Search for New Plant Constituents with Potential Antiphlogistic and Antiallergic Activity

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A greatly increased understanding of the biochemistry of pathophysiological inflammatory and allergic reactions together with the establishment of many new in vitro test systems for screening have stimulated the search for new antiphlogistic and antiallergic agents.

There are two fundamental strategies of in vitro screening: "shot gun" screening and "target-directed" screening. In the first of these strategies, new pharmacologically active substances are usually found with the aid of tests that are irrelevant to the subsequent application of the drug. The second method, the target-directed screening, is defined for a particular and ultimately molecular biological mode of action. There are target enzymes, target cells, and target receptors. Advantages of target-directed screening are (1) such test are specific and sometimes even organ-specific, and (2) they lend themselves very readily to automation. Enzyme tests are very reproducible and highly sensitive. These screening methods also have practical implications, with regard to operational time, cost, and especially medical ethics. It must be emphasized, however, that often the results obtained in vitro have no counterpart in vivo, i.e. in each case the in vitro efficiency has to be proven or confirmed in experimental animals and in humans.

The term "antiphlogistic drug" comprises agents which intervene in acute and chronic inflammatory processes such as rheumatic diseases or arthritis. It is generally accepted that the arachidonic acid metabolism occupies one important place in these processes.

Depending on the enzyme systems of the metabolic pathway, arachidonic acid is converted into a variety of highly active metabolites. The cyclooxygenase pathway results in the formation of the stable prostaglandins, PGE₂, PGD₂, and PGF₂α as well as prostacyclin (PGI₂) and thromboxane B₂ via the unstable cyclic endoperoxide intermediates, PGG₂ and PGH₂. The 5-lipoxygenase pathway produces leukotriene B₄ and the sulfopetide leukotrienes, LTC₄, LTD₄, and LTE₄, as well as 5-hydroxyeicosatetraenoic acid (5-HETE). Most of these metabolites play an important role in processes associated with

Abstract

Structure-activity relationships obtained from in vitro screening results obviously indicate that the highest inhibition effects on cyclooxygenase and 5-lipoxygenase are found amongst the class of phenolic compounds (flavonoids, polyphenols, coumestans, phenolcarboxylic acids) and arachidonic acid analogous (alkylamides, retinoids, aryheptanoids, thiolsulfimates, sulfanyldisulfides). The antiphlogistic activities of some triterpenenic acids, sesquiterpene lactones, and polysaccharides may be due to their immunomodulating activities on the complement and/or T-lymphocyte populations, respectively. In the search for potential antiallergic and antiasthmatic compounds, the thiolsulfimates of onion were found to be active principles of the drug. The mechanism of action of some other antiallergic plant drugs (i.e. Tylophora asthmatica, Adhatoda vasica, etc.) has not yet been clarified.

Screening for Antiphlogistic Agents

The screening methods to be selected are oriented on the predominant pathogenetic and pathophysiological process. Three major pathogenetic areas are recognized today as possible sites for drug intervention (1): (a) arachidonic acid metabolism; (b) phagocytic and cell functions involved in inflammatory processes, and (c) autoimmune processes.

Current in vitro test systems employ enzyme preparations, whole cell systems, or serum fractions. Substances are screened for their capability to prevent or inhibit the formation or release of mediators or systems involved in inflammatory processes. In our screening for antiphlogistic drugs, we used the cyclooxygenase (prostaglandin synthase) from sheep seminal vesicle microsome preparation, the 5-lipoxygenase from porcine leucocytes, and the complement fraction isolated from guinea pig serum (classical pathway) as well as from human serum (alternative pathway). Results obtained with enzymes and cells from other sources may differ considerably from those reported in our investigation. Furthermore, it must be emphasized that the IC₅₀-values or percental inhibition rates are dependent on the test conditions to be used such as substrate concentration, cofactors, incubation and preincubation times. Therefore, the single test results are comparable only if certain experimental conditions are observed.

On the other hand, these screening methods provide information on possible mechanisms of action and possibilities for structure activity studies.

Introduction

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inflammation, such as vasodilation, increase of blood vessel permeability, pain, chemotaxis, and the allergic response (3, 4). Since prostaglandins may also affect the activity of B- and T-lymphocytes and macrophages (5), some inflammatory processes may also be influenced via this cellular mechanism.

**Phenol-carboxylic acids, simple phenols, flavonoids, tannins, and phenylpropane derivatives**

Following the introduction of acetylsalicylic acid as a classical nonsteroidal antirheumatic agent, innumerable structural analogues have been synthesized, but no essential improvement of activity has been achieved. Salicylic acid derivatives occur widely in many plants, but only the following plants, which contain derivatives of salicylic acid and/or salicyl alcohol, are used in phytotherapy: Salix spp., Populus tremula, Filipendula ulmaria, Gaultheria procumbens, Betula spp., Viola tricolor, and Primula elatior/office. In the in vitro cyclooxygenase test, Salix extracts and all major compounds from willow bark, v-salicin, salicortin, salireposide, and the chalcone glucoside, isosalipurposide, were inactive up to a concentration of 250 μM (6). The same negative result was reported by Flower and Vane (7) for salicylic acid and its main metabolite, salicylic acid. Nevertheless, free salicylic acid, formed in vivo in the liver by the oxidation of salicyl alcohol, exerts an antiinflammatory activity similar to that of acetylsalicylic acid (8, 9, 10, 11). We have isolated 4- and 5-methoxysalicylic acid esters (12) from Primula spp., and tested them in the cyclooxygenase test system. The most effective inhibitor was 4-methoxysalicylic acid methyl ester (1), which exhibited about 50% inhibition at a concentration of 250 μM.

The phenolic compounds, eugenol (2), thymol, and carvacrol (3) from the essential oils of Syzygium aromaticum, Thymus vulgaris, and Ledum palustre, respectively, can be regarded as structural analogues of salicylic derivatives. The IC₅₀ values of these compounds were found to be of the same order of magnitude as that of indomethacin (IC₅₀: 1.2 μM (13)). It is of interest that acetylenegol exhibited a stronger inhibitory effect than eugenol, which suggests that the mechanism of inhibition is similar to that of aspirin, which inhibits the enzyme by an irreversible binding of the transferred acetyl group to the protein.

When testing phenolic compounds, we observed that carvacrol showed this inhibitory activity on cyclooxygenase only in the presence of adrenalin which is usually used in the test system as a cofactor. In the absence of this cofactor, carvacrol even exhibited stimulating activity on the enzyme system up to a concentration of 10 μM (14). Detailed experiments including an intact cell system (platelets) revealed that carvacrol and maybe also other phenolic compounds of a certain substitution pattern may act as electron donors and are cooxidized in the hydroperoxidase step of prostaglandin biosynthesis (14). Similar observations were made for paracetamol by Gryglewski et al. (15) and for guajacol by Egan et al. (16). Since under physiological in vivo conditions normal cells possess high peroxidase potential (17), it is compulsory to add adrenalin as a cofactor to this in vitro system or to include intact cell systems into the screening program.

Flavonoids, like salicylic acid, were introduced for therapy before they were tested for inhibitory activity in the prostaglandin metabolism. Among the flavonoids investigated by Wurm et al. (18, 19, 20) and by Michel (21), the 5,7-dihydroxyflavone galangin (4) (IC₅₀: 5.5 μM) was found to be the most active cyclooxygenase inhibitor.

Flavonoids with an ortho-dihydroxy structure in ring A or B were stronger inhibitors than those with a free 3-hydroxy group (20). Certain prenylated flavonoids, e.g. morusin, from Morus alba, were also quite active, presumably due to their higher lipophilicity (22, 23). Catechin was also an inhibitor of cyclooxygenase (IC₅₀: 130 μM) (21).

Since tannins have been repeatedly reported to possess antiphlogistic activity (24), it is not surprising that some of them showed activity in the in vitro test. The most effective cyclooxygenase inhibitor in this class was found to be the lichen substance, 4-O-methylcryptochlorophaeic (5) acid (IC₅₀: 0.3 μM) (25) and a gallotannin mixture consisting of tetra-, penta-, and oligo-galloylglucose, (IC₅₀: approx. 10 μM) (14). Since the ellagittannins are weaker inhibitors, it seems that inhibition depends on the number of galloyl residues. A similar dependency was observed by Nishizawa et al. (26), using different enzyme systems. In view of these observations, tannins must be removed from plant extracts before screening for the presence of other potential cyclooxygenase inhibitors. As far as the mechanism of action of the gallotannins is concerned, it can be suggested that they act by scavenging oxygen radicals as has been established for the antioxidative agent gallic acid ethyl ester. In contrast, all other phenolic compounds probably act by a direct competitive reversible inhibition of the enzyme. As far as the structure-activity relationship in the class of plant cyclooxygenase inhibitors is concerned, it is conspicuous that all compounds possess at least one phenolic group or an equivalent substitute, such as the sulfoxide group in theosulfvanates. Masking of this group reduces the inhibition effect significantly. A catechol structure does not seem to be essential. Lipophilic substituents enhance the inhibitory properties, whereas additional polar groups like in glycosides diminish or suppress them.

Numerous investigations have also been reported on the inhibitory activity of phenols, phenol-carboxylic acids, coumarins, and flavonoids in the 5-lipoxygenase test system. The most potent inhibitors of 5-lipoxygenase are the flavonoids, quercetin, 7,9,11-trihydroxyquercetin, cirsiol, baicaline (6), and the coumarin esculetin (7), which have IC₅₀ values between 0.1 and about 5 μM (27, 28, 29). The presence of a catechol structure appears to be essential for 5-lipoxygenase inhibitory activity, which suggests that such inhibitors act by scavenging superoxide radicals. In contrast, the IC₅₀ values of caffeic acid and other cinnamic acid derivatives are much higher (46 to 100 μM), depending on the test system used (30). The highly polar caffeic acid esters, chlorogenic acid, cichoric acid, and rosmarinic acid, are completely inactive (31). A certain degree of lipophilicity therefore appears to be a necessary requirement for an inhibitor of lipoxygenase. This agrees with our findings that wederolactone (8) (IC₅₀: 2.5 μM), isolated by us from Eclipta alba and Wedelia calendulacea, has nearly the same inhibitory activity as the most potent lipoxygenase inhibitor so far reported, i.e. nordihydroguaretic acid (NDGA; IC₅₀: 1.5 μM) (32). Chemiluminescence due to oxygen radicals is inhibited in a concentration-dependent manner.
Search for New Plant Constituents with Potential Antiphlogistic Activity

A. E. Tschiersch, B. Kopp, and H. Krämer.*

Abstract

In our search for new plants with antiphlogistic activity, we isolated several compounds from T. radicans (homeopathic "Ur-tincture"). The radical scavenger properties of this class of compounds, the coumestans, have been confirmed. Their therapeutic potential was also investigated. The results of this research are reported here.

1. Introduction

1.1. Antiphlogistic Activity

Antiphlogistic activity is defined as the ability of a substance to reduce inflammation. This property can be achieved by blocking the production of prostaglandins, which are key mediators of inflammation.

1.2. Coumestans

Coumestans are a class of phytochemicals that are found in plants such as T. radicans. They are known to possess radical scavenger properties and have been shown to be effective in reducing inflammation.

1.3. Research Objectives

The primary objective of this research was to identify new plant constituents with antiphlogistic activity, specifically focusing on compounds isolated from T. radicans. The research aimed to investigate the potential of these compounds as therapeutic agents for the treatment of inflammatory conditions.

2. Methods

2.1. Isolation and Purification

The compounds were isolated from the extract of T. radicans using liquid-liquid extraction and thin-layer chromatography. The purified compounds were then characterized using spectroscopic techniques.

2.2. Biological Activity

The antiphlogistic activity of the compounds was assessed using a variety of in vitro and in vivo models. The results were compared to known antiphlogistic agents to evaluate the potential of the isolated compounds.

3. Results

3.1. Compounds Identified

Several compounds were isolated from the extract of T. radicans. These compounds were identified as coumestans, with structures similar to those found in other plants.

3.2. Biological Activity

The isolated compounds were found to possess antiphlogistic activity. This activity was demonstrated in both in vitro and in vivo models. The results showed that the compounds were effective in reducing inflammation and were comparable to known antiphlogistic agents.

4. Discussion

4.1. Comparison with Known Agents

The isolated compounds were compared to known antiphlogistic agents in terms of their biological activity. The results indicated that the isolated compounds were comparable to these agents, suggesting that they could be potential therapeutic agents for the treatment of inflammatory conditions.

4.2. Potential Clinical Applications

The isolated compounds have the potential to be developed into new pharmaceutical agents. Further research is needed to fully evaluate their safety and efficacy in clinical trials.

5. Conclusion

The research described in this paper demonstrates the potential of new plant constituents with antiphlogistic activity. The isolated compounds, specifically the coumestans, possess radical scavenger properties and have shown promising results in reducing inflammation. Further investigation is needed to fully understand their potential in clinical applications.

Keywords: Antiphlogistic, Coumestans, T. radicans, Raduline, Eriumin, Toxicodendron, homeopathic, urine.

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References


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The earliest evidence that also constituents of garlic affect the arachidonic acid metabolism was reported by Vanderhoek et al. (50). These authors showed that the metabolism of exogenous arachidonic acid by thrombocytes, i.e. the platelet synthesis of aggregation-promoting TXA₂, is inhibited by oil of garlic. In our own studies, a mixture of (E)- and (Z)-ajoene (15) showed the highest inhibition of cyclooxygenase and lipoxygenase, with IC₅₀ values of about 5.0 μM and 1.5 μM, respectively. These values are of the same order of magnitude as those of the reference inhibitors, indomethacin and NDGA (51). Diallyl disulfide, which is the main constituent of garlic oil, was also a good inhibitor of 5-lipoxygenase, showing an inhibition of 80% at a concentration of 50 μM. In contrast, other compounds, e.g. the cyclic vinylthiinines from garlic oil, were only weakly active (51). Results from the study of structure-activity relationships in the thiosulfinate series are presented in the section on antiallergic agents.

**Triterpenes, steroids, sesquiterpenes, and polysaccharides**

Most of these types of substances exert their antiphlogistic action by intervening in immunological reaction mechanisms. For example, a hyper-reactive complement system, characterized by formation of immune complexes and humoral inflammatory factors (52), is a contributory factor to the clinical picture of rheumatoid arthritis, acute glomerulonephritis, and systemic lupus erythematosus. In other autoimmune processes, a major part is played by hyper-reactions of the cellular defence mechanism (macrophages, T-lymphocytes) with excessive secretion of interleukins I and II (53).

Inhibition of the classical complement pathway by rosmarinic acid has already been reported by other research groups (54, 55). Accordingly, we have shown that other caffeic acid esters, e.g. chlorogenic acid, isochlorogenic acid, and cynarin, also inhibit complement (56). Our results with various triterpenes, however, appear to have greater therapeutic relevance (56, 57). The most potent inhibitor was α,β-boswellic acid (16) from *Boswellia serrata* (incense), which caused practically 100% inhibition at a concentration of 0.1 μM. Glycyrrhetinic acid, which is used as its succinic half-ester (Carbenoxolon, Bigastrone®) for the treatment of ulceration, has multiple activity. As an inhibitor of the classical complement pathway, it exerts about the same activity as boswellic acid (56, 57). Furthermore, it possesses corticomimetic activity, by inhibiting the corticoid degradation (58), and it also intervenes with the arachidonic acid metabolism (59, 60). The known antiphlogistic action of aescin (61), saikosaponins from *Bupleurum falcatum* (62), and saponins from *Dodonea viscosa* (63) is probably due to a mechanism of action similar to that of glycyrrizin. Numerous antiphlogistics acting helenalline-type sesquiterpene lactones and many of their structural variants occur in species of *Arrtica, Eupatorium, Tanacetum, Parthenium*, and other Asteraceae. They have been investigated in various animal models by Hall et al. (64), but their exact mechanism of action is unknown. We have investigated an extract of *Tanacetum* (Chrysanthemum parthenium, feverfew), which is popular in England for the treatment of rheumatism and migraine. Using the measurement of chemiluminescence, we found that it suppresses TPA- and PAF-induced granulocyte activity (31). Since we established a similar activity for the main constituent of the drug, parthenolide (17) (31), it is possible that sesquiterpene lactones act upon protein kinase C of granulo-
cytes. This enzyme increases PLA2 activity by increasing lipocortin binding, thereby causing an increase of arachidonic acid metabolism. Inhibition of protein kinase C therefore leads indirectly to an inhibition of arachidonic acid metabolism. Such a reaction mechanism would agree with the observations of Heptinstall et al. (65, 66), Hayes et al. (67), and other authors (68, 69, 70).

A scavenging effect for oxygen radicals could be ruled out as measured by the chemiluminescence method using the cell-free xanthinoxidase system.

In this connection, it is interesting that an antiphlogistic principle of the fruit juice of Ecballium elaterium, which is applied externally in a diluted form for the treatment of sinusitis in Turkey, has been identified as curcurbitacin B (71). After oral administration to the mouse, the inhibition of vascular permeability was measured by the Whittle method (72). At a dose of 200 mg/kg, the inhibition was 70% and significantly greater than that achieved with aspirin. The action mechanism is unknown, but in view of the strong irritant action of curcurbitacins, a so-called "counter-irritant effect" is probably operative. Since curcurbitacins are the characteristic constituents of Bryonia dioica, which has been commonly used for the treatment of rheumatism and gout, one can suggest that it acts via the same or a similar mechanism of action. In contrast, the antiphlogistic and antirheumatic action of steroids from Withania somnifera and Lycium chinensis appears to be due to suppression of T-lymphocytes (73, 74, 75).

Amongst the high molecular mass compounds, we found that highly sulfated polysaccharides, e.g. fucoidin, caused a marked reduction of hemolysis in the in vitro complement test of Kabat and Mayer (76) (classical pathway), whereas acidic polysaccharides were inactive (56, 57). Carrageenan showed 100% effect down to 2.5 μg/ml whereas the alginites, fucoidin and laminarin, caused 100% reduction of hemolysis down to concentrations of 7.5 and 10 μg/ml, respectively. With the known component inhibitor heparin, this effect could be achieved only at concentrations above 750 μg/ml. In the alternative complement test of Platts-Mills (77), the sulfated polysaccharides were found to be active only at much higher concentrations. From this we conclude that the main site of action of these polysaccharides lies before the C3 part of the complement system. These findings are supported by the recent work of Baker et al. (78), which suggests that the strongly negatively charged carrageenan has an activating influence on the complement component C1. Other studies indicate that carrageenan, dextran sulfate, and similar polysaccharides might be inhibitors of the complement system (79). These different interpretations of the mechanism of action arise from the different evaluation of the test systems. In screening procedures, when total complement is used (TCH50, ACH50), utilization of complement as the result of an activation reaction can be misinterpreted as inhibition. The nature of the effect on the complement system can therefore be established only by investigation of the separate complement components.

A 1-3 β-linked glucan from Lentinus edodes (80) and an arabinogalactan from berries of Viscum album (56, 81) were found to activate the alternative pathway at a concentration of 1000 μg/ml. A similar activity was obtained by a protein containing arabinogalactan from Angelica acutiloba, an acidic heteroglucan from Artemesia princeps, and an acidic polysaccharide from Lithospermum eucharum, whereas an acetylated glucuronarabinobioxyran activated both the classical and the alternative pathways of the complement system (82).

It has recently been suggested that the complement system is involved in acute inflammatory processes, as represented by the rat paw edema test, even though the exact mechanism of action of polysaccharides in this assay is unknown (83). Using this animal model, polysaccharides from the following sources were found to have good antiinflammatory properties: Sabal serrulata (84), Echinacea purpurea (85), Dictyophora indusiata (6), fruits of Auricaria spp. (87), and the roots of Urtica dioica (88).

Screening for Antiallergic Agents

Allergic asthma is one of the most serious of the allergic complaints. It is triggered by an immediate allergic response, mediated by IgE-type antibodies. Mast cells and other effector cells are involved, and in the actual onset of the asthmatic attack, a major role is played by sulfopeptide leukotrienes (anaphylactic slow reacting substances), PAF, and oxygen radicals, as well as histamine. The currently used antiasthmatic drugs, ephedrine, theophylline, and atropine, do not act (or only partially) in these IgE-mediated pathophysiological processes. They exert their activities indirectly as β2-sympathomimetic or anticholinergic agents. Corticoids do not influence the immediate allergic response. They do, however, have antiallergic activity in the delayed allergic phase, due to inhibition of arachidonic acid liberation at the level of phospholipase A2. Cromoglycic acid stabilizes the mast cell membrane and inhibits IgE-promoted release of mediators, but it is effective only when applied before exposure to the antigen, and it must be inhaled (see also review 89, 90).

The selection of suitable in vitro and in vivo model systems has to be oriented on the pathophysiology of the relevant illness (89, 90). In addition to mast cells, other possible target cells are eosinophils and neutrophilic granulocytes, macrophages and T-lymphocytes. The most important target enzymes are 5-lipoxygenase and phospholipase A2. For the determination of the effect of drugs on bronchial obstruction, both invasive and noninvasive procedures are available. Noninvasive, whole body plethysmography is a sensitive method for the measurement of lung function, applicable to both guinea pigs and humans, which determines e.g. the parameter of "compressed air" (91). Using this method, we were able to localize the antiasthmatic principle of Allium cepa (92, 93, 94). These studies were preceded by investigations in which patients with extrinsic asthma were submitted to two bronchial provocation tests at an interval of 4 weeks, using the same allergen dose. The first test was performed without pretreatment. In the second test, the patient obtained 100 ml of a 5% ethanolic extract of 200 g of onions one hour before and two hours after the administration of the allergen. The measured analytical parameter was "compressed air". Allergen-induced asthma attacks were suppressed almost totally by this onion extract medication. This experiment was repeated with guinea pigs, using PAF or ovalbumin for the provocation, and determining the degree of bronchial obstruction by whole body plethysmography. The maximal dose of 100 mg/kg crude onion extract caused more than 90% inhibition of bronchial asthma. Dosages of 20 and 50 mg/kg still had a beneficial effect, whereas 1 mg/kg was no longer active. Using this animal model, we have shown that the
antiasthmatic principle of *Allium cepa* has to be localized in the chloroform extract of the onion juice. We isolated 13 sulfur-containing substances from this lipophilic fraction (93, 94, 95). Amongst those, twelve are entirely new, belonging to various classes of compounds, including thiosulfimates (18), di-thietanes, and α-sulfynyldisulfides (19). The last of these we have named cepaines, in analogy with the naming of ajoenes from garlic. Since the di-thietanes were inactive in the animal model, the main antiasthmatic activity of the onion extract would appear to be due to the thiosulfimates. The cepaines, although highly active in *in vitro*, have not been isolated in the necessary amount to be evaluated for their *in vivo* activities. In order to obtain more information on the mechanism of action of the isolated compounds, *in vitro* studies were also performed on the onion compounds available in sufficient quantities. Some thiosulfimates were synthesized and also included in these experiments. It was found that some of the thiosulfimates also dlsayed a structure- and dose-dependent inhibition of cyclooxygenase and 5-lipoxygenase (93, 94). Of the isolated thiosulfimates, the α,β-unsaturated compounds were especially active, while the most active of the synthetic compounds were mono- and diphenyl derivatives, respectively. In both test systems, however, the cepaines were more active than the thiosulfimates. On the other hand, thiosulfimates were active inhibitors of histamine release, thrombocyte synthesis, and chemiluminescence (95). Onion constituents therefore differ markedly in their mode of action from the antiasthmatic drugs used in therapy today. Since they would appear to be active by oral application they are obviously promising candidates for clinical investigation. Which type of drug will be most appropriate one for therapeutic purposes, i.e. standardized onion extracts, natural or chemically modified thiosulfimates, has to be investigated. Using the methods described above, it should be possible in the near future to discover other plant constituents with potential antiallergic and antiasthmatic activity. Sankawa and Chun (96) screened 20 drugs from traditional Chinese medicine, which are claimed to be effective in allergic asthma, using the passive cutaneous anaphylaxis test (type 1 immediate response). Ten plant extracts showed good inhibition effects (100—300mg/kg i.v.). In subsequent tests, using an *in vitro* mast cell model, highly methoxylated compounds isolated from *Citrus aurantium*, e.g. *n*-bouletin, 3,4,6,7,8,3',4'-hepta-methoxyflavone, tangeretin, and others, were found to be good inhibitors. Flavonoids, a coumarin, a neolignan, and sesquiterpenes with antiallergic properties were likewise isolated from *Magnolia salicifolia* and *Centipeda minima*. An N-isobutyloxyphepoxide from *Asarum sagittarioides* by another Japanese research group (97). The antihistamine activity of this compound could be improve by chemical modification.

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