Abietane Acids: Sources, Biological Activities, and Therapeutic Uses

Arturo San Feliciano[1,2], *Marina Gordaliza*[1], *Miguel A. Salinero*[1], *and José M. Miguel del Corral*[1]

[1] Laboratorio de Química Farmacéutica, Facultad de Farmacia, Universidad de Salamanca, E-37007 Salamanca, Spain
[2] Address for correspondence

Received: February 15, 1993; Revision accepted: April 27, 1993

Abstract

The biological activities of natural abietane acids and their derivatives have been reviewed from 1967 to 1992. Antimicrobial, antiulcer, and cardiovascular activities are the most representative for this class of diterpenoids, while others like allergenic, antiallergic, filmogenic, surfactant, antifeedant, etc. activities, which determine several uses of abietane acids, have also been reported.

Key words

Abietane acids, antimicrobial, antiulcer, cardiovascular, toxicity.

Introduction

Abietane acids are a group of phenanthrene diterpenoids which do not seem to have been the object of a recent pharmacological review. Nevertheless, they seem to merit attention, due to their varied biological activities and the folk-medicinal uses of extracts containing them as well as their toxicities and secondary effects.

The main source of abietane acids is colophony, the distillation residue of pine resins. Directly, or after stabilization through partial polymerization or dehydrogenation, this product is mainly used in the paints, varnishes, and coatings industries. The acid part of colophony is composed of abietic acid (**15**), its equilibrium isomers levopimaric (**23**), palustric (**21**), and neoabietic (**24**) acids, and dehydroabietic acid (**27**), as well as some other non-abietanic compounds.

Additionally, abietane acids are components of extracts or resins from many other conifers belonging to the families Araucariaceae, Cupressaceae, Pinaceae, and Podocarpaceae, but they also occur in several Angiosperm species and, particularly, in the families Asteraceae, Celastraceae, Hydrocharitaceae, and Lamiaceae.

Structure and Occurrence

The skeletal structure and numbering of abietane acids are exemplified by that of abietic acid (**15**). It displays an equatorial carboxylic group (C-18) and two conjugated double bonds at positions 7 and 13. In other natural congeners the carboxylic group adopts the axial configuration (C-19) or represents C-20 while the number and positions of double bonds varies from one to four and are predominantly located on ring C, giving rise to a particular type of aromatic diterpenoids commonly known as dehydroabietic derivatives. Other functionalities such as hydroxy and carbonyl groups are often present and in some substances an endoperoxide moiety can also be found. Natural abietanic acids reported in the literature (1–65) and covered by Chemical Abstracts (1967 to date) and MEDLINE (1985 to date) are arranged in Tables **1** and **2** according to the number of double bonds and/or the location of the carboxylic group in the skeleton.

Biological Activities and Uses

The use of pine resin as a whole or its derivatives, essence, and colophony as expectorants, modifiers of bronchial secretions, and antiseptics for the urinary tract, as well as rubefacients and vessicants in poultices and creams in veterinary practice is described in several Pharmacognosy and Medicinal Plant treatises (66, 67). In recent years (1967–1992), studies on the biological activities of abietane acids have been performed with pure compounds and activities like antimicrobial, antiulcer, cardiovascular, allergenic, antiallergic, and many uses in cosmetics and dermatologic preparations have been reported for some of them.

Antimicrobial Activity

The antimicrobial activity of pisiferic acid (**48**) and its derivatives has been established against *Pseudomonas, Proteus*, and *Klebsiella* (68) as have its antibacterial actions against Gram-positive microorganisms, its antifungal activity, and its activity in experimental carcinoma of the uterus (HeLa-S_3 cells) (55, 58). In the systems assayed, pisiferic acid (**48**) was active against *Proteus vulgaris, Staphylococcus aureus, Bacillus subtilis, Pyricularia oryzae*, and HeLa-S_3 cells, while methylation of the

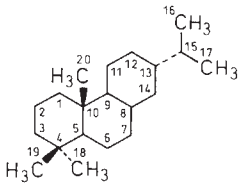

Table 1 Structures and sources of abietene and abietadiene acids.

Acid	Structure	Plant (Family)*	Ref.
13-*epi*-8-abieten-18-oic	**1**	*Cistus ladaniferus* (Ci)	1
14α-hydroxy-13-*epi*-8-abieten-18-oic. (suaveolic acid)	**2**	*Hyptis suaveolens* (La)	2
13-hydroxy-7-oxo-8(14)-abieten-18-oic	**3**	*Larix kaempferi* (Pi)	3
9β,13β-epidioxy-8(14)-abieten-18-oic (palustric acid β-endoperoxide)	**4**	*Elodea canadensis* (Hy)	4
9α,13α-epidioxy-8(14)-abieten-18-oic (palustric acid α-endoperoxide)	**5**	*Elodea canadiensis* (Hy)	4
3β-hydroxy-9α,13α-epidioxy-8(14)-abieten-18-oic	**6**	*Salvia oxyodon* (La)	5
3β-acetoxy-9α,13α-epidioxy-8(14)-abieten-18-oic	**7**	*Salvia oxyodon* (La)	5
7β-hydroxy-9α,13α-epidioxy-8(14)-abieten-18-oic	**8**	*Lepichinia caulescens* (La)	6
8,15-dihydroxy-13-abieten-18-oic	**9**	*Larix sibirica* (Pi)	3
8-hydroxy-12-oxo-13-abieten-18-oic	**10**	*Pinus sylvestris* (Pi)	7
8α,12α-epidioxi-13-abieten-18-oic	**11**	*Abies marocana* (Pi)	8
9-hydroxy-7-oxo-15-abieten-18-oic (wiedemanic acid)	**12**	*Salvia wiedemannii* (La)	9
13α-methoxy-8(14)-abieten-19-oic	**13**	*Juniperus phoenicea* (Cu)	10
9α,13α-epidioxi-8(14)-abieten-19-oic	**14**	*Juniperus sabina* (Cu)	11, 12
7,13-abietadien-18-oic (abietic acid)	**15**	*Pinus* sp. (Pi)	13–18
12α-hydroxyabietic	**16**	*Pinus sylvestris* (Pi)	8, 19, 20
12-oxoabietic	**17**	*Pinus sylvestris* (Pi)	19
15-hydroxyabietic	**18**	*Agathis robusta* (Ar)	20–22
15-methoxyabietic	**19**	*Cedrus deodara* (Pi)	22
7,13-abietadien-19-oic (4-*epi*-abietic acid)	**20**	*Juniperus phoenicea* (Cu)	12, 13, 23
8,13-abietadien-18-oic (palustric acid)	**21**	*Pinus palustris* (Pi)	24–27
8,13-abietadien-19-oic (4-*epi*-palustric acid)	**22**	*Juniperus phoenicea* (Cu)	23
8(14),12-abietadien-18-oic (levopimaric or sapietic acid)	**23**	*Pinus sylvestris* (Pi)	28–31
8(14),13(15)-abietadien-18-oic (neoabietic acid)	**24**	*Pinus palustris* (Pi)	25, 27, 32–34
8(14),13(15)-abietadien-19-oic (4-*epi*-neoabietic acid)	**25**	*Juniperus sabina* (Cu)	18
11,14-dioxo-8,12-abietadien-19-oic (gymindione)	**26**	*Gyminda costarricensis* (Ce)	35

* Abbreviations: Ar = Araucariaceae, As = Asteraceae, Ce = Celastraceae, Ci = Cistaceae, Cu = Cupressaceae, Hy = Hydrocharitaceae, La = Lamiaceae, Pi = Pinaceae, Po = Podocarpaceae.

acid or phenol group abolished its activity against *Proteus* and *Pyricularia*, respectively. Methylation of both groups simultaneously abolishes almost all antimicrobial activity, although its effect on HeLa-S_3 cells persists (57).

Structure-activity relationship studies have been performed in the light of these findings. In the case of the activity against Gram-negative bacteria, a carboxy group at C-10 is clearly necessary. The hydroxy group at position 12 seems to be a requirement for antibacterial activity against Gram-positive organisms, and is an indispensable structural requirement for antifungal activity since the *O*-methyl derivatives are inactive. However, the cytotoxicity does not seem to be determined by any specific structural factor.

Comparative studies have also been conducted on the antimicrobial actions of pisiferic (**48**), dehydroabietic (**27**), and podocarpic acids and ferruginol; the results have shown that the aromatic ring C and the isopropyl group are necessary for the Gram-positive antibacterial action. The authors also concluded that the hydroxy group *ortho* to the isopropyl group increases antimicrobial activity whereas a change of the carboxy group to position 4 decreases it (56). Abietic (**15**), dehydroabietic (**27**), and neoabietic (**24**) acids are the main compounds responsible for the antibacterial activity of the mixture of resin acids (69–71).

The lipid nature of the derivatives of pisiferic acid (**48**) has been correlated with their antimicrobial potencies, it being concluded that the greater lipophilicity leads to higher activity against Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) while a lower degree of lipophilicity elicits an increase in activity against *Proteus vulgaris* (68).

Pisiferic acid (**48**), Δ^8-dihydroabietic (**1**), and dehydroabietic (**27**) acids show antifungal properties when formulated in a fungicidal powder for use against the disease in rice caused by *Pyricularia oryzae* (72). The tuberculostatic activity of dehydroabietylguanidine, active against *Mycobacterium tuberculosis* and some bacteria, is also interesting due to its low toxicity (73).

Antiulcer Activity

Another of the properties studied in the abietic acids is their capacity to inhibit gastric secretions, suggesting their possible use as antiulcer compounds. In a program aimed at searching for new antiulcer agents with a broad cytoprotective effect, Wada et al. (74) prepared

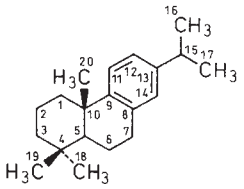

Table 2 Abieta-8,11,13-triene (dehydroabietic) acids and their occurrences.

Acid	Structure	Plant (Family)*	Ref.
8,11,13-abietatrien-18-oic- (dehydroabietic acid)	**27**	*Pinus* sp., *Cedrus* sp. (Pi)	13, 25, 26, 36–39
3β-hydroxydehydroabietic	**28**	*Salvia oxyodon* (La)	5
7β-hydroxydehydroabietic	**29**	*Cedrus deodara* (Pi)	22
7α-hydroxydehydroabietic	**30**	*Pinus* sp. (Pi)	38, 40
12-hydroxydehydroabietic	**31**	*Pinus sylvestris* (Pi)	19
15-hydroxydehydroabietic	**32**	*Agathis robusta* (Ar)	27, 38, 39
7β,15-dihydroxydehydroabietic	**33**	*Cedrus deodara* (Pi)	39
7-oxodehydroabietic	**34**	*Pinus silvestris* (Pi)	19, 38, 39, 41
15-hydroxy-7-oxodehydroabietic	**35**	*Larix kaempferi* (Pi)	3
6,8,11,13-abietatetraen-18-oic	**36**	*Pinus nigra* (Pi)	41–43
8,11,13,15-abietatetraen-18-oic	**37**	*Pinus abies* (Pi)	41, 44
3β-hydroxy-8,11,13,15-abietatetraen-18-oic	**38**	*Salvia tomentosa* (La)	37
8,11,13-abietatrien-19-oic (callitrisic acid)	**39**	*Callitris collumellaris* (Cu)	12, 13, 18, 45–49
7α-hydroxycallitrisic	**40**	*Juniperus phoenicea* (Cu)	13, 18
12-hydroxycallitrisic (lambertianic acid)	**41**	*Podocarpus lambertius* (Po)	50
7-oxocallitrisic	**42**	*Juniperus phoenicea* (Cu)	13, 18
14-hydroxycallitrisic	**43**	*Gyminda costarricensis* (Ce)	51
12,16,17-trihydroxycallitrisic (pododacric acid)	**44**	*Podocarpus dacrydioides* (Po)	50, 52–54
12-*O*-acetylpododacric	**45**	*Podocarpus comosum* (Po)	50
11,14-dihydroxycallitrisic	**46**	*Gyminda costarricensis* (Ce)	35
11,14-dimethoxycallitrisic	**47**	*Gyminda costarricensis* (Ce)	35
12-hydroxy-8,11,13-abietatrien-20-oic (pisiferic acid)	**48**	*Chamaecyparis pisifera* (Cu)	55–57
O-methylpisiferic	**49**	*Chamaecyparis pisifera* (Cu)	56–59
11,12-dihydroxy-8,11,13-abietatrien-20-oic (carnosic acid)	**50**	*Salvia officinalis* (La)	60, 61
12-*O*-methylcarnosic	**51**	*Salvia lanigera* (La)	62
7-oxocarnosic	**52**	*Salvia canariensis* (La)	63
6-oxo-7β-hydroxycarnosic	**53**	*Salvia canariensis* (La)	63
6-oxo-7α-hydroxycarnosic	**54**	*Salvia canariensis* (La)	63
16-hydroxycarnosic	**55**	*Salvia apiana* (La)	64
12-formyl-11-hydroxy-8,11,13-abietatrien-20-oic	**56**	*Lepechinia meyeni* (La)	65

* Abbreviations: Ar = Araucariaceae, Ce = Celastraceae, Cu = Cupressaceae, La = Lamiaceae, Pi = Pinaceae, Po = Podocarpaceae.

more than sixty derivatives of dehydroabietic acid (**27**), introducing a hydrophilic residue (amino, carbamoyl, carbamate, ureide, sulfonyl, or sulfamoyl) on the lipophilic residue of the dehydroabietane moiety and evaluated the antisecretory and antipeptic activity. The results obtained showed that dehydroabietic acid (**27**) has a moderate antisecretory action (22% inhibition of secretion at an oral dose of 30 mg/100 g in the rat) although it lacks antipeptic activity. These activities were overcome by amides and other nitrogen derivatives at position 18.

Additionally, the antipeptic activity was very high in the salts of 12-sulfodehydroabietic acid (75), suggesting that the presence of two acid functions in the molecule is a requirement for antipeptic activity to appear. These derivatives have cytoprotective properties and lack the collateral mineralocorticoid effects shown by other antiulcer agents. For this reason, several of the derivatives of 12-sulfodehydroabietic acid have been reported as being useful therapeutical and prophylactic agents in gastrointestinal disease (ulcers, gastritis) free of collateral effects and with a low degree of toxicity (76–82). Recently, the ability of abietic acid (**15**) to inhibit the secretion of gastric acid caused by (H^+, K^+)-ATPase has been described (83).

Cardiovascular Activities

Reports have appeared on effects of abietic (**15**) and dehydroabietic (**27**) acids on serum cholesterol levels (84) that have induced the search for hypocholesterolemic derivatives more potent than natural ones (85). Thus, the primary amides of tetrahydroabietic and Δ^8-dihydroabietic (**1**) acids do not display hypocholesterolemic activity and the *N*-alkyl secondaries lead to increases in serum cholesterol levels, whereas the presence of benzene rings in the substituent increases the hypocholesterolemic activity to a considerable extent (86). Additionally, the antiarrhythmic effect of *N*-[2-(diethylamino)ethyl]dehydroabietamide is higher than that of procainamide, although it is less effective than guanidine. The antithrombotic action of abietic acid (**15**) has also been described (87).

Dehydroabietic acid (**27**), together with *p*-coumaric acid, have been considered the main anti-nicotinic substances of the oleoresin from *Pinus densiflora* both *in vitro* and *in vivo* (88); at a dose of 10 μg/cigarette it is able to reduce the hypertensive and tachycardic effects of tobacco and administered intravenously it produces vasodilation, blocking the arterial constriction caused by nicotine (89). Abietic acid (**15**) inhibits (Na^+, Ka^+)-ATPase at concentrations of 25 mg/ml in a non-specific way (83), suggesting that this acid, like other biologically active diterpenoids, could essentially elicit disorganization of the cell membrane.

Other Activities and Uses

The *allergenic* and *antiallergic* power of the acid components of resins has been debated in depth and is controversal. Abietic acid (**15**), considered as the classic allergen involved in contact with colophony, has been proven to be non-allergenic (90–92) and is indeed used in antiallergic formulations (93). By contrast, one product of its autooxidation, 15-hydroperoxyabietic acid and other abietanic hydroxyacids have been identified as being responsible for the allergic reactions produced by colophony (94–97). In a test on passive anaphylaxis of the skin, it has also been demonstrated that dehydroabietic (**27**) and Δ^8-dihydroabietic (**1**) acids, their salts and their esters are inhibitors of skin allergies induced by IgE (98).

The *surfactant* properties of abietic (**15**) and dehydroabietic (**27**) acids, their salts, and their amides with glycine and other amino acids make them useful in the softening of water (99) and they are therefore included in preparations for skin and hair treatments (100, 101). Abietic acid (**15**) has also been described as the active ingredient of certain anti-dandruff shampoos (102) and it is used in the manufacture of nail varnishes and hair glossers (103). The esters of tetrahydroabietic acid are found as components of lipstick, massage creams, and other cosmetic products (104–107).

Other properties that potentiate abietic acids as therapeutic acids are *filmogenic*. Abietic (**15**) and neoabietic (**24**) acids in solution, aerosol, or other pharmaceutical forms are used in cases of severe burns and wounds to protect the skin against infections and parasites (108–109).

A mixture of resinic acids [levopimaric (**23**), neoabietic (**24**), palustric (**21**), abietic (**15**), and isopimaric acids] and triglycerides has also been indicated in the treatment of chronic diseases such as *rheumatism* and *gout* (100). The monoethylamide and diethanolamide of abietic acid are indicated as aromatizing agents (110) in chewing gum and, at high concentrations, palustric acid (**21**) acts as an *antifeedant* (98).

Toxic Effects

Abietic acid (**15**) is toxic for the pulmonary epithelium; it is a dose- and time-dependent toxic agent and causes the cells of the alveolar epithelium to lyze, possibly causing asthma and chronic pulmonary diseases (111).

However, the best studied toxic effects are those derived from their contamination as micropollutants of water in the paper industry. Its toxicity to *Salmo gairdneri* (the rainbow trout) (112) has received particular attention, and it has been observed that at concentrations above 15 mg/l dehydroabietic acid (**27**) causes a decrease in cellular ATP levels and in the consumption of oxygen and hence an increase in the hemolysis of erythrocytes and the development of jaundice (113). Studies conducted with resinic acids (114) have shown that liver RNA and protein concentrations are altered; all this involves, above certain limits, a subacute toxicity in fish exposed to the effluent of resinic acids from the paper industry. Dehydroabietic acid (**27**) inhibits the production of methane by *Methanosaeta* sp. and is the most toxic of all the benzene derivatives assayed (115–116).

Acknowledgements

Financial support during this work came from DGICYT (Spain) grant PB89/394 is gratefully acknowledged.

References

[1] Tabacik-Woltzka, C., Mousseron, M., Chafai, M. A. (1963) Bull. Soc. Chim. Fr. 2299–2306.
[2] Manchand, P. S., White, J. D., Fayos, J., Clardy, J. (1974) J. Org. Chem. 39, 2306–2308.
[3] Bol'shakova, V. I., Schmidt, E. N., Pentegova, V. A., Mamatyuk, V. I. (1986) Khim. Prir. Soedin 5, 571–576 [Eng. Transl. (1987) Chem. Nat. Comp. 22, 536–541].
[4] Monaco, P., Parrilli, M., Previtera, L. (1987) Tetrahedron Lett. 28, 4609–4610.
[5] Escudero, J., Perez, L., Rabanal, R. M., Valverde, S. (1983) Phytochemistry 22, 585–587.
[6] Delgado, G., Sanchez, E., Hernandez, J., Chavez, M. I., Alvarez, L., Martinez, E. (1992) Phytochemistry 31, 3159–3161.
[7] Buratti, L., Allais, J. P., Barbier, M. (1990) Phytochemistry 29, 2708–2709.
[8] Barrero, A. F., Sánchez, J. F., Alvarez, E. J., Muñoz, M., Haidour, A. (1991) Phytochemistry 30, 593–597.
[9] Topcu, G., Ulubelen, A. (1990) Phytochemistry 29, 2346–2348.
[10] San Feliciano, A., Miguel del Corral, J. M., Gordaliza, M., Moreno de Vega, C., unpublished data.
[11] San Feliciano, A., Miguel del Corral, J. M., Gordaliza, M., Castro, M. A. (1991) Phytochemistry 30, 695–697.
[12] San Feliciano, A., Miguel del Corral, J. M., Gordaliza, M., Salinero, M. A., del Rey, B. (1993) Fitoterapia 64, 185–186.
[13] Pascual, J. de, San Feliciano, A., Tabernero, M. L., Miguel del Corral, J. M., Barrero, A. F., Grande, M. (1978) An. Quim. 74, 459–464.
[14] Lavy, S. (1928) Angew. Chem. 41, 233–237.
[15] Ruzicka, L., Andersmith, F. (1932) Helv. Chim. Acta 15, 1289–1294.
[16] Ruzicka, L., Sternbach, L. (1941) Helv. Chim. Acta 24, 504–515.
[17] Smith, W. B. (1978) Org. Magn. Reson. 11, 427–428.
[18] Pascual, J. de, San Feliciano, A., Miguel, del Corral, J. M., Barrero, A. F. (1983) Phytochemistry 22, 300–301.
[19] Roshchin, V. I., Kolodynskaya, L. A., Raldugin, V. A., Pentegova, V. A. (1985) Khim. Prir. Soedin. 3, 345–351.
[20] Puzanova, V. Y., Schmidt, E. N., Rabdil, B. A., Pentegova, V. A. (1986) Izv. Sib. Otd. Akad. Nauk. SSR. Ser. Khim. Nauk. 5, 129–132; Chem. Abstr. 106, 34964.
[21] Carman, R. M., Marty, R. A. (1970) Austral. J. Chem. 23, 1457–1464.
[22] Ohmoto, T., Saito, M., Yamaguchi, K. (1987) Chem. Pharm. Bull. 35, 2443–2447.
[23] Tabacik, C., Poisson, C. (1969) Bull. Soc. Chim. Fr. 9, 3264–3265.
[24] Wenkert, E., Afonso, A., Bredenberg, J. B., Kaneko, C., Tahara, A. (1964) J. Am. Chem. Soc. 86, 2038–2043.
[25] Gough, L. J. (1970) Phytochemistry 9, 1093–1096.

[26] Norin, T., Winell, B. (1972) Acta Chem. Scand. 26, 2289–2296.
[27] Zinkel, D. F., Critchfield, W. B. (1974) Phytochemistry 13, 2876–2877.
[28] Ruzicka, L., Balas, F., Willim, F. (1924) Helv. Chim. Acta 7, 458–462.
[29] Burgstahler, A. W., Ziffer, H., Weiss, U. (1961) J. Am. Chem. Soc. 83, 4660–4661.
[30] Norin, T., Winell, B. (1972) Acta Chem. Scand. 26, 2297–2304.
[31] Konopleva, N. R., Skvortsov, N, P. (1983) Khim. Drev. 4, 18–20; Chem. Abstr. 99, 106968.
[32] Harris, G. C., Sanderson, T. F. (1948) J. Am. Chem. Soc. 334–339.
[33] Audier, H. E., Bory, S., Fetizon, M., Anh, N. T. (1966) Bull. Soc. Chim. Fr. 12, 4002–4010.
[34] Bardysher, I. I., Degtyarenko, A. S., Pertsovskii, A. L., Krynk, S. I. (1981) Khim. Drev. 3, 102–104; Chem. Abstr. 95, 44975.
[35] Castro, V., Calzada, J. (1984) Rev. Latinoamer. Quim. 15, 135–136.
[36] Harris, G. C. (1948) J. Am. Chem. Soc. 70, 3671–3674.
[37] Ulubelen, A., Miski, M., Marby, T. J. (1981) J. Nat. Prod. 44, 119–124.
[38] Ayer, W. A., Migaj, B. S. (1989) Can. J. Bot. 67, 1426–1428.
[39] Ohmoto, T., Katanaki, K., Yamaguchi, K. (1987) Chem. Pharm. Bull. 35, 229–234.
[40] Roshchin, V. I., Kolodynskaya, L. A., Razina, N. Yu., Solov'ev, V. A. (1985) Khim. Drev. 2, 106–107; Chem. Abstr. 103, 3690.
[41] Ekman, R. (1979) Acta Acad. Abo. Ser. B. 39, 1–7; Chem. Abstr. 91, 207623.
[42] Dupont, G., Dolou, R., Thibault, C. (1953) Compt. Rend. Acad. Sci. 236, 2408.
[43] Lorbeer, E., Kratzl, K. (1985) Holzforsch. Holzverwert. 37, 109; Chem. Abstr. 104, 145539.
[44] Lorbeer, E., Zelman, N. (1988) Holzforschung 42, 241–246; Chem. Abstr. 109, 31093.
[45] Proença, A., Roque, O. R., Cardoso, J. (1977) Bol. Fac. Farmacia Coimbra 2, 9–23.
[46] Gough, L. J. (1968) Tetrahedron Lett. 3, 295–298.
[47] Chamy, M. C., Piovano, M., Gambarro, V., Garbarino, J. A., Nicoletti, M. (1987) Phytochemistry 26, 1763–1765.
[48] Hongjie, Z., Handong, S. (1989) Phytochemistry 28, 3405–3409.
[49] Campello, J. P., Fonseca, S. F. (1975) Phytochemistry 14, 243–248.
[50] Cambie, R. C., Cox, R. E., Croft, K. D., Sidwell, D. (1983) Phytochemistry 22, 1163–1166.
[51] Castro, V., Mojica, E., Calzada, J. (1986) Ing. Cienc. Quim. 10, 5–6.
[52] Briggs, L. H., Cambie, R. C., Seelye, R. N., Warth, A. D. (1959) Tetrahedron 7, 270–276.
[53] Cambie, R. C., Mander, L. N. (1962) Tetrahedron 18, 465–475.
[54] Cambie, R. C., Mathai, K. P. (1971) Chem. Commun. 154–155.
[55] Yatagai, M., Shirato, T., Hayashi, Y., Fukuhara, N., Takahashsi, T. (1978) Mokuzai Gakkaishi 24, 267–269; Chem. Abstr. 91, 16655.
[56] Fukui, H., Koshimizu, K., Egawa, H. (1978) Agric. Biol. Chem. 42, 1419–1423.
[57] Kobayashi, K., Nishino, C. (1986) Agric. Biol. Chem. 50, 2405–2407.
[58] Ahn, J. W., Wada, K., Marumo, S., Tanaka, H., Osaka, Y. (1984) Agric. Biol. Chem. 48, 2167–2169.
[59] Yatagai, M., Takahashi, T. (1980) Phytochemistry 19, 1149–1151.
[60] Linde, H. (1964) Helv. Chim. Acta 47, 1234–1239.
[61] Narayanan, C. R., Linde, H. (1965) Tetrahedron 41, 3647–3649.
[62] Al-Hazimi, H. M. G., Miana, G. A., Deep, M. S. H. (1987) Phytochemistry 26, 1091–1093.
[63] González, A. G., Rodriguez, C. M., Luis, J. G. (1987) Phytochemistry 26, 1471–1474.
[64] Dentali, S. J., Hoffmann, J. J. (1990) Phytochemistry 29, 993–994.
[65] Bruno, M., Savona, G., Piozzi, F., Torre de la, M. C., Rodriguez, B., Marlier, M. (1991) Phytochemistry 30, 2339–2343.
[66] Paris, R. R., Moise, H. (1976) Matière medicale, p. 386, Masson, Paris.
[67] Font-Quer, P. (1980) Plantas Medicinales, pp. 82–87, Labor, S. A., Madrid.
[68] Kobayashi, K., Nishino, C., Fukushima, M., Shibara, Y., Kodama, M. (1988) Agric. Biol. Chem. 52, 77–83.
[69] Soderberg, T. A., Gref, R., Holm, S., Elmrost, T., Hallmans, G. (1990) Scand. J. Plast. Reconstr. Surg. Hand. Surg. 24, 199–205.
[70] Sodergerg, T. A., Holm, S., Gref, R., Hallmans, G. (1991) Scand. J. Plast. Reconstr. Surg Hand. Surg. 25, 19–24.
[71] Sodergerg, T. A. (1990) Scand. J. Plast. Reconstr. Surg. Suppl. 22, 1–87.
[72] Akatsuka, T., Kodama, O., Matsuo, K., Esaki, Y. (1988) Jpn. Pat. 6317805; Chem. Abstr. 109, 106543.
[73] Harima Kasei Kogyo Co. (1980) Ltd. Jpn. Pat. 8072112; Chem. Abstr. 94, 20384.
[74] Wada, H., Kodato, S. I., Kawamori, M., Morikawa, T., Nakai, H., Takeda, M., Onoda, Y., Tamaki, H. (1985) Chem. Pharm. Bull. 33, 1472–1487.
[75] Onoda, Y., Magaribuchi, T., Tamaki, H. (1989) Jpn. J. Pharmacol. 51, 65–73.
[76] Ito, Y., Fukushima, T., Sugawara, Y., Takaiti, O., Nakamura, S. (1991) J. Pharmacobio-Dyn. 14, 533–546.
[77] Ito, Y., Sugawara, Y., Takaiti, O., Nakamura, S. (1991) J. Pharmacobio-Dyn. 14, 547–554.
[78] Onoda, Y., Iwasaki, H., Magaribuchi, T., Tamaki, H. (1991) Arzneim.-Forsch. 41, 546–548.
[79] Kohli, Y., Kato, T., Suzuki, K., Yamazaki, Y., Iwaki, M., Hata, M. (1990) Kyotofuritsu Ika Daigaku Zasshi 99, 1085–1090; Chem. Abstr. 114, 156931.
[80] Magaribuchi, T., Onoda, Y., Narida, H., Yabana, H., Yamada, K., Nagasaki, M., Sasaki, Y., Inaeki, M., Yamaguchi, I. (1990) Yakurito Chiryo 18, 4511–4529; Chem. Abstr. 114, 94662.
[81] Onoda, Y., Magaribuchi, T., Tamaki, H. (1990) Arzneim.-Forsch. 40, 576–578.
[82] Onoda, Y., Takido, M., Magaribuchi, T. (1990) Jpn. J. Pharmacol. 52, 63–73.
[83] Sekido, H., Takezawa, J. I., Motori, G., Akatsuka, T. (1990) Agric. Biol. Chem. 54, 287–290.
[84] Vrbosky, L., Siklova, M. (1969) Bratislav. Lek. Listy 53, 275–285; Chem. Abstr. 77, 160082.
[85] Fujita, Y., Sempuku, K., Kitaguchi, K., Mori, T., Murai, H., Yoshikuni, Y., Enomoto, H., Löser, R. (1980) Chem. Pharm. Bull. 28, 453–458.
[86] Fujita, Y., Yoshikuni, Y., Sotomatsu, T., Mori, T., Ozaki, T., Sempuku, K., Ogino, A., Kise, M., Enomoto, H. (1991) Chem. Pharm. Bull. 39, 1193–1198.
[87] Liu, T. P., Gao, C. Z., Feng, L. Z. (1985) J. Tradit. Chin. Med. 5, 115–118.
[88] Suzuki, A., Asano, M., Ohkubo, C., Tamura, S. (1972) Agric. Biol. Chem. 36, 2051–2053.
[89] Asano, M., Olikubo, C., Suzuki, A., Tamura, S. (1973) Koshu, Eiseiin Kenkyo Hokoku 22, 1–8; Chem. Abstr. 81, 145821.
[90] Karlberg, A. T. (1988) Acta Derm. Veneorol. Suppl. Stockh. 139, 1–43.
[91] Karlberg, A. T., Bergsted, E., Boman, A., Bohlinder, K., Lars, J., Nilsson, G., Wahlberg, J. E. (1985) Contact Dermatitis 13, 209–215.
[92] Karlberg, A. T. (1989) Contact Dermatitis 21, 282–285.
[93] Institute for Production and Development Science (1984) Jpn. Pat. 5967219; Chem. Abstr. 101, 78846.
[94] Karlberg, A. T., Bohlinder, K., Boman, A., Hacksell, U., Hermannson, J., Jacobsson, S., Lars, J., Nilsson, G. (1988) J. Pharm. Pharmacol. 40, 42–47.
[95] Hausen, B. M., Krohn, K., Budianto, E. (1990) Contact Dermatitis 23, 352–358.
[96] Soderberg, T. A., Elmros, T., Gref, R., Hallmans, G. (1990) Contact Dermatitis 23, 346–352.
[97] Ayala, F., Lembo, G., Balato, N., Patruno, C., Scognamiglio, G., Strazzullo, S. S. (1990) Contact Dermatitis 22, 262–266.
[98] Schuh, B. A., Benjamin, D. M. (1984) J. Econ. Entomol. 77, 802–805.
[99] Fujii, R., Okumura, M., Kine, M. (1986) Jpn. Pat. 61212547; Chem. Abstr. 106, 156857.
[100] Proserpio, G., Gatti, S. (1979) Riv. Ital. EPPOSS 61, 53–62.
[101] Jonnsen, V. L., Stern, E. S. (1978) U. S. Pat. 4128543; Chem. Abstr. 90, 76409.
[102] Emori, S. (1979) Jpn. Pat. 79117037; Chem. Abstr. 92, 64539.
[103] Uehara, K., Kawabata, A., Iwasa, S., Inone, Y., Tutsumi, Y., Ichikawa, H. (1988) Jpn. Pat. 63183512; Chem. Abstr. 111; 45052.
[104] Uehara, K., Kawabata, A., Iwasa, S., Inone, Y., Tutsumi, Y., Ichikawa, H. (1988) Jpn. Pat. 63183511; Chem. Abstr. 111, 140201.

[105] Takatsu, A. (1991) Jpn. Pat. 3173811; Chem. Abstr. 116, 27852.
[106] Ohastti, Y., Yakeuchi, K., Suda, M., Yoshino, K., Kawamata, A., Mastui, Y., Suzuki, Y. (1991) Eur. Pat. 7446938; Chem. Abstr. 116; 22505.
[107] Kikuchi, Y., Suzuki, Y., Suzuki, T., Suda, M., Ohashi, Y., Kawamata, A. (1991) Jpn. Pat. 91118311; Chem. Abstr. 115, 263054.
[108] Le Grouyellec, A. (1985) Fr. Pat. 2557799; Chem. Abstr. 104, 10630.
[109] Collard, A. (1977) Fr. Pat. 2338700; Chem. Abstr. 88, 110544.
[110] Emori, S. (1979) Jpn. Pat. 79117031; Chem. Abstr. 92, 99466.
[111] Ayars, G. H., Altman, L. C., Frazier, C. E., Chi, E. Y. (1989) J. Allergy Clin. Immunol. 83, 610–618.
[112] Bushnell, P. G., Nikinmaa, M., Oikari, A. (1985) Comp. Biochem. Physiol C. 81, 391–394.
[113] Mattsoff, L., Nikinmaa, M. (1987) Ecotoxicol. Environ. Safety 14, 157–163.
[114] Oikari, A. O., Nittyla, J. (1985) Ecotoxicol. Environ. Safety 10, 159–172.
[115] Patel, G. B., Angew, B. J., Dicaire, C. J. (1991) Appl. Environ. Microbiol. 57, 2969–2974.
[115] Orpiszewsk, J., Hebda, C., Szykula, J., Powls, R., Clasper, S., Rees, H. H. (1991) FEMS Microbiol. Lett. 66, 233–236.