ISSN: 3065-5196
Research Article

World Journal of Molecular Medicine

Can you Create Low Molecular Weight Pharmacologically Active Substances and Maintain Mental Function Normal? Yes, we Can

Masanori Somei[1*], Hiizu Somei, Kazuko Somei[1], Katsumasa Yoshino[2], Koichi Noguchi[2], Yoshikazu Fukui[2], Kyoko Nakagawa[2], and Fumio Yamada[2].

[1]*SOMEIYAKKO Kenkyusho, 56-7 Matsuhidai, Matsudo, Chiba 270-2214, Japan*
[2]*Kanazawa University, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8641, Japan*

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

Submitted: 04 June 2025 **Accepted:** 11 June 2025 **Published:** 18 June 2025

DOI: https://doi.org/10.63620/MKWJMM.2025.

Citation: *Somei, M., Somei, H., Somei, K., Yoshino, K., Noguchi, K., Fukui, Y., Nakagawa, K., & Yamada, F.(2025) Can you Create Low Molecular Weight Pharmacologically Active Substances and Maintain Mental Function Normal? Yes, we Can, Word Jour of Molecule Medicine, 2(3), 01-22.*

Abstract

The author has made the chemistry of 1-hydroxyindole, a fictional chemical substance that did not actually exist, a reality. He developed a general method for synthesizing 1-hydroxyindole, and the resulting 1-hydroxy-N-acyltryptamine derivative is a2-blocker that has the effects of eliminating active oxygen, improving blood circulation, promoting metabolism, and anti-aging, and reduces the "itching" caused by atopic dermatitis. It also has the effect of inhibiting platelet aggregation, and has been found to have the potential to be a stronger dementia treatment than cilostazol. He also discovered a nucleophilic substitution reaction that leads to serotonin and melatonin derivatives, and found that melatonin tribromo derivatives can activate osteoblasts and become a treatment for osteoporosis. Furthermore, by incorporating the 1-hydroxyindole structure into the chemical structures of phytoalexins, β-carbolines, ergot alkaloids, yohimbine, etc., it has become possible to create new pharmacologically active substances that add the above effects to the pharmacological actions of the original substances. We also demonstrated that 1-methoxyindole derivatives function as anticancer agents in our daily diet and are useful for maintaining health. Furthermore, we found that acetaldehyde produced from ethanol by oxidation with active oxygen reacts with the neurotransmitter serotonin in the presence of nicotine and KF and is easily converted into neurotoxins such as 1H-azepino[5,4,3-cd]indole and/or tryptamine-4,5-dione, revealing that refraining from smoking and drinking is important for maintaining healthy physical and mental functions and suppressing aging.

Introduction

When synthetic organic chemists or pharmaceutical researchers aim to create a low molecular weight pharmacologically active substance, or "drug," there is a general methodology for proceeding research. Using a computer, we can search through amounts of past knowledge and literatures for new and complex natural product isolated and structure-determined by natural product chemists, or drugs or ingredients that exhibit the desired pharmacological action discovered by medical researchers. This method attempts to synthesize the natural products or compounds obtained in this way, or a group of analogues, as target compounds. The joy of achieving the total synthesis of a target compound by discovering and creating new reactions and incorporating them into the synthetic process, even when a synthesis is deemed extremely difficult even when various known synthetic reactions are combined, is exceptional. You can feel a sense of accomplishment and pride in being the first to complete the total synthesis. Furthermore, you can obtain the target substance and its structural modifications as "seeds" that can be developed into new drugs with the desired pharmacological activity [1].

If the target compound exists in the world, it is easy to conduct synthetic research. The fact that it definitely exists guarantees the possibility of achieving the goal from the beginning. However, if the target compound does not exist, or if it is a fictional compound whose existence is unknown, a whole different dimension of difficulties awaits. The unknown world that has never been seen yet exists in the researcher's "creativity, inspiration,

imagination, fantasy, and/or belief"[2]. He must continue to approach the target while secreting a large amount of dopamine to increase his motivation to challenge himself, and accumulating the joy of small results from his tireless efforts. A challenge to the impossible may waste his research life. It will be a lonely challenge without any allies, and he will have to spend his whole life on it.

The author has suffered for many years from the itchiness of atopic dermatitis and sleep disorders caused by damaged skin. He desperately longed for an effective treatment and sleeping pill that would eliminate the itchiness and pain. All of the drugs prescribed by dermatologists and internal medicine doctors, such as antihistamines, steroids, and sleeping pills, which were said to be effective against the itchiness, were ineffective. Even folk remedies that had spread by word of mouth were of no help.

The author can use himself (a human) instead of mice to evaluate the effectiveness of treatment for itchiness. Taking this advantage, he decided to create a drug that would definitely work on humans and stop the itchiness and pain, so that he could sleep soundly, in order to save himself. However, there were no specific candidate compounds that could be used as a target to suppress the itchiness, either at the time or now. He had to aim for an imaginary target compound [3, 4].

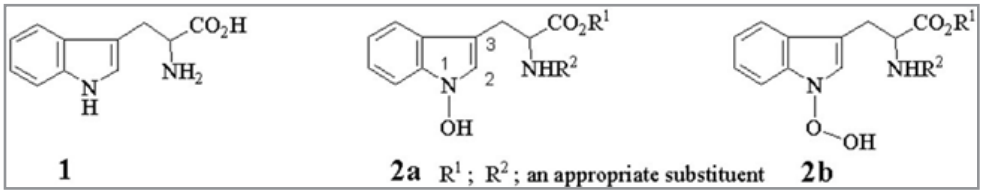
Itching is a special sensation, and the pathological mechanism that causes itching has not yet been determined as of 2025. Medical experts claim that the histamine theory, dry skin theory, and cytokine theory are the causes of itching, and that staphylococcus aureus is the cause of its worsening. Therefore, corresponding small molecule drugs and interleukins are targeted, and biopharmaceuticals such as genetically modified drugs, antibody, nucleic acid drugs, and immune preparations have been approved and developed one after another. We wish to believe that data proving their effectiveness had been obtained in experimental animals. However, the evaluations of human patients who have been prescribed them, including the author, are unsatisfactory. In addition to the appearance of many unnecessary side effects, they are extremely expensive, causing suffering to patients. The definition of a "medicine" claimed by the author is a substance that satisfies the following two points: first, a substance that is effective and has no unnecessary side effects, and second, a substance that is affordable and available to anyone.

The author disregarded the many existing theories. And calmly observed and analyzed the condition of his own skin and body where the itching occurred in order to identify the cause of the "itch". As a result, he came up with his own hypothesis that the "itch" occurs when peripheral blood vessels narrow, blood flow is stagnant, and microthrombi begin to form, and that it is caused by the time and place when surrounding cells begin to sense the damage due to the "partial generation of active oxygen" [3, 4]. Based on this theory, the author imagined that the itching could be stopped by eliminating active oxygen, improving blood flow, and developing a peripheral vasodilator. When asked about a "removal agent for active oxygen", medical professionals would immediately think of vitamins, carotenoids, polyphenols, glutathione, superoxidase dismutase, etc., and select related compounds as development targets.

Imaginary 1-Hydroxyindole Chemistry

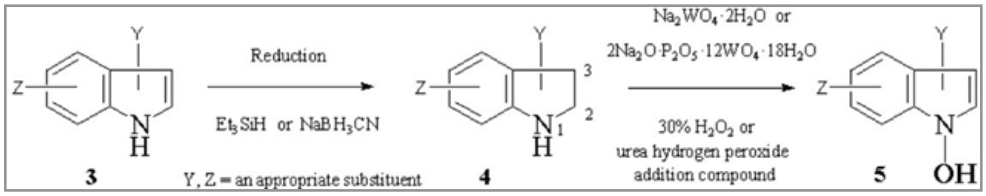
The author, an organic chemist, changed his way of thinking and indulged in his own imagination. He focused on tryptophan (1, Figure 1), an essential amino acid that is a component of proteins and has an indole skeleton, as a "candidate for removing active oxygen". The reactive site for tryptophan to remove active oxygen must be the nitrogen atom at position 1, which has the highest electron density in the molecule. This nitrogen atom is hydroxylated or hydroperoxylated by oxidation. He imagined that it would be oxidized to 1-hydroxy-tryptophan (2a) or 1-hydroperoxy-tryptophan (2b) (1-hydroxy-indole hypothesis). However, there has been no precedent for the isolation and structural determination of natural products with the structures 2a and/or 2b. The imaginary and original 2a and 2b, which no one has ever seen before, make them a fantastic synthetic target worth challenging. The author began his research with a strong belief that he could discover and create a substance that suppresses "itchiness".

Figure 1



This challenge took more than 30 years of trial and error. As a result, our tenacity bore fruit and we were able to develop a simple general synthetic method, as shown in Scheme 1, in which 1-hydroxyindole (5) is synthesized via 2,3-dihydroindole (4) from indole (3). By applying this method to N-acyltryptamine, we succeeded in developing a group of compounds that instantly relieve "itching".

Scheme 1



Development of 1-Hydroxyindole Chemistry [5-10]

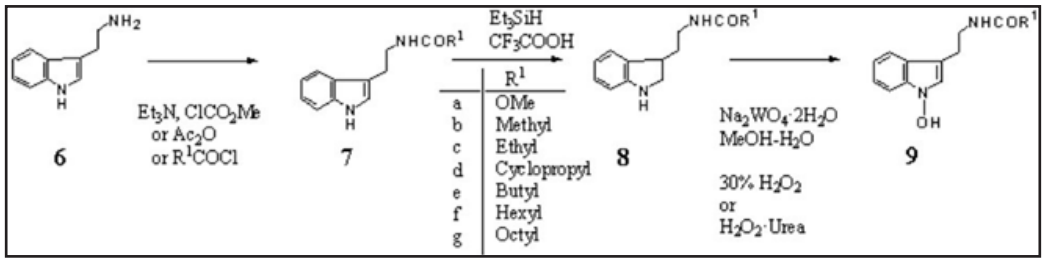
The general synthesis of 1-hydroxyindole involves first reacting indole (3, Y=Z=H) with Et3SiH or NaBH3CN in trifluoroacetic acid to give 2,3-dihydroindole (4, Y=Z=H) (Scheme 1). Next, the dihydro compound is reacted with 30% H2O2 (or urea-hydrogen peroxide adduct) using Na2WO4·2H2O as a catalyst. This allows a mild oxidation reaction to occur, synthesizing 1-hydroxyindole (5, Y=Z=H). Unsubstituted 1-hydroxyindole itself is an extremely unstable substance that immediately reacts with oxygen in the air to form tar as soon as it is isolated and purified.

When the 1-hydroxyl group was alkylated or acylated, when an electron-withdrawing group such as a nitro group or an acyl group or a 2-oxo group was present as Y or Z, or when an aminoethyl group was present at the 3-position, the 1-hydroxyindole derivative became a stable substance. When the 1-position was a methoxy group, it was particularly stable. 1-Methoxyindole could be stored in the dark for more than two years at room temperature in the presence of air. [5-10]

Discovery of a Novel α2-Blocker and Instant Relief of "Itching"

We therefore attempted to synthesize N-acyl-1-hydroxytryptamines, which were expected to be stable. As shown in Scheme 2, the acid anhydride or fatty acid chloride prepared by reacting the desired fatty acid with methyl chloroformate was reacted with tryptamine (6) to give N-acyltryptamines (7a-g) in high yield. The compounds 7a-g were then reduced with Et3SiH in the presence of trifluoroacetic acid to synthesize N-acyl-2,3-dihydrotryptamines (8a-g). Furthermore, N-acyl-1-hydroxytryptamines (9a-g) were synthesized by reacting 8a-g with 30% H2O2 or urea-H2O2 adduct using Na2WO4·2H2O as a catalyst.

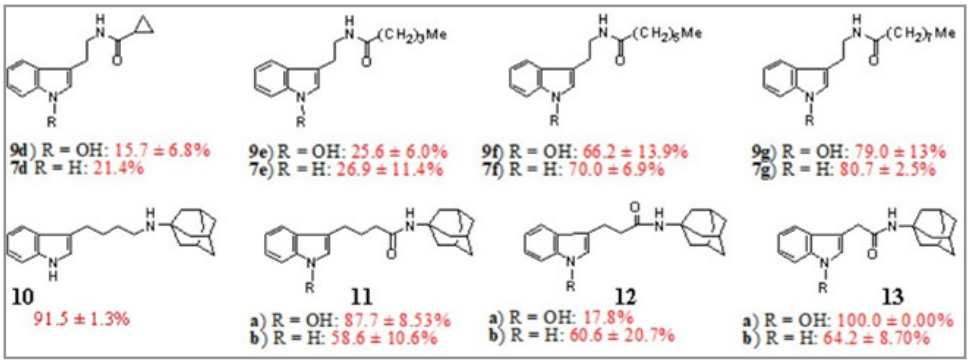
Scheme 2



In the same manner, various N-acyltryptamine derivatives (10-13) were synthesized (Figure 2). The efficacy of yohimbine, a known potent α2-blocker with peripheral vasodilatory properties, was set at 100% and the efficacy of the N-acyltryptamine derivatives was compared. The results are shown in Figure 2 as percentages using red text. The potency of the α2-blocker activity of the N(1)-OH compound, N-acyl-1-hydroxytryptamines (9), was found to be equivalent to that of the corresponding N(1)-H compound, N-acyltryptamines (7). In other words, 7g has an α2-blocker activity almost as strong (80%) as yohimbine. Moreover, after 7g worked as dilating peripheral blood vessels and removed active oxygen, the resultant oxidized product 9g, also had a peripheral vasodilatory activity almost as strong (79%).

Furthermore, the α2-blocker effect was found to increase with the number of carbon atoms in the Nb side chain from four (7d, 9d) to nine (7g, 9g), reaching the highest level. It was also found that the effect was enhanced when the side chain contained an adamantyl group, as seen in 10-13. [11-14]

Figure 2



Since the author obtained the desired compound, 7g and 9g, he created a skin care cream using these. When he applied it to the itchy area, the "itching" disappeared instantly, to his surprise. After repeated trials, he asked an acquaintance who suffers from atopic dermatitis to try it, and the same effect was confirmed. After that, he requested oral administration toxicity tests in mice and allergy patch tests in humans to confirm safety. In response to requests from people who wanted to try it after hearing about it through word of mouth, he provided the cream. It has relieved many people who were long time suffering from "itching" that could not be cured by dermatologists [15-17].

During this time, the author asked specialists to perform a bioassay using mice to suppress "itching". However, the tests repeatedly returned the answer that there was no effect. Recently, research on "itch" has begun using fish as an assay other than

mice. Can mice and fish claim that this substance has eliminated "itch"? The author is very skeptical [18].

As a result, his time was wasted in vain. Recently, when the author asked a different researcher, he was finally able to get a report that the effect was seen in mice [19]. However, five years ago, if he had not tested it on himself, a human, he would not have been able to discover the effect of eliminating "itching", including the absence of side effects. We reminded of the development story of the asthma treatment Intal (sodium cromoglycate) [20]. As the author states, if there was no method to evaluate the effectiveness in humans (himself), Intal probably would not have been developed. Recently research using IPS cells progresses. Recently, research using IPS cells has progressed. If an assay method for measuring "itch" using IPS cells can be established, it could be a solution, and we look forward to future developments.

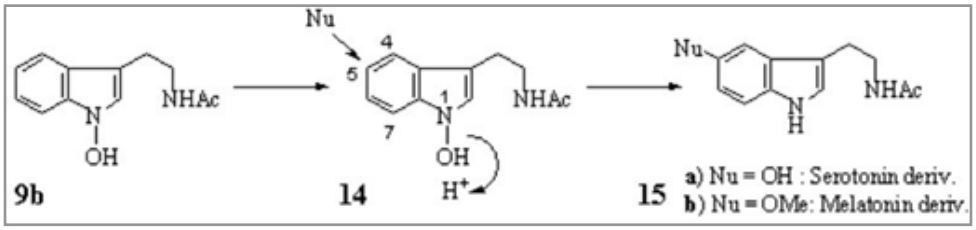
As we will discuss later, we found that N-acyl-1-hydroxytryptamine compounds (7g and 9g) have the effects of treating blemishes, treating acne (scars), healing muscle pain, wound healing, hair growth, promoting metabolism, activating osteoblasts, inhibiting apoptosis, treating erectile dysfunction, and anti-aging [21-22]. The chemistry of 1-hydroxyindole derivatives is linked to serotonin and melatonin, and treasure trove of pharmacologically active substances.

Discovery of Nucleophilic Substitution Reactions in Indole Chemistry

In indole chemistry, only electrophilic substitution reactions have been known, and there are no examples of nucleophilic substitution reactions, in the past.[23-25].

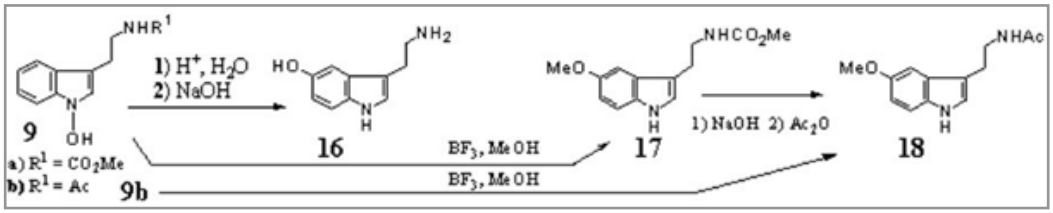
In the 1-hydroxyindole hypothesis, the author imagined an attractive nucleophilic substitution reaction. Thus when the side chain at the 3-position is an aminoethyl or N-acetylaminoethyl group (Scheme 3, 9b), we hypothesized that a nucleophile (Nu) would be introduced at the 5- or 7-position of the benzene ring of the indole skeleton when the 1-hydroxyl group is dehydrated and eliminated by reaction with acid, to the product through intermediate 14. If the nucleophile is a water, the product becomes a serotonin compound (15a). When 15a is methylated in vivo, it becomes a melatonin derivative (15b). This would present a new mechanism that is not common knowledge [26, 27]. Furthermore, it may be possible to add the pharmacological action of serotonin or melatonin to 1-hydroxyindole derivatives. However, at the time, the only reaction mechanism proposed in vivo for introducing a hydroxy group to the benzene ring was NIH SHIFT [28, 29].

Scheme 3



As shown in Scheme 4, when 9a and 9b were reacted with water in the presence of acid, a nucleophilic substitution reaction occurred and a hydroxy group was introduced. The amide group in the side chain was then subjected to alkaline hydrolysis, yielding serotonin (16) in a yield of 73%. Similarly, when Nb-methoxycarbonyltryptamine (9b) was treated with BF3 in MeOH, a methoxy group was regioselectively introduced at the 5-position, yielding melatonin (18) in 85% yield. Furthermore, when 9a was treated with BF3 in MeOH, 17 was obtained. Melatonin (18) could also be synthesized by subsequently performing alkaline hydrolysis of the side chain and acetylating the free amino group with Ac2O. Thus, an unusual nucleophilic substitution reaction was discovered in indole chemistry.

Scheme 4



Melatonin and Osteoporosis

Easily and economically, we have been able to synthesize melatonin (18), a pineal hormone known as a circadian rhythm regulator and sleep aid, from N-acyl-1-hydroxytryptamine.

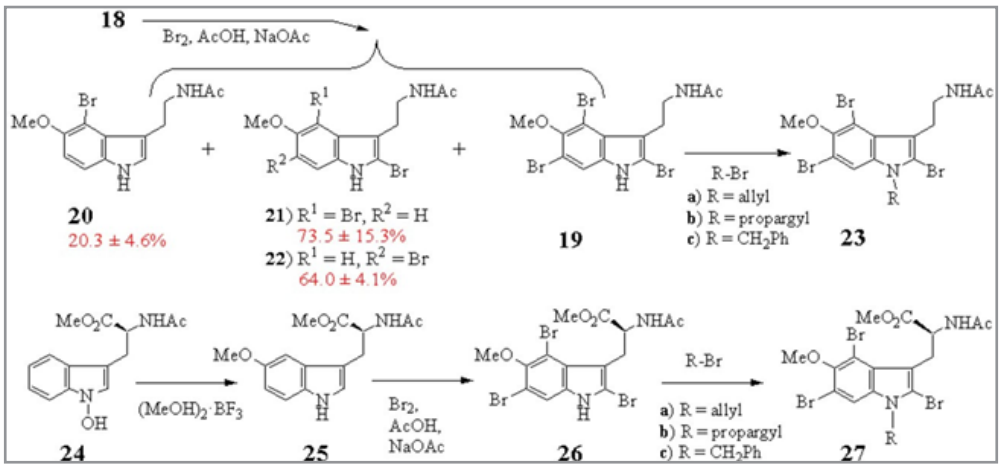
In particular, among the many pharmacological actions of melatonin, we focused on its effect on osteoporosis, which develops with aging and has become a social problem. Currently, the only osteoporosis treatment, bisphosphonates, attenuate the activity of osteoclasts. However, they do not activate osteoblasts. To be a treatment for osteoporosis, it is necessary to activate osteoblasts to increase bone mass and strengthen bones.

We have confirmed that melatonin has the effect of suppressing bone loss in astronauts living in zero-gravity space [30, 31]. Therefore, we decided to search for melatonin derivatives that activate osteoblasts.

In conventional assays, osteoclasts and osteoblasts are cultured separately, and the test substance is applied to them to determine the effect of each. This method ignores the most important interaction between osteoclasts and osteoblasts in vivo. On the other hand, Hattori and Suzuki have succeeded in developing an assay method to determine the effect in a system using goldfish gills, where osteoclasts and osteoblasts coexist and closely interact with each other [32-40]. Using this best assay method, we started to search for a drug for treating osteoporosis.

As shown in Scheme 5, melatonin (18) was first reacted with Br2–NaOAc (3 mol eq.) to synthesize 2,4,6-tribromomelatonin (19) in 94% yield. In this reaction, 4-bromo (20), 2,4-dibromo- (21), and 2,6-dibromo- (22) were also produced as by-products. Next, 19 was reacted with allyl bromides, propargyl bromides, and benzyl bromide to give 1-allyl- (23a), 1-propargyl- (23b), and 1-benzyl- (23c) in 95, 97, and 83% yields, respectively. Using a similar reaction pathway, 1-hydroxytryptophan derivative (24) was converted to 25 by nucleophilic introduction of a methoxy group at the 5-position to give 2,4,6-tribromotryptophan derivative (26). The compound 26 was then reacted with allyl bromide, propargyl bromides, and benzyl bromide to give the corresponding 27a, 27b, and 27c in yields of 99, 94, and 96%, respectively.[39-52]

Scheme 5



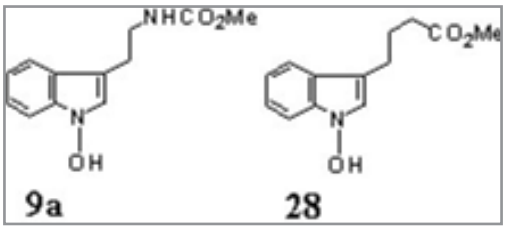
When the goldfish gill-assay was applied to these bromo-compounds, 23c was found to activate osteoblasts. In addition, the corresponding tryptophan derivative (27c) was found to activate osteoblasts and deactivate osteoclasts. As a result, it was concluded that 23c and 27c are promising candidate compounds for osteoporosis treatment, increasing bone density.

The α2-blocker activity of the bromo derivatives (20, 21, 22) obtained here was also measured in comparison with the potency of yohimbine set at 100%, and the results are shown in red and expressed as a percentage in Scheme 5.

Platelet Aggregation Inhibitor

The authors were also simultaneously searching substances that would prevent thrombus formation to prevent the onset of "itching", and improve blood flow to prevent the onset of cerebral and myocardial infarction.

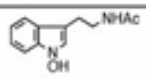
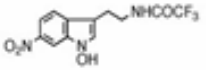
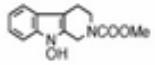
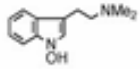
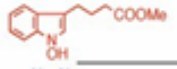
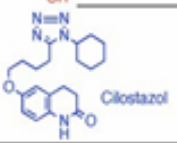
Figure 3

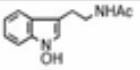
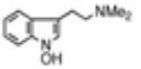
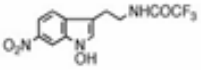
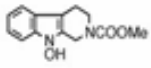
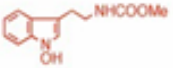
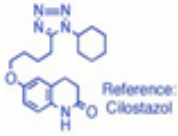


We continued to examine the anticoagulant effects of the 1-hydroxyindole compounds using platelet-rich blood from rabbits. Finally, we found that 1-hydroxyindole compounds essentially have antiplatelet aggregation effects [53-56].

That is, the IC50 values of our compounds are shown in Table 1 together with the IC50 value of cilostazol (Entry 7), which is known as a platelet aggregation inhibitor. These data show that the platelet aggregation inhibitory potency of all 1-hydroxyindole compounds is equal to that of cilostazol. In particular, 9a and 28 in Figure 3 were found to be potent. Furthermore, when the percentage of aggregation inhibition was examined when the sample concentration was changed, 9a and 28 were found to be stronger than cilostazol. These compounds showed an inhibitory effect on aggregation even at low concentrations of 10^{-8} to 10^{-7} (M). Thus, as expected, we were able to discover a potent substance that inhibits thrombus formation.

Table 1:

Entry	Compound	IC_{50} (μM)
1		3.10
2		3.31
3		1.00
4		2.90
5		0.32
6		0.32
7		3.10

Entry	Compound	Inhibition Percent of Control Platelet Aggregation				
		10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4} (M)
1		-	-	2.2	**92.1**	93.5
2		-	-	11.3	**95.1**	95.8
3		-	-	2.3	**94.0**	94.7
4		-	-	51.4	**94.9**	94.2
5		1.5	6.2	**93.3**	**92.3**	92.3
6		2.9	4.4	**94.1**	**89.7**	92.6
7		-	-	7.1	**94.3**	92.9

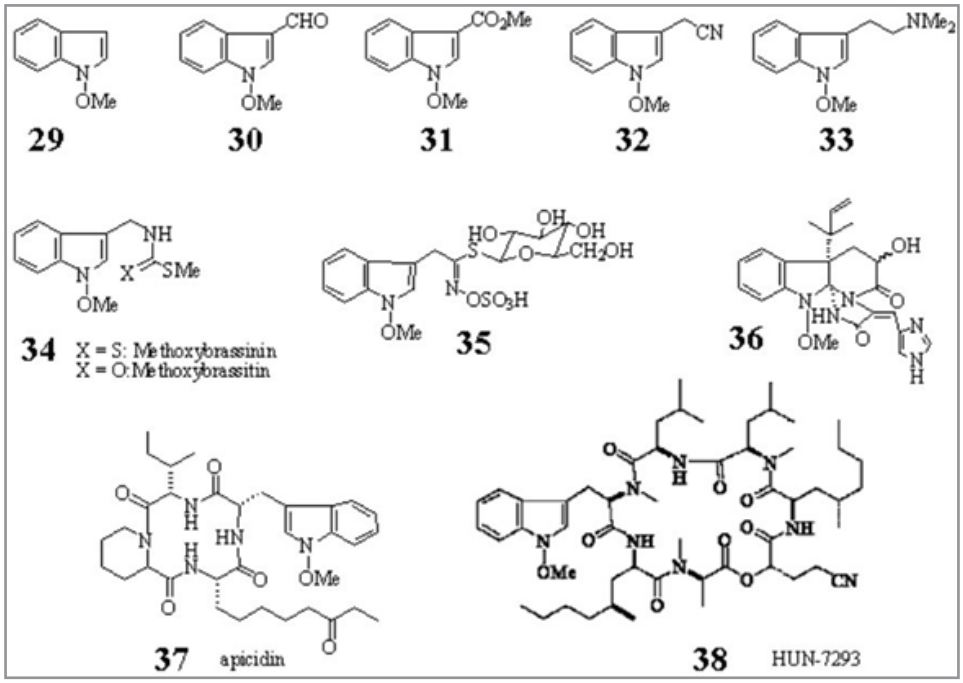
Dementia

Cilostazol, a platelet aggregation inhibitor, has been found to be effective in treating dementia [57]. Therefore, the compounds shown in Table 1 are expected to have similar therapeutic effects. Furthermore, the authors discovered that Nb-acyl-1-hydroxytryptamines such as 9a have an apoptosis inhibitory effect. Apoptosis inhibitors can stop the decrease in normal cells that occurs in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, dementia, Huntington's disease, and cerebral ischemia, as well as diseases such as AIDS. They are also expected to prevent and improve side effects caused by apoptosis that occur in myocardial infarction, arteriosclerosis, and ultraviolet light such as radiation or anticancer drug treatment. We hope that our compounds may become platelet aggregation inhibitors and dementia treatments that are more powerful than cilostazol.

Phytoalexin and Anticancer Drugs

Reflecting the extremely stable nature of 1-methoxyindole, many natural products with the 1-methoxyindole (29) structure have been isolated and their structures determined in recent years. For example, as shown in Figure 4, there are phytoalexins from radish (daikon) (30) and wasabi (31) indole acetonitrile derivatives (32), tryptamine derivatives, N,N- dimethyltryptamine (33), methoxybrassinin (34) indole glucosinolate (35), and peptide derivatives, neoxaline (36), apicidin (37), and HUN-7293 (38) [59-71].

Figure 4

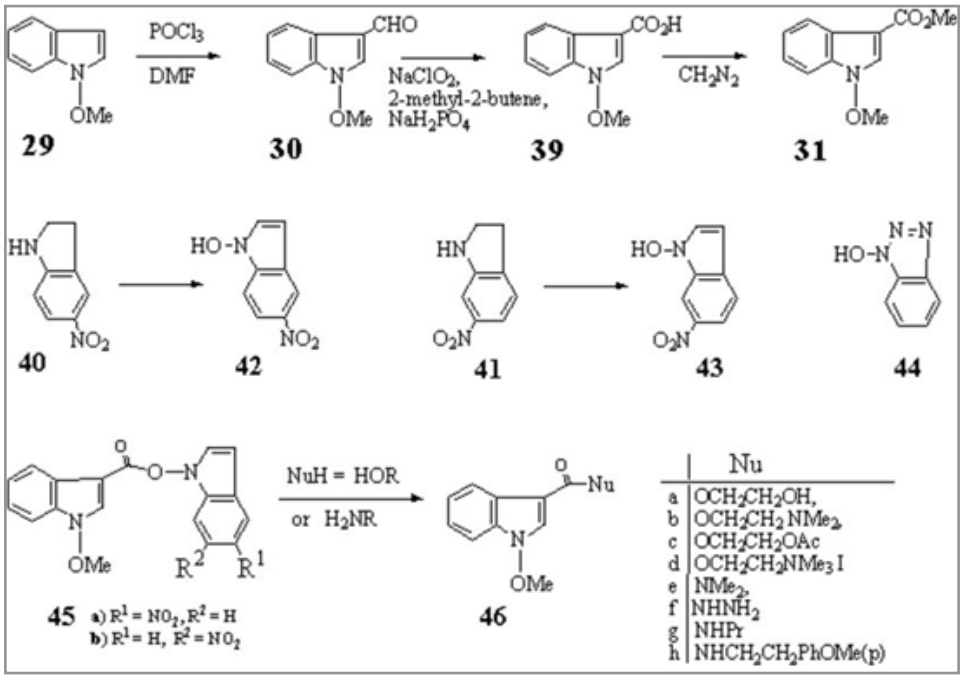


The authors believe that the existence of these compounds in nature is supporting evidence that natural products with the corresponding 1-hydroxyindole structure exist in the plants, microorganisms, and so on. Furthermore, these compounds have useful pharmacological effects. The authors speculate that natural products with the corresponding 1-hydroxyindole structure are necessarily present in the body and play an important role in maintaining health in daily life, such as antioxidant effects, cognitive function improvement effects, blood flow improvement, skin beautifying effects, and anticancer effects.

The author attempted to synthesize daikon (radish) and wasabi phytoalexin (31) and its derivatives (Scheme 6). Specifically, the Vilsmeier reaction of 1-methoxyindole (29) afforded daikon phytoalexin (30) in 88% yield. Subsequent oxidation of 30 with NaClO2 afforded 1-methoxy-indole-3-carboxylic acid (39) in 95% yield. The subsequent methylation with CH2N2 afforded quantitative synthesis of wasabi phytoalexin (31).

By applying the 1-hydroxyindole synthesis method to 5-nitro- (40) or 6-nitroindoline (41), 1-hydroxy-5-nitro- (42) and 1-hydroxy-6-nitroindole (43) could be synthesized in high yields. Both 42 and 43 had the same acyl group activating properties as 1-hydroxy-1,2,3-benzotriazole (44). In other words, when 39 was reacted with 42 or 43 in the presence of DCC, the activated esters 45a and 45b were obtained in 84% and 89% yields, respectively. Then, when 45a and 45b were reacted with nucleophiles, various wasabi phytoalexin derivatives (46a-h) with nucleophiles were obtained. The yields of 46a-h were better than those of 44, and the highest yield was obtained when the activated ester 45b was used. If a certain peptides or proteins containing 1-hydroxytryptophan exist in the body, we can assume that they play a role in acylation or phosphorylation of important substances in the body by activating the acyl or phosphoryl group through 1-acyloxy- or 1-phosphoryloxy-tryptophan.

Scheme 6



On the other hand, we ingest various allergens and carcinogens with every meal, including burnt food, yet the incidence of stomach cancer and allergies is low. The author believes that this is because we simultaneously ingest anticancer and/or antiallergy substances such as indole glucosinolate contained in cruciferous plants that we eat as side dishes. Therefore, it is important to examine the pharmacological effects of phytoalexin, 46a-h, and their analogues contained in radishes and wasabi.

We hope that from these compounds, anticancer drugs, diabetes, arteriosclerosis, colon cancer, dementia, depression, and other diseases will be developed, and that skin health promoting agents will be developed to improve the distribution of intestinal bacteria and metabolic syndrome.

Ergot Alkaloids

Ergot alkaloids are indole alkaloids produced by the ergot fungus (Claviceps purpurea, etc.) that parasitizes cereals such as wheat and rye (Scheme 7) [72, 73]. They have a 4-ring structure, such as lysergic acid (47) and agroclavine (48), and act on adrenaline, dopamine, and serotonin receptors. They exhibit a variety of pharmacological actions, including cerebral vasoconstriction, uterine smooth muscle contraction, hallucinations, and nervous system actions that induce euphoria and a cheerful mood. The homologous 3-ring alkaloid chanoclavine (49) has been reported to have no ergot-like activity and no significant pharmacological action. We expected that by adding our 1-hydroxyindole chemistry to the chanoclavine derivative, 6,7-secoagroclavine (50), we could create novel pharmacological substances.

Then, radish phytoalexin (30) was reacted with Tl(OCOCF3)3, followed by treatment with KI, to obtain 1-methoxy-4-iodoindole-3-carbaldehyde (51) in 91% yield. Next, 51 was reacted with 2-methyl-3-buten-2-ol under Pd(OAc)2 catalyst, which introduced a C-5 unit at the 4-position, and 52 was synthesized in 93% yield. Further aldol condensation with nitromethane gave 53 in 97% yield. The nitrovinyl group was reduced with NaBH4, and in the presence of the nitronate formed in the reaction solu-

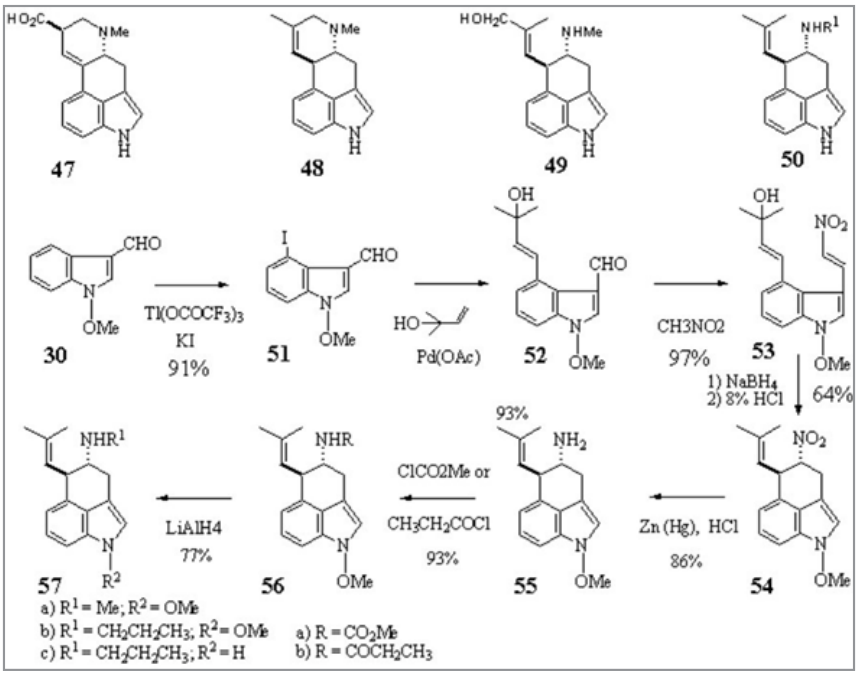
tion, it reacted with the allyl cation formed on the side chain to cause a ring-closing reaction, and 54, which formed a tricyclic ergot alkaloid skeleton, was synthesized in 64% yield. Next, reduction with Zn (Hg) in HCl gave the amino compound (55) in 86% yield. The reaction of 55 with ClCO2Me or CH3CH2CO-Cl afforded 56a and 56b in 93%, 90%, respectively. Reduction of 56a and 56b with LiAlH4 afforded 1-methoxy-6,7-secoagroclavine (57a) and 4,5-trans-1-methoxy-5-(2-methyl-1-propen-1-yl)-4-propylamino-1,3.4,5-tetrahydrobenz[cd]indole (57b) in 77%, 63%, respectively. Catalytic reduction of 57b with 10% Pd/C catalyst afforded quantitatively 4,5-trans-5-(2-methyl-1-propen-1-yl)-4-propylamino-1.3.4,5-tetrahydro[cd] indole (57c) [74-76].

When we examined their pharmacological effects, we found that 57b and 57c, which are chanoclavine-type ergot alkaloid derivatives, exhibit dopamine agonist activity, although it is weaker than bromocriptine and ergometrine [77, 78].

Parkinson's disease, which affects many patients, is characterized by resting tremor, bradykinesia/akinesia, and muscle rigidity. As the disease progresses, dementia may develop, and when "itching" is added to these symptoms, the hellish suffering begins.

We believe that the dopamine agonists 57b and 57c may be applicable as treatments for Parkinson's disease.

Scheme 7

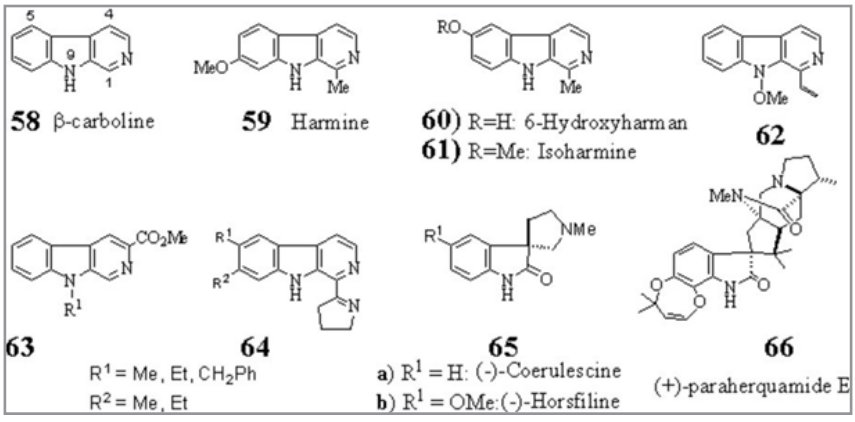


β-Carboline Derivative, Metabolism Promotion

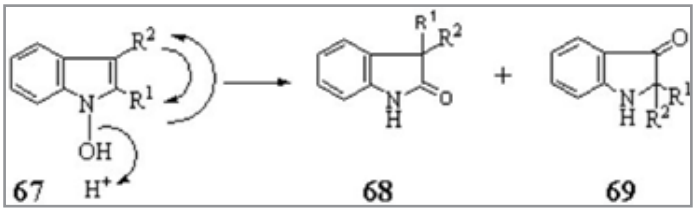
Many pharmacologically active substances containing an indole skeleton, i.e., β-carboline (58, 9h-pyrido[3,4-b]indole) are known as natural products. Examples include harmine (59), 6-hydroxyharman (60), isoharmine (61), and 9-methoxy-1-vinyl-β–carboline (62), which exert hallucinogenic effects in the central nervous system; 9-alkyl-3-methoxycarbonyl-β-carboline (63), which exhibits antiviral and anticancer effects, and eudistomin alkaloids (64a-d) [79-82]. Furthermore, β-carboline derivatives are the base for compounds that exhibit a variety of biological activities, including antiparasitic, anti-inflammatory, anticonvulsant, antibacterial, and antiviral. Among the natural indole

alkaloids, pharmacologically active compounds with 2-oxindole or 3-oxindole structures, such as (-)-coerulescine (65a), (-)-horsfiline (65b), and (+)-paraherquamide B (66), are known, as shown in Figure 5 [83-91].

Figure 5



Scheme 8



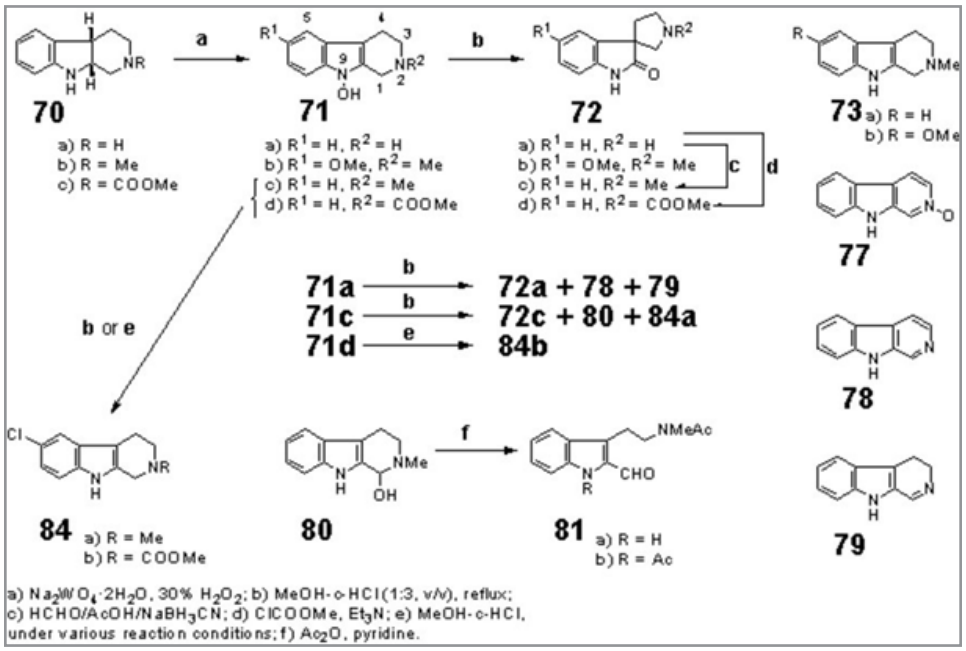
It has been found that 1-hydroxyindole compounds undergo a wide variety of reactions specific to their structures when the reaction conditions are changed [92]. Based on the 1-hydroxyindole hypothesis, the author predicted that when the compound with the structure 67 (Scheme 8) reacts with an acid and the 1-hydroxyl group is dehydrated, substituents at the 2- or 3-position may rearrange to form 2-oxindole (68) and/or 3-oxindole (69) [2].

Furthermore, we imagined that if we could create a new group of derivatives with a β–carboline skeleton (58), 2-oxi- (68) or 3-oxindole skeleton (69), we would be able to discover new compounds with the desired peripheral vasodilatory and thrombolytic properties. In addition, by applying the 1-hydroxyindole synthesis method to 70c, we were able to synthesize 71d. The compound 71d also has platelet aggregation inhibitory properties, and as shown in Table 1, it showed the same efficacy as cilostazol.

Therefore, by introducing a 1-hydroxyindole structure into the β-carboline structure, it is possible to create a new compound. Furthermore, in addition to the inherent pharmacological effects of the β–carboline structure, it is possible to add the α2 blocker effect, antithrombosis effect, and peripheral vasodilator effect of 1-hydroxyindole, and it is predicted that this will open the door to a new group of pharmacologically active substances.

Meanwhile, Colegate and co-workers isolated and identified (–)-coerulescine (65a) from Phalaris coerulescens. We noted that Phalaris plants generally contain 1,2,3,4-tetrahydro-β-carbolines (70a,b), and hypothesized that the related alkaloids (–)-horsfiline (72b) and 72a were biosynthesized from 70a and 70b via the corresponding 9-hydroxy-β-carbolines (71a and 71b), respectively (Scheme 9). The general method for the synthesis of 1-hydroxyindoles was applied to the synthesis of 9-hydroxy-1,2,3,4-tetrahydro-2-methoxycarbonyl-β-carboline (71d).

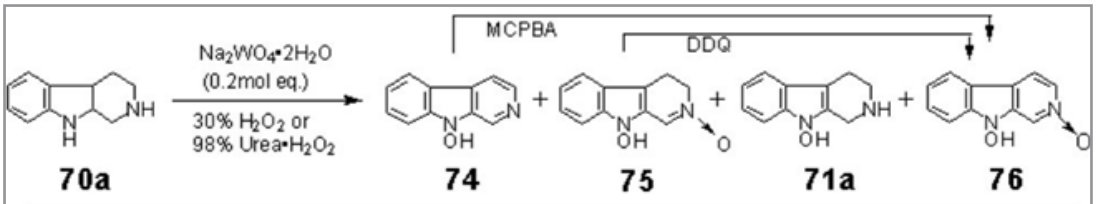
Scheme 9



Specifically, the oxidation of the corresponding 1,2,3,4,4a,9a-hexahydro compound (70a) by the Na2WO4·2H2O-30% H2O2 method [7] was investigated. Representative results are summarized in Scheme 10. Under the reaction conditions of Entry 3, compound (71a) was obtained in 65% yield. Under other conditions, by-products (74, 75, 76) were formed.

Oxidation of 74 with MCPBA afforded β-carboline N-oxide (77) and β-carboline (78) in the respective yield of 31% and 11%, as well as 76 in 29% yield. Dehydrogenation of 75 with DDQ afforded 76 in 75% yield.

Scheme 10



Entry	solvent system	Reaction Conditions: Reagents	Temp (°C)	Time (min)	Products and Yeild (%): 74	75	71a	76
1	t-BuOH:H_2O 4:1 (v/v)	30%H_2O_2 (10 mol eq.)	21	10	trace	22	11	15
2	MeOH:H_2O 9:1 (v/v)	30%H_2O_2 (10 mol eq.)	27	5	trace	5	55	5
3	MeOH:H_2O 9:1 (v/v)	98%Urea$\cdot H_2O_2$ (10 mol eq.)	25.5	5	trace	5	65	2
4	t-BuOH:H_2O 4:1 (v/v)	30%H_2O_2 (10 mol eq.)	21	10	15	29	trace	9

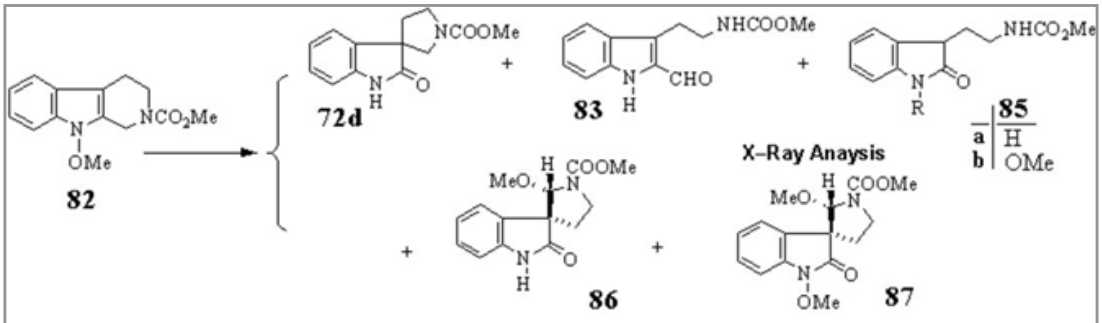
Similarly, oxidation of 1,2,3,4,4a,9a-hexahydro-2-methyl-β-carboline (70b) afforded 9-hydroxy- 1,2,3,4-tetrahydro-2-methyl-β-carboline (71c) in 69% yield (Scheme 9). Interestingly, treatment of 75 with chloroacetyl chloride afforded 77 and 78 in 60% and 33% yields, respectively. Thus, four novel 9-hydroxy-β-carboline compounds (71a, 74, 75, 76) are readily available. These compounds are useful building blocks for the synthesis of β-carboline alkaloids and are currently being investigated for their pharmacological activities.

Obtained 71a, 71c, and 71d were treated with MeOH-cHCl (1:3, v/v). No reaction occurred at room temperature, but 71a underwent the expected rearrangement reaction at reflux for 1 h to give 72a in 47% yield, with 78 and 79 in 2% and 36% yields, respectively. Subsequent methylation of 72a with HCHO-AcOH-NaBH3CN afforded (dl)-72c in 91% yield, and reaction of 72a with methyl chloroformate afforded 72d in 99% yield.

Similarly, treatment of 71c with MeOH-cHCl (1:3, v/v) at reflux for 3 h afforded (dl)-72c, 80, and 6-chloro-2-methyl-1,2,3,4-tetrahydro-β-carboline (84a) in 42, 46, and 9% yields, respectively. Treatment of 71d with MeOH-cHCl (1:3, v/v) at reflux for 3 h afforded 84b in 15% yield. The structure of (dl)-72c was confirmed by direct comparison with an authentic sample prepared alternatively according to the reported procedure. The spectral data of our sample, the authentic sample, and the reported (-)-72c were identical in all respects. The structure of the relatively unstable 80 was based on its spectral data and the fact that it reacts with Ac2O-pyridine to give the formyl compounds (81a and 81b).

Similarly, refluxing 71d in MeOH-cHCl (1:3, v/v) for 3 h afforded 84b in 7% yield. Refluxing 82 in MeOH-cHCl (1:3, v/v) for 3 h afforded (dl)-72d, 83, 85a, 85b and interesting rearrangements products 86 and 87. The yields of these products varied with reaction conditions as shown in Scheme 11.

Scheme 11

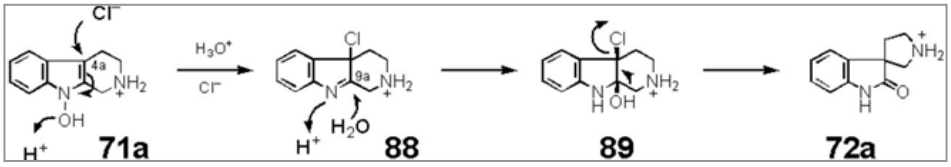


Entry	Ratio of MeOH-cHCl (v/v)	Reaction Conditions: Temp. (°C)	Time (h)	Yield (%) of: 72d	83	85a	85b	86	87	Recovery
1	1 : 3	23	0.5	21	3	3	0	0	0	0
2	2 : 1	19	38	4	0	19	6	3	5	27

The structure of (dl)-72d was confirmed by direct comparison with an authentic sample, which was synthesized independently following the reported procedure.[4c] The spectral data for our sample, the authentic sample, and the reported (-)-72d were identical in all respects. The structure of the relatively unstable 80 was based on its spectral data and on the fact that it reacts

with Ac2O-pyridine to give the formyl compounds (81a and 81b). The structure of 87 was determined by X-ray crystallography.

Scheme 12

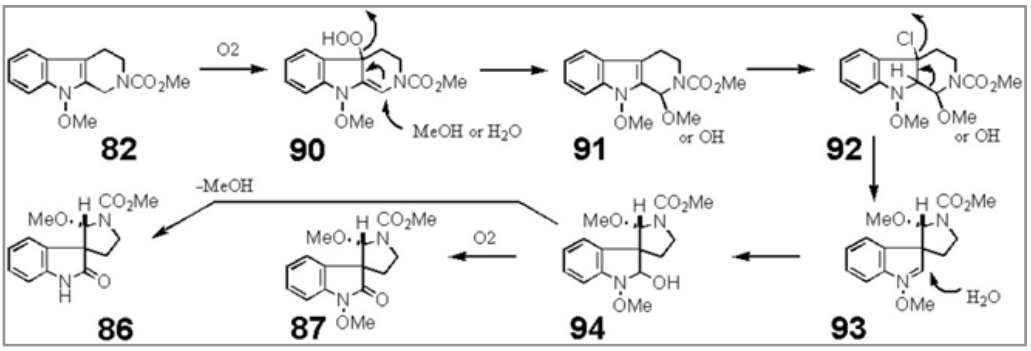


The reaction mechanism of the rearrangement from 71a to 72a can be explained as shown in Scheme 12. First, the N-hydroxy group is protonated, followed by the attack of chloride at the 4a-carbon to generate chloroindolenine (88). Water is added to the 9a-imine carbon atom to give 89, followed by the concerted elimination of chloride and rearrangement of the alkyl side chain attached to the 9a-carbon atom to give the 3,3-disubstituted 2-oxindole structure (72a).

In the reaction of 71d with methanolic hydrochloric acid, 72d was not produced under various reaction conditions. In this case, a nucleophilic substitution reaction occurred to give 6-chloro-1,2,3,4-tetrahydro-2-methoxycarbonyl-β-carboline 84b in 8–16% yield, with a recovery rate of 21–30%.

The mechanism of the rearrangement from 82 to 86 and 87 can be explained as shown in Scheme 13. Oxygen reacts with 82 to produce hydroperoxide (90), after which MeOH or water is added to the 1-position to give 91. HCl is then added to the indole ring to give 92. The chloride ion is then eliminated and the bond at the 9a-position rearranges to give 93. Water is added to the resultant imine moiety to produce 94. Next, elimination of MeOH from 94 produce 86, while oxidation of 94 with the air produce 87.

Scheme 13



In conclusion, we have synthesized a novel 9-hydroxy-β-carboline that can be used as a useful building block for the synthesis of β-carboline compounds. We also discovered a novel rearrangement reaction of the 1-hydroxyindole skeleton, providing a useful tool for the synthesis of 3,3-disubstituted oxindole alkaloids.

The findings suggest that natural product chemists should be extremely careful when using acids to isolate indole alkaloids from natural sources; otherwise, they may end up with acid by-product oxindole compounds as the natural products, even if the true 1-hydroxy- or 1-methoxyindole alkaloids are present.

Yohimbine

Yohimbine (95) (Scheme 14), extracted from the bark of the yohimbe tree, is also an indole alkaloid [93].

It is a strong α2-blocker and dilates peripheral blood vessels. It is known as a traditional Chinese medicine and is used to treat erectile dysfunction, which affects an estimated 100 million people worldwide. Viagra, Cialis, and related compounds have been developed for similar purposes, but there are many hidden victims due to side effects. There is a need to develop a safe drug with vasodilatory and erectile enhancing effects that reduces the toxicity of 95.

By incorporating the 1-hydroxyindole skeleton into yohimbine, a new yohimbine chemistry could be developed, which would add the pharmacological action of 1-hydroxyindole to the pharmacological action of 95.

We anticipated that this would open the door to the discovery of a new group of peripheral vasodilators. In other words, the authors hoped that by synthesizing 1-hydroxyyohimbine and its 1-hydroxy derivatives, we could reduce the toxicity of 95 and become a safe α2-blocker that would have the same or stronger pharmacological action as yohimbine. As a result, we succeeded in developing the desired lead, and preliminary test results showed that the toxicity was lower than that of yohimbine [94, 95].

Yohimbine Rearrangement

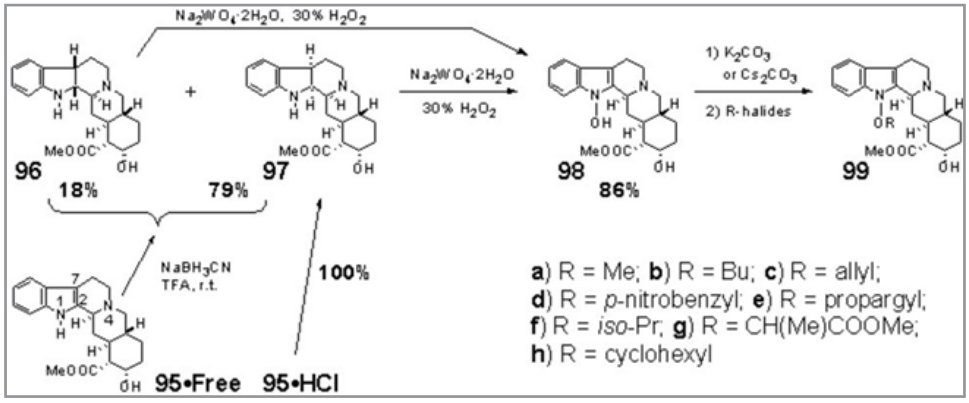
Now, we decided to test whether the rearrangement predicted in Scheme 8 actually occurs in the case of the yohimbine alkaloid skeleton. First, a novel 1-hydroxyyohimbine was required. Following the 1-hydroxyindole synthesis method, yohimbine (95) was reduced with NaBH3CN in TFA to give 2β,7β-(96) and 2α,7α-dihydroyohimbine (97) in 18 and 79% yields, respectively (Scheme 14). Then, the Na2WO4·2H2O and 30% H2O2 method was applied to 97 to obtain the desired 98 in stable crystal form in 86% yield for the first time. The formation of

by-product (96) at the first step not only reduces the yield of 98, but also complicates its separation. To improve the process, we discovered that the reduction of yohimbine hydrochloride (95·HCl) with NaBH3CN in TFA produced 97 in quantitative yield and stereoselectively while suppressing the by-production of 96. As a result, by carrying out the two reduction and oxidation steps sequentially, 98 could be obtained in 86% yield from 95·HCl [94, 95].

For the purpose of developing biologically active substances, we found that new 1-acyloxyyohimbine derivatives could be synthesized by reacting 98 with acylating reagents. Furthermore, we investigated the synthesis of various derivatives. As a result, when 98 was methylated with CH2N2, the 1-methoxy compound (99a) was obtained in 77% yield.

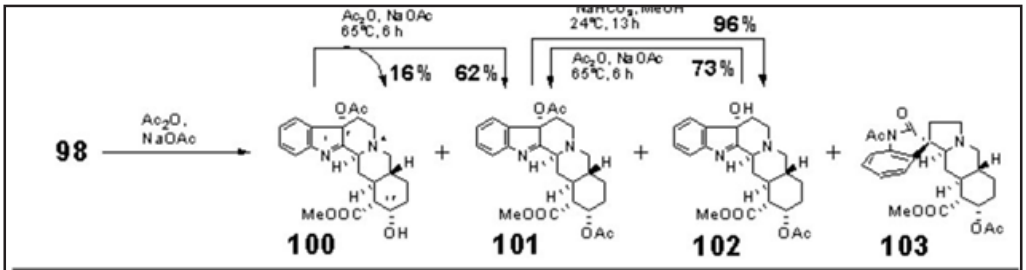
By using alkylating agents in DMF with K2CO3 or CsCO3 as a base, 1-butyloxyyohimbine (99b), 1-allyloxyyohimbine (99c), and 1-p-nitrobenzyloxyyohimbine (99d) were synthesized in 93, 99, and 90% yields. 1-Propargyloxyyohimbine (99e), 1-isopropyloxyyohimbine (99f), 1-(2-methoxycarbonyl)ethoxy- yohimbine (99g), and 1-cyclohexyloxyyohimbine (99h) were also obtained in nearly quantitative yields. These products, including 98 itself, showed potent α2 blocker activity [94, 95].

Scheme 14



The compound 98 in hand, we next attempted its reaction with Ac2O in the presence of NaOAc, which is a suitable condition to promote the rearrangement of the 1-hydroxy group, and the results are summarized in Table 2. As can be seen from the table, four possible products were stereoselectively produced: 7α-acetoxy- (100), 7α-acetoxy-17-O-acetyl- (101), 17-O-acetyl-7α-hydroxyyohimbine (102), and the predicted rearranged 2-oxindole (103).

Table 2



Entry	NaOAc (mol eq)	Reaction Conditions Temp. (°C)	Time (h)	Yield (%) of 100	101	102	103
1	2	63	0.5	52	12	0	0
2	2	65	1	71	8	0	0
3	"	"	6	23	41	0	9
4	"	"	40	0	40	0	15
5	20	"	6	0	0	12	12
6	—	"	48	9	44	0	16

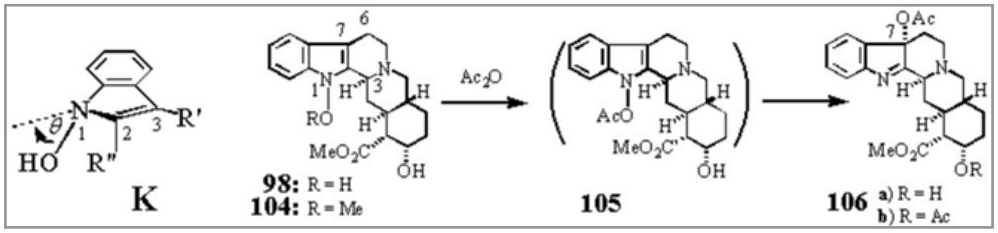
The rearrangement of the 1-acetoxy group to the 7α position was best achieved under the reaction conditions described in Entry 2, giving 100 (71%) and 101 (8%). With increasing reaction time (Entry 1–4), the yield of 100 decreased and that of 101 increased. In Entries 3 and 4, 2-oxindole (103) was produced as expected. The use of excess NaOAc made the reaction heterogeneous, resulting in a decrease in the overall yield of products (102 and 103) (Entry 5). When the reaction was carried out

without NaOAc, the yield of 103 was slightly improved (16%), and the yields of 100 and 101 were 9% and 44%, respectively (Entry 6). Thus, we discovered a new rearrangement reaction of the 1-acetoxy group to the 7α position in the reaction of 98 with Ac2O and NaOAc resulting in 7α-acetoxy- (100) and 7α,17α-di-acetoxy-7H-yohimbine (101) [94, 95].

The driving force for the migration reaction of the 1-acetyloxy group to the 7-position can be understood from the results of a large number of X-ray crystallography studies of 1-hydroxyindole compounds as follows. The N(1)-OH bond was found to be tilted at an angle θ from the indole plane (Scheme 15, Figure K). The nitrogen atom is sp3 hybridized, not sp2 hybridized, and this explains why 98 is acetylated at the 1-position to give 105, which then undergoes a [3,3] sigmatropic rearrangement, with the acetoxy group migrating from the less sterically hindered α-position to the 7-position [96, 97].

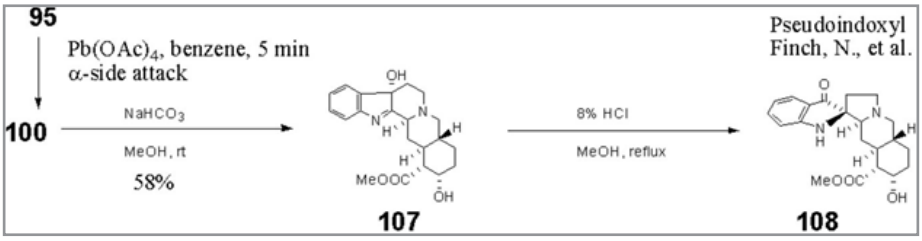
The structures of 101 was unambiguously determined by X-ray single crystal structure analysis, and their ORTREP drawing is shown in the X-ray section. The structures of 100 and 102 were confirmed by chemical correlation with 101. For example, treatment of 100 with acetic acid and pyridine at 65 °C for 6 h gave 101 in 62% yield and unreacted 100 in 16% yield. Under similar reaction conditions, 102 gave 101 in 73% yield, while 102 was obtained in 96% yield by regioselective hydrolysis of the 7α-acetoxy group by treatment of 101 with NaHCO3 in MeOH at room temperature.

Scheme 15



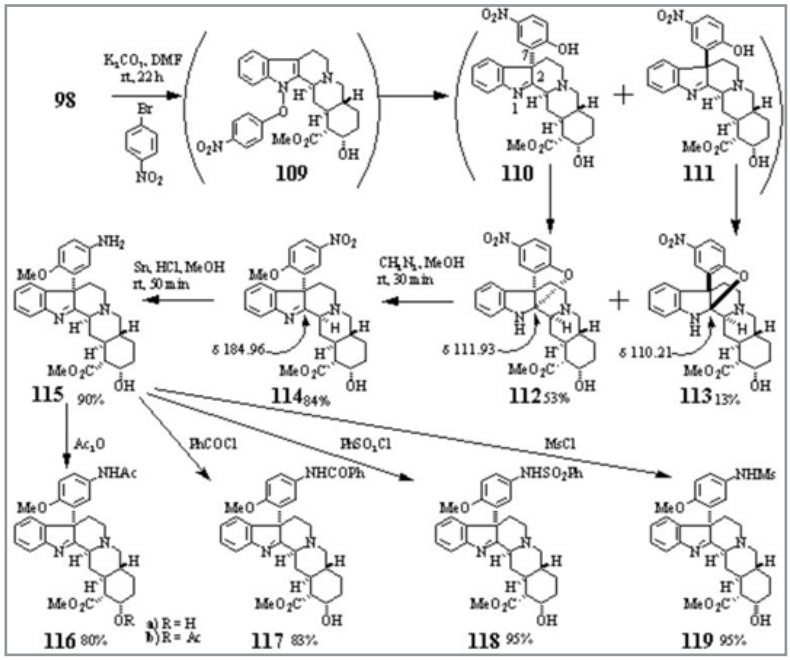
On the other hand, as shown in Scheme 16, Finch et al. reacted yohimbine (95) with Pb(OAc)4 to synthesize 100, which was then hydrolyzed by alkali to give 107. The compound was then rearranged by treatment with HCl/MeOH to give pseudoindoxyl (108, 3-oxindole) [97, 98].

Scheme 16



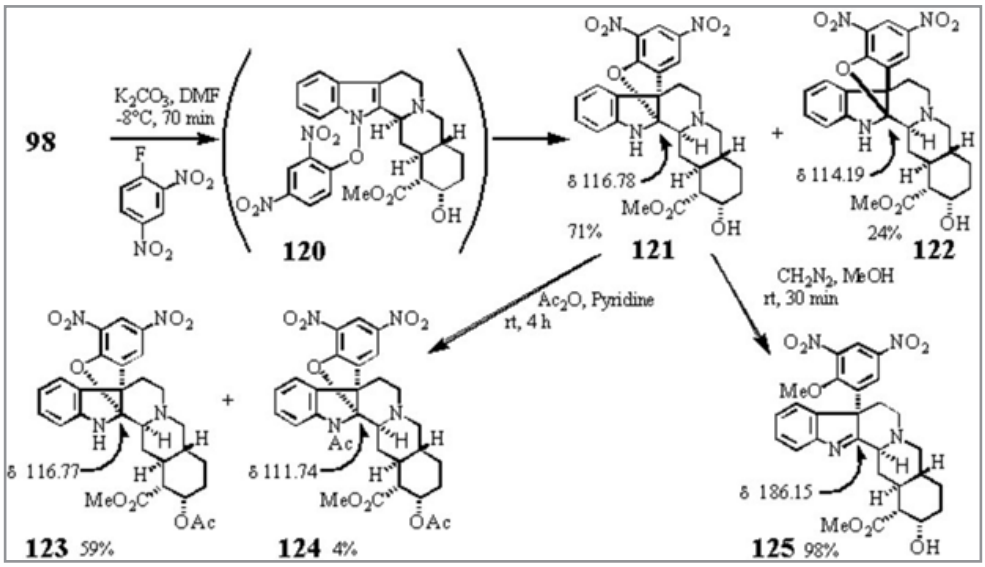
Since we have already synthesized 107 from 95, we have succeeded in realizing the skeletal rearrangement to 2-oxy- and 3-oxindole derivatives as predicted, as originally hypothesized [2].

Scheme 17



We were able to confirm that a rearrangement reaction similar to the above-mentioned 1-acetoxy group rearrangement also occurs with various 1-oxy derivatives (Scheme 17). That is, the reaction of 98 with p-nitrobromobenzene in the presence of K2CO3 produces 1-(p-bromonitrophenoxy)yohimbine (109). The 1-substituent then rearranges to the 7α-position to produce 110 and 111. The newly generated phenoxy oxygen then binds to the 2-indolenine carbon to form a furan ring intramolecularly to give (2α,7α)- (112) and (2β,7β)-26-nitro-benzofurano[2,3-n] yohimbine (113) in 53% and 13% yields, respectively (Scheme 17).

Scheme 18



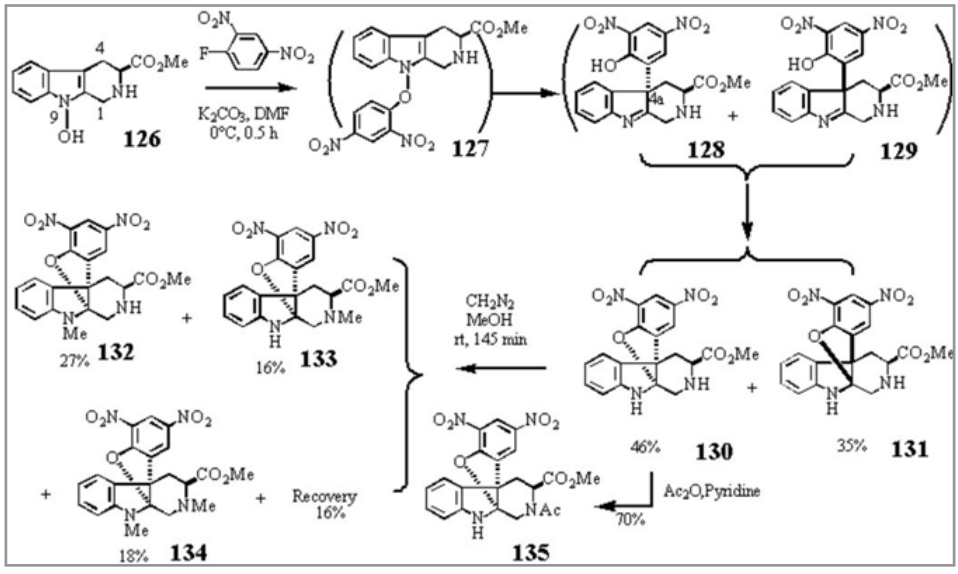
Reaction of the main product 112 with CH2N2 opened the benzofuran ring and the newly formed phenoxy group was captured by CH2N2 to give 114 in 84% yield. Further reduction of 114 with Sn-HCl afforded the corresponding amine compound 115 in 90% yield. Subsequent acylation of 115 with acetic anhydride, benzoyl chloride, phenylsulfonyl chloride, and methanesulfonyl chloride afforded the corresponding acylated compounds 116, 117, 118, and 119 in 80%, 83%, 95%, and 95%, respectively.

Similarly, reaction of 98 with 2,4-dinitrofluorobenzene afforded 120, followed by 121 and 122 in 71% and 24%, respectively (Scheme 18). Reaction of 121 with acetic anhydride afforded 123 and 124 in 59% and 4%, respectively. Reaction of 121 with CH2N2 opened the furan ring and the resulting phenol was methylated to give 125 in 98% yield.

A similar rearrangement reaction was observed with β-carbolines as with yohimbine (Scheme 19). [95] The reaction of 1,2,3,4-tetrahydro-3-methoxycarbonyl-9-hydroxy-β-carboline (126) with 2,4-dinitro- fluorobenzene in the presence of K2CO3 afforded (S)-(4aα,9aα)-(130) and (S)-(4aα,9aα)- 3α-methoxycarbonyl-1,13-dinitro-1,2,3,4-tetrahydro-9H-benzofurano[2,3-m]-β-carboline (131) in 46% and 35% yields, respectively. The reaction first afforded the 9-(2,4-dinitrophenyloxy) derivative (127), followed by rearrangement of the 9-(2,4-dinitrophenyloxy) group to the 4a-position to give 128 and 129.

Subsequent ring closure of the phenoxy oxygen to give the benzofurans, 130 and 131.

Scheme 19



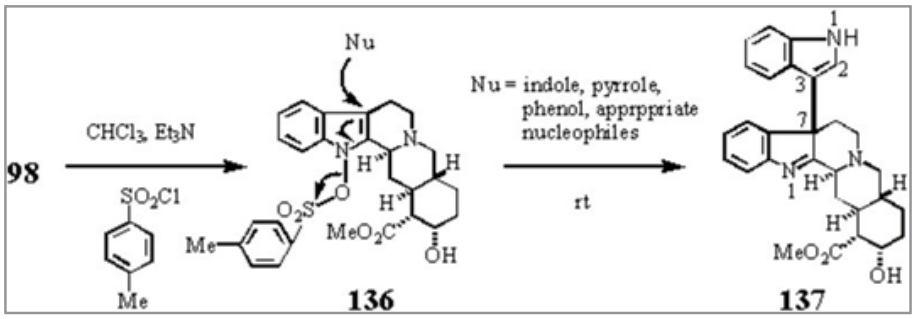
Treatment of 130 with CH2N2 afforded the methylated analogs 132, 133, and 134 in 27%, 16%, and 18%, respectively. Acetylation of 130 with Ac2O and pyridine afforded 135 in 70% yield. [92, 93, 94, 95] The compound 135 crystallized well, and its structure was confirmed by X-ray crystallography.

Discovery of Nucleophilic Substitution at the 7α Position of Yohimbine

When 1-hydroxyyohimbine (98) is reacted with p-toluenesulfonylchloride in the presence of a base, an unstable 1-tosyloxyyohimbine (136) is obtained with the 1-tosyloxyl group as a leaving group Scheme 20. Therefore, we thought that if a nucleophile is present in the reaction system, the nucleophile will attack the 7-position following the SN2' mechanism as the 1-substituent eliminates, and a 7-substituted yohimbine derivative will be obtained. Indole was selected as a nucleophile with strong nucleophilic ability, and reacted with 98 in the presence of triethylamine in $CHCl_3$. As expected, 137 was produced in 19%, with the nucleophile added from the 3-position of the indole ring to the 7-position of yohimbine.

In the same way, by using appropriate nucleophile, such as pyrrole, phenol, and N,N-dimethylaniline, it became possible to synthesize yohimbine derivatives with the desired nucleophile added to the 7-position. What pharmacological effects will these compounds have? We look forward to seeing future research results [93, 94, 95].

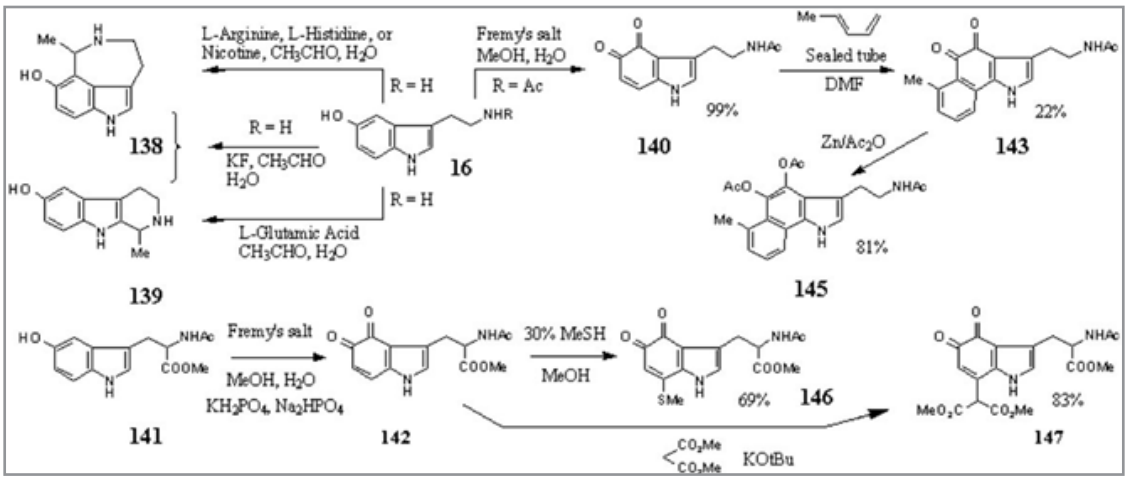
Scheme 20



How to Keep Mental Function Normal

Serotonin is a neurotransmitter that reduces stress and anxiety, stabilizes the mind, improves mental agility, and enhances intuition and imagination. It is also known as a brain substance that activates the brain, improving sleep, suppressing appetite, relieving pain, etc. Social problems such as depression, dementia, mental illness, and alcoholism caused by a lack of serotonin are endless.

Scheme 21



It is well known that ethanol is metabolized to acetaldehyde in the cytoplasm of brain neurons. We hypothesized that acetaldehyde is converted into a substance that inhibits normal mental function.

In fact, we demonstrated that when serotonin and acetaldehyde are allowed to coexist in water at body temperature (36.5°C) in the presence of acidic amino acids such as L-glutamic acid, the known Pictet-Spengler type cyclization product 1,2,3,4-tetrahydro-6-hydroxy-1-methyl-β-carboline (139) is produced, as shown in Scheme 21. [99, 100]

On the other hand, we discovered that under similar conditions, in the presence of basic amino acids such as L-histidine and L-arginine, 3,4,5,6-tetrahydro-7-hydroxy-6-methyl-1H-azepino[5,4,3-cd]indole (138) was produced as shown in Table 3. Furthermore, under similar conditions, it was found that 138 was also produced in the presence of nicotine, and both compounds 138 and 139 were produced in the presence of KF [99, 100]. It is reasonable to predict that 138 and 139 will be produced in the brain and nerves in the same way if fluoride ion and/or nicotine accidentally enter nerve cells after smoking or drinking alcohol and/or when using fluoride contained toothpaste or tap water.

Table 3

16·HCl —(MeCHO in Solvent; Air (Entries 1 and 3); Ar (Entries 2,4—13))→ 139 + 138 + 16

Entry	Solvent	Additive (mol eq.)	MeCHO (mol eq.)	Reaction Conditions Temp. (°C)	Time (h)	Yield (%) of 139	138	16
1*1	MeOH	—	50	reflux	1	26	0	0
2	Pyridine	—	5	"	9	34	trace	37
3*2	MeOH	—	50	"	20	53	27	0
4	MeOH-H_2O (3:1)	K_2CO_3 (1)	5	"	20	11	12	52
5	Pyridine-H_2O (3:1)	K_2CO_3 (1)	"	"	3	0	30	4
6	MeOH	Imidazole (2)	"	"	4	3	7	28
7	MeOH-H_2O (3:1)	KF (2)	"	"	4	24	30	33
8	H_2O	L-Glutamic acid (2)	0.9	36.5	6	45*3	0	40
9	"	"	"	"	48	55*3	0	38
10	"	L-Histidine (2)	"	"	24	trace	12*3	63
11	"	L-Arginine (2)	"	"	15	5*3	31*3	38
12	"	Nicotine (2)	"	"	48	trace	17*3	42
13	"	KF (2)	"	"	120	22	5	53
14	"	—	"	"	72	55	0	39

*1 The reaction was carried out at pH 4. *2 The reaction was carried out at pH 5. *3 The product was not optically active.

Serotonin was also oxidized to give tryptamine-4,5-dione (140), a neurotoxin.[101-110] Similarly, 5-hydroxytryptophan (141) was oxidized to give the similar tryptophan-4,5-dione (142). The reactivity of 140 was extremely high, and it reacted with 1,3-pentadiene to give the adduct 143 in 22% yield [101].

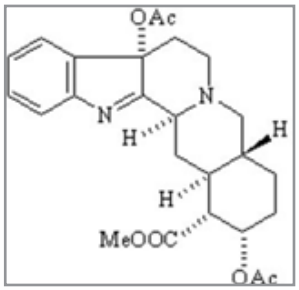
The reaction of 143 with Zn/Ac2O gave well-crystalline 4,5-diacetoxy-3-(2-acetylaminoethyl)-6-methyl-1H-benz[g]indole (145) in 81% yield. The structure of 145 was confirmed by X-ray crystallography. The corresponding tryptophan-4,5-dione (142) was also highly reactive, and reacted with methyl mercaptan or dimethyl malonate to give 146 and 147 in 69% and 83% yields, respectively. These facts demonstrated that when serotonin or 5-hydroxytryptophan is oxidized by reactive oxygen species in vivo, it generates the 4,5-diones and reacts with the surrounding cellular components.

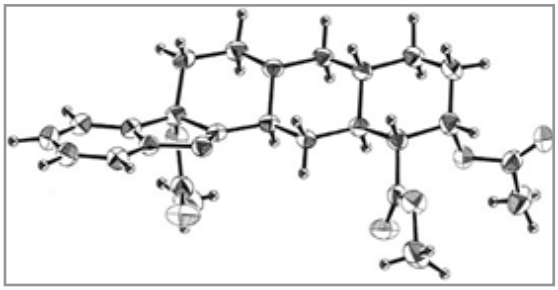
Both 138 and 139 are neurotoxic substances. 140 and 142 are neurotoxins that react with components (proteins and nucleic acids) of nerve cells in the brain and spinal cord, gradually degenerating nerves. They are highly likely to reduce normal function, cause hallucinations, and promote dementia, Parkinson's disease, epilepsy, multiple sclerosis, amyotrophic lateral sclerosis (ALS), and brain aging. In order to maintain normal brain function and live a healthy lifespan, it is important to refrain from drinking alcohol and smoking as part of our lifestyle. It is also important to prevent the production of neurotoxic substances 138, 139, 140, and 142 in the body. [101-110]

The active oxygen scavengers 7g and 9g, which we developed as an extension of the chemistry of 1-hydroxyindole, will suppress the generation of acetaldehyde and also suppress the production of 140 and 142, and will serve the purpose of maintaining and improving people's health and preventing diseases. Knowledge of phytoalexin can suppress the occurrence of cancer by reviewing and improving daily dietary habits. In this paper, we learned the limitations of current osteoporosis drugs, clarified the causes of various diseases such as neurodegeneration, and showed the direction of drugs that are expected to be developed in the future. It will contribute to extending people's healthy lifespan.

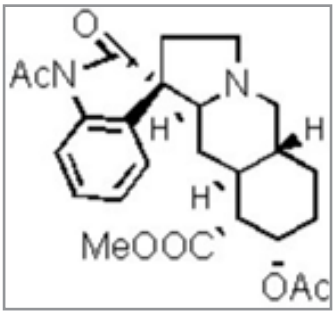
Structure Determination by X-ray Single Crystal Analysis

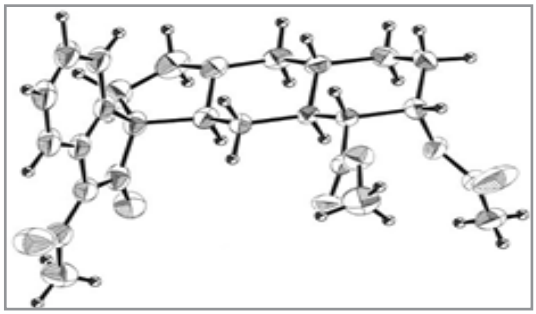
The structures of the novel compounds (101, 103, 87, 135, 136, and 145) were determined by the X-ray single crystal structure analysis results. ORTEP drawings are shown below.



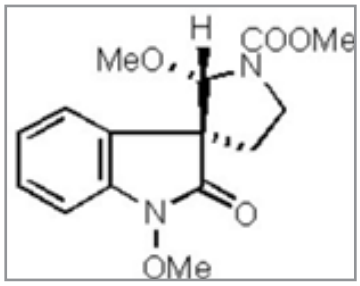


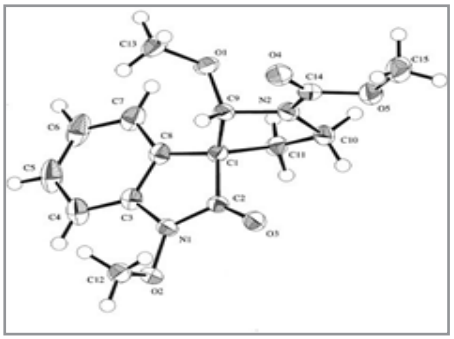
The Final R- and Rw-factors After Full-matrix Least-squares Refinements were 0.030 and 0.036 for 1632 Observed Reflections [I>3.00σ (I)], Respectively.



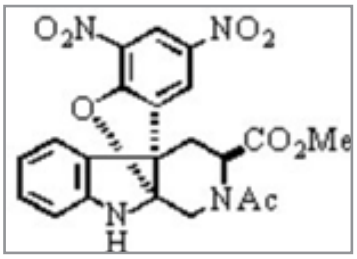


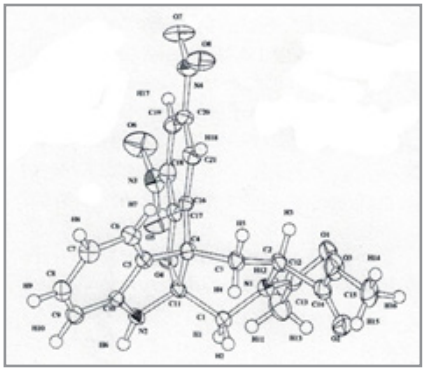
The Final R- and Rw-factors after Full-matrix Least-squares Refinements were 0.031and 0.036 for 1632 Observed Reflections [I>3.00σ (I)], Respectively.



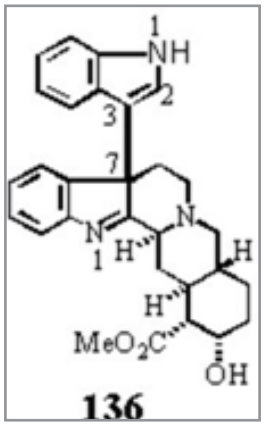


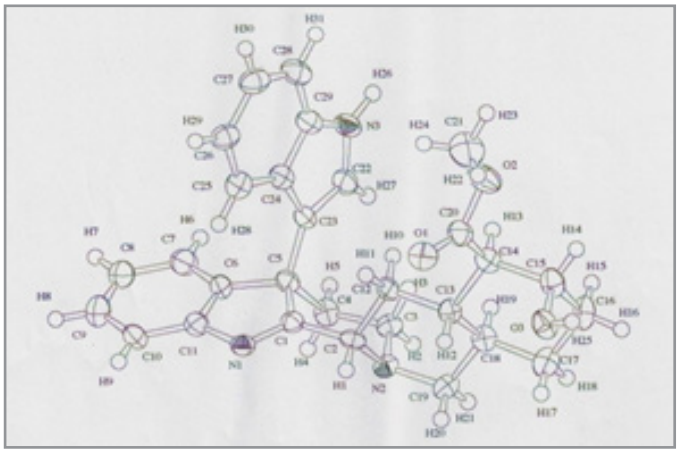
The Final R- and Rw-factors After Full-matrix Least-squares Refinements were 0.060 and 0.091for 3248 Observed Reflections [I>3.00σ (I)], Respectively.



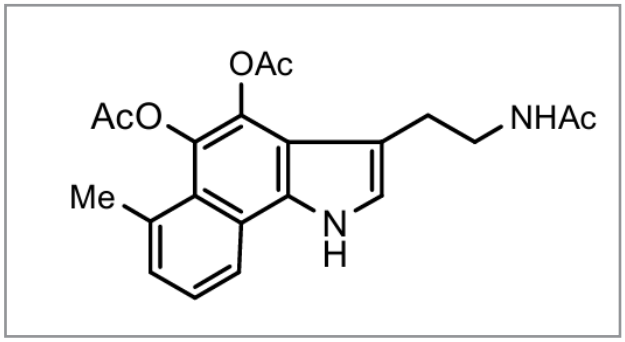


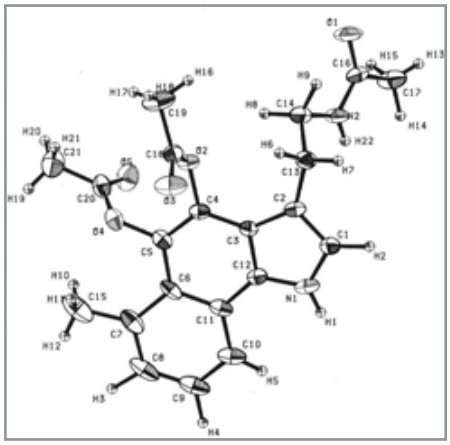
The Final R- and Rw-factors After Full-matrix Least-squares Refinements were 0.060 and 0.091for 5781 Observed Reflections [I>3.00σ (I)], Respectively.





The Final R- and Rw-factors After Full-matrix Least-squares Refinements were 0.060 and 0.091 for 5781 Observed Reflections [I>3.00σ (I)], Respectively.





The Final R- and Rw-factors After Full-matrix Least-squares Refinements were 0.070 and 0.112 for 5144 Observed Reflections [I>3.00σ (I)], Respectively.

Conclusion

We proposed the 1-hydroxyindole hypothesis. We succeeded in synthesizing the author's imagined compounds 1-hydroxyindole and 1-hydroxytryptophan, proving that the hypothetical world is a real frontier. We also succeeded in synthesizing the imaginary compound 1-hydroxy-N-acyltryptamine, and discovered that it, along with N-acyltryptamine, is an α2 blocker that instantly stops itching, has a vasodilatory effect, improves blood circulation, and has an inhibitory effect on thrombosis. As an application of this, it has saved many patients, including the author, who suffer from the itchiness and pain of atopic dermatitis.

In addition, we synthesized phytoalexin derivatives from radish and wasabi, proving that the chemistry of 1-hydroxyindole is useful as an anti-cancer and anti-allergic substance through daily diet. We then discovered the nucleophilic substitution reaction of 1-hydroxy-N-acyltryptamine to afford serotonin and melatonin. Furthermore, we demonstrated the possibility that brominated derivatives of melatonin and 1-hydroxytryptophan could be promising osteoporosis treatments that suppress the activity of osteoclasts and activate osteoblasts. Meanwhile, by incorporating 1-hydroxyindole chemistry into ergot alkaloids, we discovered that 6,7-secoagroclavine is a dopamine agonist.

Furthermore, by incorporating 1-hydroxyindole chemistry into the β–carboline and yohimbine skeletons, we discovered a new rearrangement reaction and succeeded in synthesizing many β–carboline derivatives and new yohimbine skeleton rearrangements.

We also succeeded in synthesizing an α2 blocker with reduced toxicity of yohimbine. Furthermore, we discovered a reaction that allows any nucleophile to be introduced into the 7-position of the yohimbine skeleton, opening the way to freely synthesize new derivatives.

We hope that many of the new compounds described in this paper will play an active role in the world in the future as treatments for dementia and osteoporosis, which the elderly face. We sincerely hope that researchers will appear who will carry out further pharmacological tests on the new derivatives described in this paper in order to contribute to society.

As an important part of daily life, we found that acetaldehyde produced from ethanol reacts with serotonin in neurons to produce neurotoxins such as azepino[5,4,3-cd]indole and 6-hydroxy-1-methyl-β-carboline derivatives. We also clarified that the substances that catalyze this reaction are nicotine and fluoride ions, which shows that refraining from smoking and drinking is one way to maintain mental function normal.

In 2024, utilizing the chemistry of 1-hydroxyindole, Chinese researcher found that 1-hydroxyindole derivatives inhibit cancer growth by suppressing the action of lactate dehydrogenase [111]. In 2025, Dr. Takahashi of kyoto university disclosed that cancer cells metastasize by avoiding sources of reactive oxygen [112]. The high metastasis ability of cancer cells makes cancer treatment difficult. Based on this new discovery, it can be thought that an active oxygen scavenger could rob cancer cells of their ability to metastasize throughout the body, and could potentially become a new drug for cancer treatment. We believe if 1-hydroxy- and/or N-acyl-tryptamine is used in combination with an anticancer drug, it would be possible to prevent metastasis and effectively attack cancer cells.

Our research results will help create low molecular weight pharmacologically active substances that will help maintain normal mental function and resolve social problems caused by aging and disease.

Acknowledgements

We would like to express our deep gratitude to all the graduate students and students cited in the references. We would also like to thank Prof. Hattori, A., Tokyo Medical and Dental Univ., Prof. Suzuki, N., Kanazawa Univ., Prof. Mikami, Y., Niigata Univ.,

Prof. Tanaka, Y., Toho Univ., Prof. Watanabe, H., Toyama Univ., Dr. Kurashina, K., Kissei Pharmaceutical Co., for their pharmacology tests.

References

1. Professor Emeritus of Kanazawa University. SOMEIYAKKO Kenkyusho, director, 56-7 Matsuhidai, Matsudo, Chiba 270–2214, Japan.
2. Somei, M. (2008). Imagination and Creation: 1-Hydroxyindole Chemistry and the dream Challenge, Yakugaku Zasshi, 2008, 128, 527—563.
3. SOMEI, M., Somei, H., Somei, K. Tanaka, Y., (2025). Effective Treatment for Itching Caused by Atopic Dermatitis, World Journal of Molecular Medicine, 2(1), 01-10. doi.org/10.63620/MKWJMM.2025.1014
4. SOMEI, M., Somei, H., Somei, K. (2025). Proposals of A Concrete and Practical 'Cure for The Earth' With 'SOMRE' And 'VED' As The "Medicine of The Earth", Eliminating World Hunger, Global Warming, And Restoring the Green Earth, Word Jour of Molecule Medicine, 2(1), 01-82. DOI : doi.org/10.63620/MKWJMM.2025.1012
5. Somei, M., (1991). Chemistry of 1-hydroxyindole and its derivatives, J. Synth. Org. Chem. Jpn., 49, 205—217.
6. Somei, M. (1999). 1-Hydroxyindoles, Heterocycles, 1999. 50, 1157—1211.
7. Somei, M. (2002). Recent Advances in the Chemistry of 1-Hydroxyindoles, 1-Hydroxytryptophans, and 1-Hydroxytryptamines, Advances in Heterocyclic Chemistry, Vol. 82, ed. by A. R. Katritzky, Elsevier Science (USA), pp. 101—155.
8. Somei, M. (2006). A Frontier in Indole Chemistry: 1-Hydroxyindoles, 1-Hydroxytryptamines, and 1-Hydroxytryptophans, Topics in Heterocyclic Chemistry; Vol. 6, ed. by Shoji Eguchi, Springer-Verlag, Berlin, pp. 77—111.
9. Somei, M., 1-Hydroxyindole derivatives, JP Patent 3795093.
10. Somei, M., and Shoda, T., (1981). A Facile Route to 1-Acetoxy- and 1-Methoxyindoles, Heterocycles, 16(9), 1523—1525.
11. Yamada, K., Tanaka, Y., and Somei, M., (2009). Synthesis of Nb-acyl tryptamines and their 1-hydroxytryptamine derivatives as new α2-blockers, Heterocycles, 79, 635—645.
12. Somei, M., Shigenobu, H., and Tanaka, Y., α2 Receptor antagonists and vasodilators containing indole derivatives as active ingredients, JP Patent 3964417.
13. Somei, M., Shigenobu, H., and Tanaka, Y., α2 Receptor blocker and vasodilator comprising indole derivative as active ingredient, US Patent 7,872,040 B2.
14. Somei, M., Somei, K., Somei, H., Atopic dermatitis treatment that reduces itching, JP Patent 7048051.
15. Somei, M., Somei, K, Somei, H., Atopic dermatitis treatment that reduces itching, US Patent 11,065,229 B2.
16. Somei, M., Yamada, K., Tanaka, Y., Somei, H., Somei, K., (2023). Development and application of N-acyltryptamine (VED) which can treat almost all skin problems, 122nd Symposium on Organic Synthesis, Japan, Symposium Paper, O-31, 72—73.
17. Somei, M., Somei, K, Somei, H., Atopic dermatitis treatment that reduces itching, US Patent 11,065,229 B2.
18. Sakamoto, H., Takanami, K., (2025). Itch research in fish and mammals, Farumashia, 61, 50—54.
19. Andoh, M., Nishida, S., Somei, M., Kuraishi, T., (2023). Effect of N-nonanoyltryptamine on itching in mice with surfactant-induced eczema dermatitis, The 97th Annual meeting of the Japanese Pharmacological Society, Abstract. Session ID: 97_3-B-009-2.
20. Altounyan, R. (1977). The discovery of Intal as told by Roger Altounyan to the Society for Drug Research, Shinryou Shinsha Ltd., Harata printing Co., Ltd., Japan.
21. Natui, M., Kawagoe, M., Someki, M., Koizumi, Y., Oyamada, Y., Sugiyama, T. (2014). Stimulation of the hair growth by α2-blocker SST-VED, Akita j. Med, 41, 23-33.
22. Somei, M., Yamada, F., Kurauchi, T., Nagahama, Y., Hasegawa, M., Yamada, K., Teranishi, S., Sato, H., and Kaneko, C., (2001). The chemistry of indoles. CIII. 1) simple syntheses of serotonin, N-methylserotonin, bufotenine, 5-methoxy-N-methyltryptamine, bufobutanoic acid, N-(indol-3-yl) methyl-5-methoxy-N-methyltryptamine, and lespedamine based on 1-hydroxyindole chemistry. Chemical and pharmaceutical bulletin, 49(1), 87-96.
23. Gribble, G. W. (1994). Recent developments in indole ring synthesis—Methodology and applications. Contemporary Organic Synthesis, 1(3), 145-172.
24. Pindur, U., & Adam, R. (1988). Synthetically attractive indolization processes and newer methods for the preparation of selectively substituted indoles. Journal of heterocyclic chemistry, 25(1), 1-352.
25. Sundberg, R. J. (1970). 'The Chemistry of Indoles', Academic Press, New York, 1-489.
26. Guroff, G., Daly, J.W., Jerina, D.M., Renson, J., Witkop, B., & Undenfriend, S. (1967). NIH shift: Hydroxylation of alkylaromatics is through arene oxide by the action of mlonooxygenase, Science, 157, 1524-1530
27. Hanzlik, R. P., Hogberg, K., & Judson, C. M. (1984). Microsomal hydroxylation of specifically deuterated monosubstituted benzenes. Evidence for direct aromatic hydroxylation. Biochemistry, 23(13), 3048-3055.
28. Hayashi, T., Peng, W., Nakai, Y. Y., Yamada, K., & Somei, M. (2002). Nucleophilic substitution reaction on the nitrogen of indole nucleus: A novel synthesis of 1-aryltryptamines. Heterocycles, 57(3), 421-424.
29. Somei, M., & Fukui, Y. (1993). Nucleophilic substitution reaction of 1-hydroxytryptophan and 1-hydroxytryptamine derivatives regioselective syntheses of 5-substituted derivatives of tryptophan and tryptamine. Heterocycles, 36(8), 1859-1966..
30. Suzuki, N., Kitamura, K-I., Omori, K., Nemoto, T., Satoh, Y., Tabata, M.J., Ikegame, M., Yamamoto, T., Ijiri, K., Furusawa, Y., Kondo, T., Takasaki, I., Tabuchi, Y., Wada, Shimizu, N., Sasayama, Y., Endo, M., Takeuchi, T., Nara, M., Somei, M., Maruyama, Y., Hayakawa, K., Shimazu, T., Shigeto, Yano, Y.S. and Hattori, A., (2009). Response of osteoblasts and osteoclasts in regenerating scales to gravity loading, Biological Sciences in Space, 23, 211-216.
31. Suzuki, N., Kuroda, K., Ikegame, M., Takino, H., Tsunoda, K., Izumi, R., Tabuchi, Y., Y., Yachiguchi, K., Endo, M., Matsubara, H., Yano, S., Shimazu, T., Honda, M., Maruyama, Y., Watanabe, K., Takahashi, A., Hirayama, J., Hattori, A., (2025). Goldfish regenerated scale culture at low temperatures improves osteoblast and osteoclast survival in scales without loss of the osteoblast and osteoclast response

to changes in gravity. Life Sciences in Space Research, 46, 128-136. DOI: 10.1016/j.lssr.2025.04.004
32. Somei, M., Suzuki, N., Hattori, Y., (2007). Indole derivatives and their uses: Osteoporosis treatment candidate (JP Patent No. 4014052).
33. Somei, M., Suzuki, N., Hattori, Y., Indole derivative and application thereof, Osteoporosis treatment candidate, US Patent 8,053,462 B2.
34. Suzuki, N., Hattori, Y. (2002). Melatonin suppresses osteoclastic and osteoblastic activities in the scales of goldfish, J. Pineal Res, 33, 253-258
35. Somei, M., (2004). A new drug for osteoporosis that builds bones and inhibits destruction, The Hokkoku Shinbun, 22.
36. Somei, M., Suzuki, N., Hattori, Y., Tryptophan derivatives and application thereof, Osteoporosis treatment candidate, US Patent 7,659,304 B2.
37. Somei, M., Suzuki, N., Hattori, Y., Tryptophan derivatives and their uses, Osteoporosis treatment candidate, JP Patent 5070050.
38. Somei, M., Tryptophan derivatives and their uses, Osteoporosis treatment candidate, EP Patent 1,911,744 B1.
39. Somei, M., Suzuki, N., Hattori, Y., Tryptophan derivatives and their uses, Osteoporosis treatment candidate, CN Patent 702,124.
40. Suzuki, N., Somei, M., Seki, A., Sekiguchi, T., Tabuchi, Y., Mishima, H., Kase1, Y., Atsushi Kaminishi, A., Koji Yachiguchi, K., Kitamura, K., Oshima, Y., Hayakawa, K., Yano, S., Hattori, A., (2015). Novel tryptophan Derivatives as potentially effective therapeutic drugs to treat bone diseases, Am. J. Life Sci., 3 (3-2), 31—38 and references cited therein.
41. Hattori, A., (2013). Melatonin research in space and anti-aging medicine. Anti-Aging Medicine, 9, 356—363.
42. Hattori, A., Suzuki, N., and Somei, M., (2006). Melatonin up to date-Melatonin-Effects on Bone, Anti-Aging Medicine, 2 (No.1), 78—86.
43. Suzuki, N., (2011). Novel effects of melatonin: Effects on bones and development of drugs for bon for bone disease using its derivatives, Comparative Endocrinology, 37 (No. 143), 194—203.
44. Iwaki, T., Fujita, Y., Yamada, F., and Somei, M., (2003). Water Soluble Melatonins: Syntheses of Melatonins Carrying a Glycosyl Group at the 1-Position, Heterocycles, 60 (6), 1411—1418.
45. Suzuki, N., Somei, M., Kitamura, K., Reiter, R.J., and Hattori, A., (2008). Novel Bromomelatonin Derivatives suppress Osteoclastic Activity and Increase Osteoblastic Activity: Implications for the Treatment of Bone Diseases, J. Pineal Res., 44, 326—334, and references cited therein.
46. Suzuki, N., Somei, M., Seki, A., Reiter, R.J. and Hattori, (2008). Novel bromomelatonin derivatives as potentially effective drugs to treat bone diseases, J. Pineal Res., 45, 229—234.
47. Suzuki, N., (2004). New osteoporosis drug shines a light, The Hokuriku Chunichi Shinbun, April 22.
48. Suzuki, N. (2004). A miracle cure for osteoporosis, The Hokkoku Shinbun, April 22.
49. Mikami, Y., Matsumoto, T., Kano, K., Toriumi, T., Somei, M., Honda, MJ., Komiyama, K., (2014). Current status of drug therapies for osteoporosis and the search for stem cells adapted for bone regenerative medicine, Anat Sci Int., 89:1—10, and references cited therein.
50. Mikami, Y., Somei, M., and Takagi, M., (2009). A new synthetic compound, SST-VEDI-1, inhibits osteoblast differentiation with a down-regulation of the osterix expressions, J. Biochem, 145, 239—247.
51. Mikami, Y., Somei, M., Apoptosis inhibitors, Treatment for diseases caused by neuronal loss, Alzheimer's disease, and Parkinson's disease, JP Patent 5370957.
52. Mikami, Y., Somei, M., Apoptosis inhibitors, Treatment for diseases caused by neuronal loss, Alzheimer's disease, and Parkinson's disease, US Patent 8,258,174 B2.
53. Somei, M., Yamada, K., Hasegawa, M., Tabata, M., Nagahama, Y., Morikawa, H., and Yamada, F., (1996). Preparations of 1-Hydroxyindole Derivatives and Their Potent Inhibitory Activities on Platelet Aggregation, Heterocycles, 43(9), 1855—1858.
54. Somei, M., Iwaki, T., Yamada, F., Tanaka, Y., Shigenobu, K., Koike, K., Suzuki, N., and Hattori, A., (2006). The Ideal Synthetic Method Aimed at the Leads for an α2-Blocker, an Inhibitor of Platelet Aggregation, and an Anti-osteoporosis Agent, Heterocycles, 68 (8), 1565—1569.
55. Somei, M., Kimura, j., and Takano, S., Platelet aggregation inhibitors: Treatment for cerebral infarction and myocardial infarction, JP Patent 4248814.
56. Somei, M., Noguchi, K., Yamagami, R., Kawada, Y., Yamada, K., and Yamada, F., (2000). Preparation and a Novel Rearrangement Reaction of 1,2,3,4-Tetrahydro-9-hydroxy-β-carboline, and Their Applications for the Total Synthesis of (±)-Coerulescine, Heterocycles, 53 (1), 7—10.
57. Ihara, M., Nishino, M., Taguchi, A., Yamamoto, Hattori, Y., Saito, S., et al., (2014). Cilostazol Add-On Therapy in Patients with Mild Dementia Receiving Donepezil: A Retrospective Study. Plos One 9(2): e89516. https://doiorg /10.1371/journal.pone.0089516.
58. Somei, M., Kobayashi, K., Shimizu, K., and Kawasaki, T., (1992). A Simple Synthesis of a Phytoalexin, Methoxybrassinin, Heterocycles, 33(1), 77—80.
59. Kawasaki, T., and Somei, M., (1990). The First Total Syntheses of 9-Methoxycarbazole-3- carboxaldehyde and Methoxybrassinin, Heterocycles, 31(9), 1605—1608.
60. Somei, M., Kawasaki, T., Shimizu, K., Fukui, Y., and Ohta, T., (1991). Syntheses of methyl 1-hydroxyindole-3-acetate, Nb-acetyl-1-hydroxytryptamine, (±)- and (S)-1-hydroxytryptophan Derivatives, Chem. Pharm. Bull., 39, 1905—1907.
61. Yamada, K., Tomioka, S., Tanizawa, N., and Somei, M., (2004). Novel Syntheses of 1-Hydroxy-6-, -5-Nitroindole-3-carbaldehyde, and Their Derivatives as Daikon-Phytoalexin Analogs, Heterocycles, 63 (7), 1601—1611, and references cited therein.
62. Yamada, F., Yamada, K., Takeda, H., and Somei, M., (2001). Simple syntheses of analogs of a wasabi phytoalexin, Heterocycles, 55, 2361—2368.
63. Pedras, M. S. C., and Sorensen, J.L., (1998). Phytoalexin accumulation and antifungal compounds from the crucifer wasabi, Phytochemistry, 49, 1959—1965. These authors did not cite us in spite of using our original 1-methoxyindole synthetic method.
64. Takasugi, M., Monde, K., Katsui , N., Shirata, A., (1988).

Novel sulfur-containing phytoalexins from the chinese cabbage Brassica campestris L. ssp. pekinensis (Cruciferae), Bull. Chem. Soc. Jpn., 61, 285—289.
65. M. Takasugi, M., Monde, K., Katsui, N., and Shirota, A., (1987). Symposium Papers, The 29th Symposium on The Chemistry of Natural Products, Sapporo, p. 629.
66. Yamada, F., Yamada, K., Takeda, H., and Somei, M., (2001). Simple Syntheses of Analogs of a Wasabi Phytoalexin, Heterocycles, 55, 2361—2368.
67. Somei, M., Tanimoto, A., Orita, H., Yamada, F., and Ohta, T., (2001). Syntheses of Wasabi Phytoalexin and Its 5-Iodo Derivative, and Their Nucleophilic Substitution Reactions, Heterocycles, 54 (1), 425—432.
68. Tanaka, M., Hashimoto, D., Kanazawa, K., (2009). Effect of Wasabi Isothiocyanate on Tumor Promotion Model Using JB6 Cells Derived from Normal Mouse Epidermis, The 3rd Wasabi Forum, Abstract, Paper 5
69. F. Yamada, Hayashi, T., Yamada, K., and Somei, M., (2000). Simple Syntheses of Indol-1-yl Glucosides, Heterocycles, 53 (9), 1881—1884.
70. Singh, S.B., Zink, D.L., Polishook, J.D., Dombrowski, A.W., Darkin-Rattray, S.J., Schmatz, D.M., and Goetz, M.A., (1966). Apicidin Tetrahedron Lett., 45, 8077.
71. Foster, C.A., Dreyfuss M., Mandak B., Meingassner J.G., Naegeli H.U., Nussbaumer A., Oberer, L., Scheel, G., and Swoboda E-M., (1994). HUN-7293: J. Dermatol., 21, 847.
72. Somei, M., Yokoyama, Y., Murakami, Y., Ninomiya, I., Kiguchi, T., and Naito, T., (2000). "Recent Synthetic Studies on the Ergot Alkaloids and Related Compounds", The Alkaloids, Vol. 54, ed. by Cordell, G.A., Academic Press, pp. 191—257.
73. Somei, M., Ohnishi, H., and Shoken, Y., (1986). Synthesis of (±)-1-methoxy-6,7-secoagroclavine, Chem. Pharm. Bull., 4, 677— 681.
74. Somei, M., (1988). Aiming for the ultimate synthesis of ergot alkaloid compounds Yakugaku Zasshi, 108 (5), 361—380.
75. Somei, M., and Yamada, F., (1984). A Practical Synthesis of the Ergot Alkaloid, (±)-6,7-Secoagroclavine, Chem. Pharm. Bull., 32(12), 5064—5065.
76. Somei, M., Ohnishi, H., and Shoken, Y., (1986). A Practical Synthesis of the 1-Methoxy Analog of an Ergot Alkaloid, (±)-1-Methoxy-6,7-secoagroclavine, Chem. Pharm. Bull., 34, 677—681.
77. H. Watanabe, M. Somei, S. Sekihara, K. Nakagawa, and F. Yamada, Dopamine Receptor Stimulating Effects of Chanoclavine Analogues, Tricyclic Ergot Alkaloids, in the Brain, Jpn. J. Pharmacol., 45, 501—506 (1987).
78. Nakagawa, K., and Somei, M., (1991). Ergot alkaloids: The first and five step total syntheses of (-)- and (+)-6,7-secoagroclavine, and the syntheses of (-)- and (+)-6-nor-6-propyl- 6,7-secoagroclavines ((-)- and (+)-KSU1415), Heterocycles, 32, 873—878.
79. Patel, K; Gadewar, M; Tripathi, R; Prasad, SK; Patel, Dinesh Kumar (2012). "A review on medicinal importance, pharmacological activity and bioanalytical aspects of β-carboline alkaloid Harmine, Asian Pacific Journal of Tropical Biomedicine, 2 (8), 660—664.
80. Ohmoto, T., Oike, K., and Sakamoto, Y., (1981). Studies on the Constituents of Picrasma quassioides BENNET. On the Alkaloidal Constituents, Chem. Pharm. Bull., 29, 390—395.
81. Lippke, K.P., Schunack, W.G., Wenning, W., Mueller, W.E., (1983). β-Carbolines as benzodiazepine receptor ligands. Synthesis and benzodiazepine receptor interaction of esters of β–carboline-3-carboxylic acid, J. Med. Chem., 26, 4, 499–503.
82. Eudistomin alkaloid. Ayoub Badre, Anna Boulanger, Eliane Abou-Mansour, Bernard Banaigs, Georges Combaut, Christian Francisco, Eudistomin U and Isoeudistomin U, New Alkaloids from the Carribean Ascidian Lissoclinum fragile, J. Nat. Prod. 1994, 57, 4, 528—533, and references cited therein.
83. Anderton, N., Cockrum, P.A., Colegate, S.M., Edgar, J.A., Flower, K., Vit, I., and Willing, R.I., (1998). Total synthesis of (±)-coerulescine and (±)-horsfiline, Phytochemistry, 48, 437—439 and references cited therein.
84. Somei, M., Noguchi, K., Yamagami, R., Kawada, Y., Yamada, K., and Yamada, F., (2000). Preparation and a Novel Rearrangement Reaction of 1,2,3,4-Tetrahydro-9-hydroxy-β-carboline, and Their Applications for the Total Synthesis of (±)-Coerulescine, Heterocycles, 53 (1), 7—10 and references cited therein.
85. Pellegrini, C., Strässler, C., Weber, M., Borschberg, H.J., (1994). Synthesis of the oxindole alkaloid (−)-horsfiline, Tetrahedron: Asymmetry, 5, 1979—1992.
86. Lakshmajah, G., Kawabata, T., Shang, M., and Fuji, K., (1999). Total Synthesis of (-)-Horsfiline via Asymmetric Nitroolefination, J. Org. Chem., 1999, 64, 1699—1704.
87. Pellegrini, C., Strassler, C., Weber, M., and Borschberg, H-J., (1994). Synthesis of the oxindole alkaloid (−)-horsfiline, Tetrahedron: Asymmetry, 5, 1979—1992.
88. Kuehne, M.E., Roland, D.M., and Hafter, R., (1978). Total synthesis of (±)-coerulescine and (±)-horsfiline. J. Org. Chem., 43, 3705—3710.
89. Jossang, A., Jossang, P., Hadi, H.A., Sevenet, T., Bodo, B., (1991). Horsfiline, an oxindole alkaloid from Horsfieldia superba, J. Org. Chem. 56, 23, 6527—6530.
90. Bascop, S-I., Sapi, J., Laronze, J-Y., and Levy, J., (1994). Construction of Spiro[pyrrolidine-3,3- oxindoles, Heterocycles, 38, 725—732.
91. Timothy D. Cushing, Juan F. Sanz-Cervera, Robert M. Williams, (1993). Stereocontrolled total synthesis of (+)-paraherquamide B, J. Am. Chem. Soc. 115, 20, 9323–9324
92. Tabata, M., Oshikiri, N., Hasegawa, M., Satoh, K., Fukui, Y., Nagahama, Y., Morikawa, H., Yamada, Y., and Somei, M., (2020). 1-Hydroxyindoles: production of feruloylserotonin, an alkaloid of safflower seed, novel ring system compound, 1,10-diaza-9,20-dioxakabutanes, 2,2'-bisindoles, and (dl)-3a, 3a'-bispyrrolo [2,3-b]indoles, Heterocycles, 100, 1987—2032 and references cited therein.
93. Tam, S.W., Worcel, M., Wyllie, M., (2001). Yohimbine: a clinical review, Pharmacol Ther., Sep. 91(3): 215—243.
94. Yoshino, K., Yamada, F., Noguchi, K., Kusuno, K., and Somei, M., (2019). Rearrangement Reaction in 1-Hydroxyindole Chemistry: A Synthesis of Novel 7-Substituted Yohimbine, and 4a-Substituted 1,2,3,4-Tetrahydro-β-Carboline Derivatives, Heterocycles, 98 (No. 10), 1384—1407, and references cited therein.
95. Yoshino, K., Yamada, F., and Somei, M., (2008). Nucleop-

hilic Substitution Reaction in Indole Chemistry: A Synthesis of Novel 7β-Substituted Yohimbine and 4aα-Substituted 1,2,3,4-Tetrahydro-β-carboline Derivatives, Heterocycles, 76, 989—994 and references cited therein.
96. Somei, M., Imai, K., Yamada, F., Hayashi, T., Nakai, Y., and Tokumura, K., (2004). 1-Hydroxytryptophan derivatives have sp3 hybrid nitrogen, The 34th Congress of Heterocyclic Chemistry, Abstract Papers, Kanazawa, Japan, 2004.
97. Acheson, R.M., Benn, M.H., Jacyno, J., and Wallis, J.D., (1983). Pyramidal bonding about nitrogen in 1-benzoyloxyindole determined by X-ray diffraction, J. Chem. Soc., Perkin Trans. 2, 497—500.
98. Finch, N., Gemenden, C.W., Hsu, I.H-C., and Taylor, W.I., (1965). Oxidative transformations of indole alkaloids, pseudoindoxyls from yohimbinoid alkaloids and their conversion to "invert" alkaloids, J. Am. Chem. Soc., 87, 2229—2235.
99. Somei, M., and Seto, M., (2003). Formation of 3,4,5,6-Tetrahydro-7-hydroxy-6-methyl- 1H-azepino[5,4,3-cd]indole in the Reaction of Serotonin with Acetaldehyde in Water in the Presence of either L-Amino Acid, Nicotine, or Fluoride, Heterocycles, 60 (3), 519—522.
100. Somei, M., Teranishi, S., Yamada, K., and Yamada, F., (2001). A Novel Synthesis of 3,4,5,6-Tetrahydro-7-hydroxy-1H-azepino[5,4,3-cd]indoles and a New Finding on Pictet-Spengler Reaction, Chem. Pharm. Bull., 49 (9), 1159—1165.
101. Somei, M., Fukui, Y., and Hasegawa, M., (1995). Preparations of Tryptamine-4,5-diones, and Their Diels-Alder and Nucleophilic Addition Reactions, Heterocycles, 41(10), 2157—2160.
102. Q-P. Han and G. Dry Hurst, (1996). Influence of glutathione on the oxidation of 1-methyl-6-hydroxy-1,2,3,4-tetrahydro-β-carboline: chemistry of potential relevance to the addictive and neurodegenerative consequences of ethanol use, J. Med. Chem., 39, 1494-1508.
103. Bowen, D.M., Allen, S.J., Benton, J.S., Goodhardt, M.J., Haan, E.A., Palmer, A.M., Sims, N.R., Smith, C.C.T., Spillane, J.A., Esiri, M.M., Neary, D., Snowdon, J.S., Wilcock, G.K., and Davison, A.N., (1983). Biochemical Assessment of Serotonergic and Cholinergic Dysfunction and Cerebral Atrophy in Alzheimer's Disease, Neurochem., 41, 266.
104. L. Volicer, P. J. Langlais, W. R. Matson, K. A. Mark, and P. H. Gamache, Arch. Neurol., 1985, 42, 1158; M. Z. Wrona, and G. Dryhurst, J. Org. Chem., 1987, 52, 2817;
105. Dryhurst, G., Anne, A., Wrona, M.Z., and Lemordant, D., (1989). Mechanism and products of b electrochemical oxidation of 5,7-dihydroxy tryptamine, J. Am. Chem. Soc., 111, 719-726.
106. Zahr, N.M., Pfefferbaum, A., (2017). Alcohol's Effects on the Brain: Neuroimaging Results in Humans and Animal Models, Alcohol Res., 38(2):183–206.
107. Jiang, X-R., Wrona, M.Z., Alguindigue, S.S., Dryhurst, G., (2004). Reactions of the Putative Neurotoxin Tryptamine-4,5-dione with l-Cysteine and Other Thiols, Chem. Res. Toxicol., 17, 3, 357—369.
108. Cai, P., and Snyder, J.K., (1990). Preparation, reactivity, and neurotoxicity of tryptamine- 4,5-dione, Tetrahedron Lett., 31, 969—972.
109. Baumgarten, H.G.; Bjorklund, A., Nobin, A., Rosengren, E., Schlossberger, H.G., (1975). Neurotoxin, Acta Physiol. Scan., Supplementary 429, 1.
110. Bjorklund, A., Hern, A.S., Baumgarten, H.G., Nobin, A., Schlossberger, H.G., (1975). Acta Physiol. Scan., Supplementary 429, 31.
111. Kim, C., Cho, H., Kim, S., Lee, S.Y., Ha, K-T. (2024). Synthesis of 1-hydroxy (and 1-alkoxy, 1-acyloxy)-1H-indoles and evaluations of their suppressive activities against tumor growth through inhibiting lactate dehydrogenase a, European Journal of Medicinal Chemistry, 283, 117104. doi. org/10,1016/j.eimech.2024.117104
112. Ueda, Y., Kiyonaka, S., Selfors, L.M., Inoue, K., Harada, H., Doura,T., Onuma, K., Uchiyama, M., Kurogi, R., Yamada, Y., Sun, J.H., Sakaguchi, R., Tado, Y., Omatsu, H., Suzuki, H., Aoun, M., Nakayama, T., Kajimoto, T., Yano, T., Holmdahl, R., Hamachi, I., Inoue, M., Mori, Y., Takahashi, N., (2025). Intratumour oxidative hotspots provide a niche for cancer cell dissemination, Nature Cell Biology. 27, 530-543. DOI 10.1038/s41556-025-01617-w