. NH3 (51.5:46:5:0.5, v/v) to give 6 (98.0 mg, 100%). 6: mp 190—193°C (colorless fine needles, recrystallized from AcOEt–hexane). IR (KBr): 3471, 2906, 1707, 1020 cm-1. 1H-NMR (CDCl3) δ: 1.36—1.61 (7H, m), 1.68 (1H, br s, disappeared on addition of D2O), 1.71—1.77 (1H, m), 1.83—2.06 (4H, m), 2.18 (1H, dt, J=11.5, 2.7 Hz), 2.30 (1H, dd, J=11.5, 2.2 Hz), 2.77 (1H, ddd, J=11.5, 3.4, 3.2 Hz), 2.83 (1H, dd, J=11.5, 2.2 Hz), 2.93 (1H, dt, J=6.6, 2.7 Hz), 3.10 (1H, s, disappeared on addition of D2O), 3.57 (1H, dd, J=6.6, 2.7 Hz), 3.76 (3H, s), 4.19 (1H, br s), 6.68 (1H, dd, J=7.8, 1.0 Hz), 6.72 (1H, ddd, J=7.6, 7.3, 1.0 Hz), 7.01 (1H, ddd, J=7.8, 7.6, 1.0 Hz), 7.08 (1H, dd, J=7.3, 1.0 Hz). High-resolution MS m/z: calcd for C21H28N2O3: 356.2100, found: 356.2111. Anal. Calcd for C21H28N2O3·1/8H2O: C, 70.31; H, 7.94; N, 7.81. Found: C,70.30; H, 7.93; N, 7.78. [α]25D +90.64° (c=0.20, CHCl3).

1-Hydroxyyohimbine (7) from yohimbine hydrochloride (5·HCl) — According to the general procedure for 6, NaBH3CN (85.5 mg, 1.3 mmol), 5·HCl (101.0mg, 0.26 mmol), and CF3CO2H (2.0 mL) were used. The resultant oil, obtained after general procedure, was dissolved in MeOH (9.0 mL). A solution of Na2WO4·2H2O (17.0 mg, 0.05 mmol) in H2O (1.0 mL) and 30% H2O2 (0.59 mL, 5.2 mmol) were added to the solution. The mixture was stirred at 0°C for 1 h. After addition of H2O, the whole was extracted with CHCl3–MeOH (95:5, v/v). The extract was washed with brine, dried over Na2SO4, and evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO2 with CHCl3–MeOH–28% aq. NH3 (46:5:0.5, v/v) to give 7 (82.1 mg, 86%). 7: mp 224—226°C (decomp., colorless fine needles, recrystallized from MeOH). IR (KBr): 3505, 2945, 1711, 751 cm-1. 1H-NMR (CD3OD) δ: 1.19 (1H, q, J=11.5 Hz), 1.33—1.39 (1H, m), 1.43—1.57 (2H, m), 1.65 (1H, br t, J=13.4 Hz), 1.91 (1H, dq, J=13.4, 2.7 Hz), 1.99 (1H, dq, J=2.7, 11.5 Hz), 2.31 (1H, br d, J=11.5 Hz), 2.40 (1H, t, J=11.5 Hz), 2.63—2.76 (2H, m), 2.88— 2.98 (3H, m), 3.10—3.15 (1H, m), 3.62 (1H, d, J=11.5 Hz), 3.73 (3H, s), 4.22 (1H, q, J=2.7 Hz), 6.98 (1H, t, J=7.6 Hz), 7.09 (1H, t, J=7.6 Hz), 7.29 (1H, d, J=7.6 Hz), 7.37 (1H, d, J=7.6 Hz). MS m/z: 370 (M+), 354 (M+–O), 353 (M+–OH). Anal. Calcd for C21H26N2O4: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.97; H, 7.13; N, 7.60. [α]30D +7.75° (c=0.20, DMF).

1-Methoxyyohimbine (8a) from 7 — An excess amount of ethereal CH2N2 was added to a solution of 7 (52.6 mg, 0.14 mmol) in MeOH (20.0 mL) and the whole was stirred at 0°C for 1 h. The solution was evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO2 with CHCl3–MeOH–28% aq. NH3 (46:3:0.3, v/v) to give 8a (42.2 mg, 77%). 8a: mp 201—203°C (decomp., colorless prisms, recrystallized from acetone). IR (KBr): 3145, 1737, 743 cm-1. 1H-NMR (CDCl3) δ: 1.36—1.45 (2H, m), 1.49—1.62 (3H, m), 1.97—2.09 (2H, m), 2.32—2.39 (2H, m), 2.46 (1H, ddd, J=12.7, 3.2, 2.9 Hz), 2.63 (1H, dt, J=4.2, 11.2 Hz), 2.66—2.71 (1H, m), 2.89—2.98 (2H, m), 3.03—3.08 (1H, m), 3.36 (1H, br s, disappeared on addition of D2O), 3.49 (1H, br d, J=11.2 Hz), 3.77 (3H, s), 3.89 (3H, s), 4.21 (1H, br s), 7.09 (1H, ddd, J=7.8, 7.1, 1.0 Hz), 7.19 (1H, ddd, J=8.1, 7.1, 1.0 Hz), 7.34 (1H, dd, J=8.1, 1.0 Hz), 7.44 (1H, dd, J=7.8, 1.0 Hz). MS m/z: 384 (M+), 353 (M+–OMe). Anal. Calcd for C22H28N2O4: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.65; H, 7.35; N, 7.23. [α]29D +20.54° (c=0.20, CHCl3).

1-Allyloxyyohimbine (8c) from 7 — General procedure: K2CO3 (59.2 mg, 0.43 mmol) and a solution of allyl bromide (24.7 mL, 0.3 mmol) in DMF (1.0 mL) were successively added to a solution of 7 (52.8 mg, 0.14 mmol) in DMF (4.0 mL) and the whole was stirred at rt for 30 min. After addition of H2O, the whole was extracted with CHCl3–MeOH (95:5, v/v). The extract was washed with brine, dried over Na2SO4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO2 with CHCl3–MeOH (95:5, v/v) to give 8c (54.6 mg, 93%). 8c: map 150—152°C (decomp., colorless fine needles, recrystallized from hexane). IR (Kabir): 3464, 2935, 1738, 1151, 737 cm-1. 1H-NMR (CDCl3) δ: 1.01 (3H, t, J=7.3 Hz), 1.34—1.43 (2H, m), 1.48—1.63 (5H, m), 1.65—1.79 (2H, m), 1.97—2.07 (2H, m), 2.34 (1H, dd, J=11.2, 2.0 Hz), 2.36 (1H, t, J=11.2 Hz), 2.53 (1H, dt, J=12.9, 2.9 Hz), 2.63 (1H, dt, J=4.2, 11.2 Hz), 2.66—2.72 (1H, m), 2.90—2.98 (1H, m), 2.96 (1H, dd, J=11.2, 2.9 Hz), 3.05 (1H, ddd, J=11.2, 5.6, 2.0 Hz), 3.29 (1H, s, disappeared on addition of D2O), 3.48 (1H, d, J=11.2 Hz), 3.76 (3H, s), 3.98 (1H, dt, J=6.6, 8.5 Hz), 4.06 (1H, dt, J=6.6, 8.5 Hz), 4.20 (1H, br s), 7.07 (1H, ddd, J=8.1, 7.8, 1.0 Hz), 7.17 (1H, dt, J=1.0, 8.1 Hz), 7.31 (1H, dd, J=8.1, 1.0 Hz), 7.43 (1H, dd, J=7.8, 1.0 Hz). MS m/z: 426 (M+), 353 (M+–On-Bu). Anal. Calcd for C25H34N2O4: C, 70.39; H, 8.03; N, 6.57. Found: C, 70.26; H, 8.12; N, 6.48. [α]32D +21.46° (c=0.21, CHCl3).

1-n-Butyloxyyohimbine (8b) from 7 — According to the general procedure for 8c, K2CO3 (56.7 mg, 0.41 mmol), n-butyl iodide (30.8 mg, 0.17 mmol), and 7 (50.5 mg, 0.14 mmol) were used. After column-chromatography, 8b (57.8 mg, 99%) was obtained. 8b: mp 126—128.5°C (decomp., colorless fine needles, recrystallized from hexane). IR (KBr): 3458, 2920, 1739, 1151, 737 cm-1. 1H-NMR (CDCl3) δ: 1.34—1.43 (2H, m), 1.48—1.64 (3H, m), 1.97—2.06 (2H, m), 2.34 (1H, dd, J=11.5, 2.2 Hz), 2.35 (1H, t, J=11.5 Hz), 2.55 (1H, dt, J=12.9, 2.9 Hz), 2.62 (1H, dt, J=4.2, 10.7 Hz), 2.66—2.72 (1H, m), 2.90—2.98 (1H, m), 2.96 (1H, dd, J=11.5, 2.9 Hz), 3.05 (1H, ddd, J=11.5, 5.6, 2.2 Hz), 3.30 (1H, s, disappeared on addition of D2O), 3.51 (1H, dd, J=11.5, 2.2 Hz), 3.75 (3H, s), 4.20 (1H, d, J=1.2 Hz), 4.49 (1H, dddd, J=11.0, 6.6, 1.2, 1.0 Hz), 4.55 (1H, dddd, J=11.0, 6.1, 1.2, 1.0 Hz), 5.39 (1H, ddd, J=10.7, 1.2, 1.0 Hz), 5.44 (1H, dq, J=17.1, 1.2 Hz), 6.05 (1H, dddd, J=17.1, 10.7, 6.6, 6.1 Hz), 7.08 (1H, ddd, J=8.1, 7.8, 1.0 Hz), 7.18 (1H, dt, J=1.0, 8.1 Hz), 7.34 (1H, ddd, J=8.1, 1.0, 0.7 Hz), 7.43 (1H, br d, J=7.8 Hz). MS m/z: 410 (M+), 353 (M+–OCH2CH=CH2). Anal. Calcd for C24H30N2O4: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.13; H, 7.50; N, 6.57. [α]30D +18.4° (c=0.21, CHCl3).

VED #1 [Nb-Nonanoyltryptamine (12d)] from tryptamine — Et3N (0.99 mL, 7.09 mmol) and ClCO2Me (0.55 mL, 7.09 mmol) were added to a solution of nonanoic acid (1.02g, 6.45 mmol) in anhydrous CHCl3 (30 mL) and the mixture was stirred at 0 °C for 30 min. To the resulting mixture, tryptamine (1.14 g, 7.09 mmol) was added and the mixture was stirred at rt for 30 min. After addition of H2O the whole was extracted with CHCl3–MeOH (95:5, v/v). The extract was washed with brine, dried over Na2SO4, and evaporated under reduced pressure to leave a residue, which was column-chromatographed on SiO2 with AcOEt–hexane (1:2, v/v) to give 12d (1.78g, 93%). 12d: mp 101–102 °C (colorless fine needles, recrystallized from CHCl3–hexane). IR (CHCl3): 2950, 1652, 1506, 1165 cm-1. 1H-NMR (CDCl3) δ: 0.87 (3H, t, J=7.0 Hz), 1.22–1.31 (10H, m), 1.57 (2H, br quint, J=7.0 Hz), 10 (2H, t, J=7.6 Hz), 2.98 (2H, t, J=6.7 Hz), 3.61 (2H, q, J=6.7 Hz, collapsed to t, J=6.7 Hz on addition of D2O), 5.52 (1H, br s, disappeared on addition of D2O), 7.04 (1H, s), 7.13 (1H, ddd, J=8.1, 7.1, 1.0 Hz), 7.21 (1H, ddd, J=8.1, 7.1, 1.0 Hz), 7.38 (1H, d, J=8.1 Hz), 7.61 (1H, d, J=8.1 Hz), 8.09 (1H, br s, disappeared on addition of D2O). Anal. Calcd for C19H28N2O: C, 75.96; H, 9.39; N, 9.33. Found: C, 75.66; H, 9.49; N, 9.24.

3-Dihydro-Nb-nonanoyltryptamine (13d) from 12d — A mixture of 12d (1.10 g, 3.65 mmol) and Et3SiH (1.45 mL, 9.10 mmol) in TFA (20 mL) was stirred at rt for 30 min. After evaporation of the solvent, the residue was made alkaline with 8% NaOH and extracted with CHCl3–MeOH (95:5, v/v). The extract was washed with brine, dried over Na2SO4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO2 with AcOEt–hexane (1:1, v/v) to give 13d (862.4 mg, 78%). 13d: mp 41–42.5 °C (colorless powder, recrystallized from AcOEt–hexane). IR (KBr): 3300, 2935, 2870, 1638, 1546, 1486, 1465 cm-1. 1H-NMR (DMSO-d6) δ: 0.84 (3H, t, J=7.0 Hz), 1.20–1.27 (10H, m), 1.45–1.57 (3H, m). 1.83 (1H, dtd, J=13.2, 7.6, 5.6 Hz), 2.04 (2H, t, J=7.5 Hz), 3.05 (1H, ddd, J=9.3, 8.1, 2.2 Hz), 3.09–3.16 (3H, m), 3.54 (1H, td, J=8.6, 1.7 Hz), 5.40 (1H, br s, disappeared on addition of D2O), 6.47 (1H, d, J=7.5 Hz), 6.52 (1H, td, J= 7.5, 0.7 Hz), 6.90 (1H, br t, J=7.5 Hz), 7.00 (1H, d, J=7.5 Hz), 7.80 (1H, br t, J= 6.1 Hz, disappeared on addition of D2O). Anal. Calcd for C19H30N2O: C, 75.45; H, 10.00; N, 9.26. Found: C, 75.25; H,10.16; N, 9.24.

VED #2 [1-Hydroxy-Nb-nonanyltryptamine] (14d) from 13d — A solution of 30% H2O2 (451.3 mg, 3.98 mmol) in MeOH (1.0 mL) was added to a solution of 13d (119.3 mg, 0.40 mmol) and Na2WO4·2H2O (26.7 mg, 0.08 mmol) in MeOH (4.0 mL) and H2O (0.5 mL) under ice cooling with stirring. Stirring was continued at rt for 30 min. After addition of H2O, the whole was extracted with AcOEt. The extract was washed with brine, dried over Na2SO4, and evaporated under reduced pressure to leave an oil, which was column-chromatographed on SiO2 with CHCl3–MeOH (99:1, v/v) to give 14d (75.8 mg, 61%). 14d: mp 82.5–83 °C (colorless powder, recrystallized from CHCl3–hexane). IR (CHCl3): 3155, 2915, 1648, 1510, 1457 cm-1. 1H-NMR (DMSO-d6) δ: 0.86 (3H, t, J=7.4 Hz), 1.15–1.30 (10H, m), 1.47 (2H, quint., J=7.4 Hz), 2.03 (2H, t, J=7.4 Hz), 2.78 (2H, t, J=7.4 Hz), 3.30 (2H, td, J=7.4, 6.1 Hz, collapsed to t, J=7.4 Hz, on addition of D2O), 6.98 (1H, ddd, J= 8.1, 7.1, 1.0 Hz) 7.12 1H, ddd, J=8.1, 7.1, 1.0 Hz), 7.24 (1H, s), 7.32 (1H, d, J=8.1 Hz), 7.52 (1H, d, J=8.1 Hz), 7.86 (1H, br t, J=6.1 Hz, disappeared on addition of D2O), 11.01 (1H, s, disappeared on addition of D2O). Anal. Calcd for C19H28N2O2: C, 72.11; H, 8.92; N, 8.85. Found: C, 72.09; H, 8.96; N, 8.85.

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