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Antifungal Compounds from *Piper* Species

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Abstract

This review documents chemical structures and antifungal activities of 68 compounds isolated from 22 *Piper* species of the plant family Piperaceae. These compounds include amides, flavonoids, prenylated benzoic acid derivatives, lignans, phenylpropanoids, butenolides, and cyclopentendiones. Some of them may serve as leads for potential pharmaceutical or agricultural fungicide development.

Keywords

Antifungal; *Piper*; Piperaceae; amide; flavonoid; prenylated benzoic acid; lignan; phenylpropanoid; butenolide; cyclopentendione

INTRODUCTION

Piper is a big genus of the plant family Piperaceae, with more than 700 species widely distributed in the tropical and subtropical regions of the world. Some species are used in folk medicine as analgesics, antiseptics, insecticides, and antimicrobials or for the treatment of toothache, haemorrhoids, dysmenorrhea, and wound [1–4]. Extensive chemical studies on *Piper* species have resulted in the isolation of a large number of structurally diverse compounds. A previous review by Parmar V et al. has covered about 600 compounds isolated from this genus for the period of 1907 to 1996 [1]. In recent years, a number of compounds from *Piper* species have been reported to possess significant antifungal activities. Thus, this review attempts to document chemical structures and antifungal activities of these compounds, with the aim of providing useful information for potential pharmaceutical or agricultural fungicide development. The antifungal compounds are classified into amides, flavonoids, prenylated benzoic acid derivatives, lignans, phenylpropanoids, butenolides, and cyclopentendiones. The trivial names of the compounds that are available in the literature have been provided.

AMIDES

Amides **1–3** and **4–10** were isolated from the stems of *P. hispidum* and the seeds of *P. tuberculatum*, respectively, and tested for antifungal activity against *Cladosporium sphaerospermum* by the TLC bioautography method. The minimum amount required (MAR) for inhibition of compounds **1–10** are 5.0, 5.0, 5.0, 5.0, 0.1, 5.0, 1.0, 5.0, 5.0, and 5.0 μg, respectively [5]. Compound **5** is 5-fold more potent than the positive controls nystatin

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and miconazole, both of which show an MAR of 0.5 μg. The potent antifungal activity of this compound may be attributed to the α,β-unsaturated piperidinone moiety. It is also interesting to note that analogous compounds **4** and **6** (piplarine) bearing a double bond (*cis* or *trans*) between the carbonyl group and the aromatic ring show significantly reduced activity by 50-fold, which may be caused by the decreased electrophilicity of the α,β-unsaturated piperidinone moiety.

N-[7-(3′,4′-methylenedioxyphenyl)-2(*Z*),4(*Z*)-heptadienoyl]pyrrolidine (**11)** was isolated from a methylene chloride extract of the leaves of *P. hispidum* by antifungal activity-guided fractionation [6]. The structural difference between compounds **11** and **1** lies in the amide moiety, with the latter possessing an isobutyl group. Compound **11** showed an antifungal activity against *C. sphaerospermum* that is one eighth of miconazole, similar to compound **1** that is one fifth of miconazole [5].

Amides 1**2–15** isolated from the Brazilian plant *P. arboretum* showed antifungal activity against *C. sphaerospermum* with MARs of 10, 5.0, 0.1, and 5.0 μg, respectively, while amide **16** from *P. tuberculatum* exhibited an MAR of 10 μg against *C. cladosporioides* [7]. The potent antifungal activity of compound **14** indicates that 5-(3′,4′-methylenedioxyphenyl)-2(*E*),4(*E*)-pentadienoyl moiety is important. However, amide **7** that has the same acyl moiety but with a piperidinyl moiety is 10-fold less active (MAR, 1.0 μg), indicating that the pyrrolidinyl moiety in compound **14** also plays a key role for antifungal activity.

Amides **17–24** isolated from the leaves of *P. scutifolium* showed varying degrees of antifungal activities against *C. sphaerospermum* and *C. cladosporioides* [8], providing further information on the structure-activity relationship (SAR) of this class of compounds. Among the eight compounds, isopiperlonguminine (**17**) is the most potent, with an MAR of 0.25 μg. Piperlonguminine (**18**), piperovatine (**19**), and corcovadine (**20**) are equipotent with the positive controls nystatin and miconazole (MARs, 1.0 μg). It appears that the geometric configurations of the double bonds in these compounds are associated with antifungal activity. The aromatic lactam piperolactum (**24**) is the least active.

Several amides were isolated from the roots of *P. sarmentosum* and tested for antifungal activity against *Candida albicans* using a method modified from the soluble formazan assay. Only brachyamide B (**25**) and sarmentosine (**26**) showed marginal antifungal activity with 50% growth inhibitory concentration (IC_{50}) of 41.82 and 32.82 μg/ml, respectively [2]. The positive control amphotericin B gave an IC_{50} of 0.01μg/ml.

The aristolactams piperumbellactam D (**27**) and *N*-hydroxyaristolam II (**28**) isolated from the branches of *P. rumbellatum* showed antifungal activity against *Aspergillus flavus*, *Trichophyton longifusus*, *Microsporum canis*, *Fusarium solani*, *C. albicans*, and *C. glabrata* using the agar tube dilution method. They exhibited higher antifungal activity than amphotericin B against *A. flavus* and *T. longifusus* in terms of inhibition rates at fixed sample concentrations [3].

FLAVONOIDS

In a bioassay-guided isolation study, the flavanones sakuranetin (**29**) and naringenin (**30**) were isolated from the leaves of *P. crassinervium* and tested for antifungal activity using the TLC bioautography method. Compound **29** gave an MAR of 1.0 μg against both *C. sphaerospermum* and *C. cladosporioides*, the same MAR generated by the positive control nystantin, while Compound **30** afforded MAR of 1.0 and 5.0 μg, respectively [9]. Compound **29** was also isolated as an antifungal constituent from *P. lhotzkyanum* [10] and

P. marginatum [11]. The analog 5,7-dihydroxy-4′-methoxyflavanone (**31**) isolated from *P. marginatum* [11] also demonstrated the same antifungal activity as sakuranetin against the aforementioned two fungal pathogens. When both 7,4′-dihydoxy groups in compound **30** are methylated, the resultant compound (7,4′-dimethoxy-5-hydroxy-flavanone, **32**) showed decreased antifungal activity by 25-fold [11].

From the Brazilian plant *P. solmsianu*, orientin (**33**), a favone C-glucoside, was isolated and showed good antifungal activity against *M. canis, M. gypseum, T. mentagrophytes, T. rubrum*, and *Epidermophyton flocosum* in an agar dilution assay with minimal inhibitory concentration (MICs) of 7, 9, 8, 8, and 9 μg/ml, comparable to the positive control ketoconazole with MICs of 8, 6, 8, 3, and >15 μg/ml [12], respectively.

Bioassay-guided fractionation of *P. mollicomum* led to the isolation of dihydrochalcone (**34**) that showed moderate antifungal activity against *C. sphaerospermum* and *C. cladosporioides* with MARs of 5 amd 10 μg, respectively [10]. Pinocembrin chalcone (**35**) gave an MIC of 100 μg/ml against *C. albicans* using a broth dilution method [13]

PRENYLATED BENZOIC ACID DERIVATIVES

This class of compounds is derived from benzoic acid (from shikimate pathways) or decarboxylated phenol coupled with an isoprenyl, geranyl, or geranylfarnesyl unit (from mevalonate pathways). Four prenylated benzoic acid derivatives (**36–39**) were isolated from *P. dilatatum* collected in Panama and showed antifungal activity against the plant pathogenic fungus *Cladosporium cucumerinum* with MARs of 1.0, 3.0, 5.0, and 5.0 μg, respectively, by the TLC bioautography method [14]. The positive controls miconazole and propiconazole gave MARs of 1.0 and 0.1 μg, respectively. When tested using a dilution method, the MICs of **36** and **39** (methyl taboganate) were 40 and 60 μg/ml, respectively. Compound **38** (taboganic acid) was not active in the dilution assay. The MICs obtained for miconazole and propiconazole were 10 and 1 μg/ml, respectively. This study provides comparative data between the two assay methods.

In another bioassay-guided fractionation of *P. lanceaefolium*, the prenylated benzoic acid derivative **40** (lanceaefolic acid methyl ester) showed an MIC of 100 μg/ml against *C. albicans* using a broth dilution method [13].

The extracts of the leaves of *P. crassinervium* and *P. hostmannianum* from Brazil showed high growth inhibitory activity against *C. sphaerospermum* and *C. cladosporioides*. Under bioassay-guided fractionation, two potent antifungal benzoic acid derivatives crassinervic acid (**41**) and hostmaniene (**42**) were isolated from *P. crassinervium* and *P. hostmannianum*, respectively. Compounds **41** and **42** are equipotent, giving the same MAR of 0.5 μg against *C. cladosporioides* and *C. sphaerospermum* [15].

Caldensinic acid (**43**) was isolated from the leaves of *P. caldense* by bioassay-guided fractionation. Using a direct TLC bioautography assay to evaluate antifungal activity, it gave MARs of 5.0 μg and 25.0 μg against *C. sphaerospermum* and *C. cladosporioides*, respectively [16].

Bioassay-guided fractionation of the extract from the leaves of Brazilian *P. hostmannianum* and *P. aduncum* led to the isolation of two antifungal prenylated methyl benzoates (**44** and **45**). Compounds **44** and **45** demonstrated equipotent antifungal activity in a bioautography assay, giving the same MAR of 1.0 μg against *C. cladosporioides* and *C. sphaerospermum* [4].

Compounds **46–48** were isolated from the leaves of *P. crassinervium* by bioassay-guided fractionation. Compound **46** with C-2′ *trans*-double bond in the monoterpenoid side chain showed antifungal activity equipotent to nystatin and miconazole against C. *sphaerospermum* and *C. cladosporioides* (MARs, all 1.0 μg), while compound **47** with C-2′ *cis*-double bond in the side chain showed decreased antifungal activity by 5 to 10-fold. Compound **48** with a peroxy group in the side chain is equipotent to **47** [17].

Compounds **49** and **50** isolated from the leaves of *P. lhotzkyanum* showed equipotent antifungal activity with a MAR of 5.0 μg against both *C. sphaerospermum* and *C.* cladosporioides. Two analogs **51** and **52** with methylation on the carboxyl group showed decreased antifungal activity (by 2-fold and 5-fold, respectively) [10].

LIGNANS

Bioassay-guided fractionation of the methylene chloride extract from the leaves of *P. fulvescens* using an agar overlay bioautography method afforded two neolignans, eupomatenoid-6 (**53**) and conocarpan (**54**). The MICs of **53** and **54** were determined by a broth dilution method. Compound **54** demonstrated antifungal activity against all the species tested, namely *C. albicans, Cryptococcus neoformans, M. gypseum, Saccharomyces cerevisiae*, and *T. mentagrophytes* with MICs of 8, 16, 16, 4, and 8 μg/ml, respectively, compared against the positive control amphotericin B with MICs of 0.0625, 0.125, 0.25, 0.0625, and 0.125 μg/ml, respectively. Compound **53** was only active against *M. gypseum, S. cerevisiae, T. mentagrophytes* with MICs of 0.5, 16, and 1 μg/ml, respectively [18]. Compounds **53** and **54** were also isolated as antifungal constituents from *P. abutiloides* [19].

The methanol extract of the leaves of *P. regnellii* showed strong activity against the dermatophyte fungi *T. mentagrophytes, T. rubrum, M. canis* and *M. gypseum*. Bioassay-guided fractionation led to the isolation of two antifungal neolignans, eupomatenoid-3 (**55**) and eupomatenoid-5 (**56**). Compounds **55** and **56** exhibited antifungal activity against *T. rubrum* with MICs of 50.0 and 6.2 μg/ml, respectively [20].

PHENYLPROPANOIDS

Three simple phenyl propanoids (**57–59**) were isolated from the leaves of *P. marginatum* by means of bioassay-guided fractionation and exhibited moderate antifungal activity against *C. sphaerospermum* with MARs of 5.0, 5.0, and 10.0 μg, respectively, and *C. cladosporioides* with MARs of 5.0, 5.0, 10.0 μg, respectively [11].

Five phenylpropenes (**60–64**) isolated the leaves of *P. betle* showed varying degrees of antifungal activities against *C. cucumerinum* with MARs of 1, 3, 3, 10, and 30 μg, respectively. The relative potencies of these compounds indicate that substitution patterns play a significant role for antifungal activity [21].

BUTENOLIDES

Bioassay-guided fractionation of the methylene chloride extract from the leaves of *P. malacophyllum* led to the identification of butenolides **65** and **66**. Antifungal testing indicated that the *trans*-geometric isomer **66** had equipotent antifungal activity with miconazole (MAR, 1.0 μg) against *C. cladosporioides* and *C. sphaerospermum*, while the *cis*-isomer **66** was 5- to 10-fold less active than **65** [22].

CYCLOPENTENDIONES

Two cyclopentenedione derivatives, coruscanone A (**67**) and B (**68**) were isolated from the ethanol extract of the Peruvian plant *P. coruscans*. Compound **67** showed potent activity against *C. albicans* (MIC 0.78 μg/ml) and *C. neoformans* (MIC 6.25 μg/ml), while compound **68** exhibited marginal antifungal activity against *C. albicans* (MIC 50.0 μg/ml) [23]. Compound **67** is probably the most potent antifungal compound isolated from plants against *C. albicans*. Synthetic analogs have been prepared by modification of the cyclopentenedione ring, the enolic methoxy functionality, and the styrene moiety to afford SAR information for this class of compounds [24].

CONCLUSION

The survey of chemical and biological investigations of *Piper* species has revealed structurally diverse antifungal compounds. A total of 68 compounds were isolated from 22 *Piper* species (*P. hispidum, P. tuberculatum, P. arboretum, P. scutifolium, P. sarmentosum, P. rumbellatum, P. crassinervium, P. lhotzkyanum, P. marginatum, P. solmsianu, P. mollicomum, P. dilatatum, P. lanceaefolium, P. hostmannianum, P. caldense, P. aduncum, P. fulvescens, P. abutiloides, P. regnellii, P. betle, P. malacophyllum*, and *P. coruscans*). While the majority of these antifungal compounds (especially amides) were only evaluated by the simple bioautography method against agricultural fungal species, it will be worthwhile to test these compounds against clinically important human fungal pathogens. In addition, a medicinal chemistry approach to synthesizing analogs may be employed to study the SAR of these antifungal compounds in order to discover better leads for the development of antifungal drugs or agricultural fungicides.

Acknowledgments

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References

1. Parmar VS, Jain SC, Bisht KS, Jain R, Taneja P, Jha A, Ali MS, Tyagi OD, Prasad AK, Wengel J, Olsen CE, Boll PM. Phytochemistry of the genus *Piper*. Phytochemistry. 1997; 46:597–673.
2. Tuntiwachwuttiku P, Phansa P, Pootaengon Y, Taylo WC. Chemical constituents of the roots of *Piper sarmentosum*. Chem Pharm Bull. 2006; 54:149–151. [PubMed: 16462055]
3. Tabopda TK, Ngoupayo J, Liu J, Mitaine-Offer AC, Tanoli SAK, Khan SN, Ali MS, Ngadjui BT, Tsamo E, Lacaille-Dubois M-A, Luu B. Bioactive aristolactams from *Piper umbellatum*. Phytochemistry. 2008; 69:1726–1731. [PubMed: 18400239]
4. Lago JHG, Chen A, Young MCM, Guimarães EF, Oliveira A, Kato MJ. Prenylated benzoic acid derivatives from *Piper aduncum*L and P hostmannianum C DC (Piperaceae). Phytochem Lett. 2009; 2:96–98.
5. Navickiene HM, Alecio AC, Kato MJ, Bolzani VS, Young MC, Cavalheiro AJ, Furlan M. Antifungal amides from *Piper hispidum* and *Piper tuberculatum*. Phytochemistry. 2000; 55:621–626. [PubMed: 11130674]
6. Alecio AC, Bolzani VS, Young MCM, Kato MJ, Furlan M. Antifungal amide from leaves of *Piper hispidum*. J Nat Prod. 1998; 61:637–639. [PubMed: 9599264]
7. Silva RV, Navickiene HM, Kato MJ, Bolzani VS, Meda CI, Young MC, Furlan M. Antifungal amides from *Piper arboreum* and *Piper tuberculatum*. Phytochemistry. 2002; 59:521–527. [PubMed: 11853747]

8. Marques JV, Kitamura RS, Lago JHM, Young MC, Guimarães EF, Kato MJ. Antifungal amides from *Piper scutifolium* and *Piper hoffmanseggianum*. J Nat Prod. 2007; 70:2036–2039. [PubMed: 18031016]
9. Danelutte A, Lago J, Young M, Kato M. Antifungal flavanones and prenylated hydroquinones from *Piper crassinervium Kunth*. Phytochemistry. 2003; 64:555–559. [PubMed: 12943774]
10. Lago JH, Young MC, Reigada JB, Soares MG, Roesler BP, Kato MJ. Antifungal derivatives from *Piper mollicomum* and *P. Lhotzkyanum* (Piperaceae). *Quim*. Nova. 2007; 30:1222–1224.
11. Reigada JB, Tcacenco CM, Andrade LH, Kato MJ, Porto ALM, Lago JHG. Chemical constituents from *Piper marginatum* Jacq. (Piperaceae) - antifungal activities and kinetic resolution of (*R*/*S*)-marginatumol by *Candida antarctica* lipase (Novozym 435). Tetrahedron: Asymmetry. 2007; 18:1054–1058.
12. Campos MP, Filho VC, Silva RS, Yunes RA, Zacchino S, Juarez S, Cruz RB, Cruz AB. Evaluation of antifungal activity of *Piper solmsianum* C. DC. var. *solmsianum* (Piperaceae). Biol Pharm Bull. 2005; 28:1527–1530. [PubMed: 16079508]
13. Lopez A, Ming DS, Towers HN. Antifungal activity of benzoic acid derivatives from *Piper lanceaefolium*. J Nat Prod. 2002; 65:62–64. [PubMed: 11809068]
14. Terreaux C, Gupta MP, Hostettmann K. Antifungal benzoic acid derivatives from *Piper dilatatum*. Phytochemistry. 1998; 49:461–464.
15. Lago JHG, Ramos CS, Casanova DCC, Morandim AA, Bergamo DCB, Cavalheiro AJ, Bolzani AS, Furlan M, Guimaraes EF, Young MCM, Kato MJ. Benzoic acid derivatives from *Piper* Species and their fungitoxic activity against *Cladosporium cladosporioides* and *C. sphaerospermum*. J Nat Prod. 2004; 67:1783–1788. [PubMed: 15568762]
16. Freitas GC, Kitamura ROS, Lago JHG, Young MCM, Guimarães EF, Kato MJ. Caldensinic acid, a prenylated benzoic acid from *Piper caldense*. Phytochem Lett. 2009; 2:119–122.
17. Danelutte A, Lago J, Young M, Kato M. Antifungal flavanones and prenylated hydroquinones from *Piper crassinervium* Kunth. Phytochemistry. 2003; 64:555–559. [PubMed: 12943774]
18. Freixa B, Vila R, Ferro EA, Adzet T, Canigueral S. Antifungal principles from *Piper fulvescens*. Planta Med. 2001; 67:873–875. [PubMed: 11745030]
19. Johann S, Cota BB, Souza-Fagundes EM, Pizzolatti MG, Resende MA, Zani CL. Antifungal activities of compounds isolated from *Piper abutiloides* Kunth. Mycoses. 2009; 52:499–506. [PubMed: 19076283]
20. Koroishi AM, Foss SR, Cortez DAG, Ueda-Nakamura T, Nakamura CV, Dias Filho BP. In vitro antifungal activity of extracts and neolignans from *Piper regnellii* against dermatophytes. J Ethnopharmcol. 2008; 117:270–277.
21. Evans PH, Bowers WS, Funk EJ. Identification of Fungicidal and Nematocidal Components in the Leaves of *Piper betle* (Piperaceae). J Agric Food Chem. 1984; 32:1254–1256.
22. Lago JHG, Tanizaki TM, Young MCM, Guimarães EF, Kato MJ. Antifungal piperolides from *Piper malacophyllum* (Prels) C. DC. J Braz Chem Soc. 2005; 16:153–156.
23. Li XC, Ferreira D, Jocob MR, Zhang QF, Khan SI, ElSohly HN, Nagle DG, Smillie TY, Khan IA, Walker LA, Clark AM. Antifungal cyclopentenediones from *Piper coruscans*. J Am Chem Soc. 2004; 126:6872–6873. [PubMed: 15174849]
24. Babu KS, Li XC, Jocob MR, Zhang QF, Khan SI, Ferreira D, Clark AM. Synthesis, antifungal activity, and structure-activity relationships of coruscanone A analogues. J Med Chem. 2006; 49:7877–7886. [PubMed: 17181171]

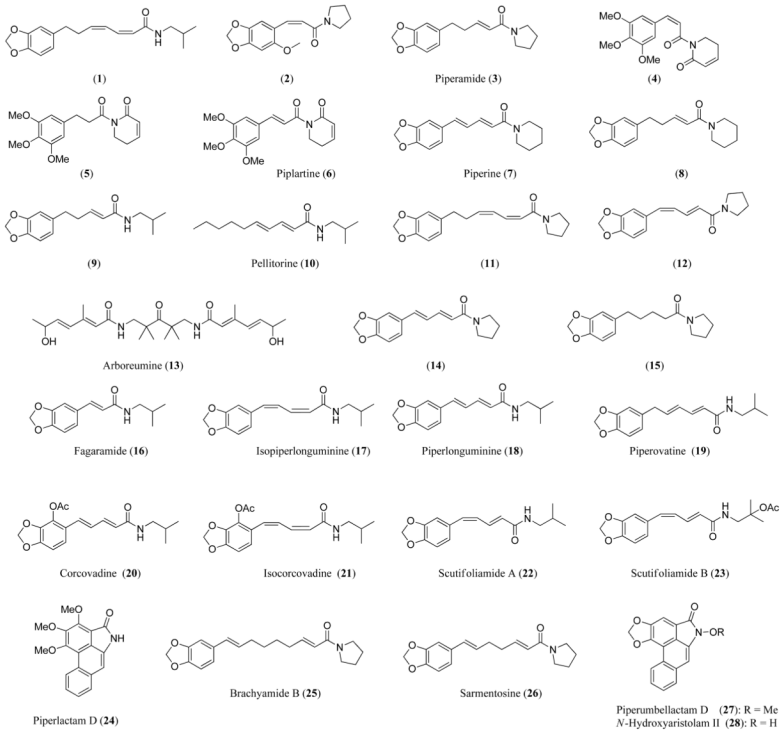


Fig. 1.
Antifungal amides from *Piper* spp.

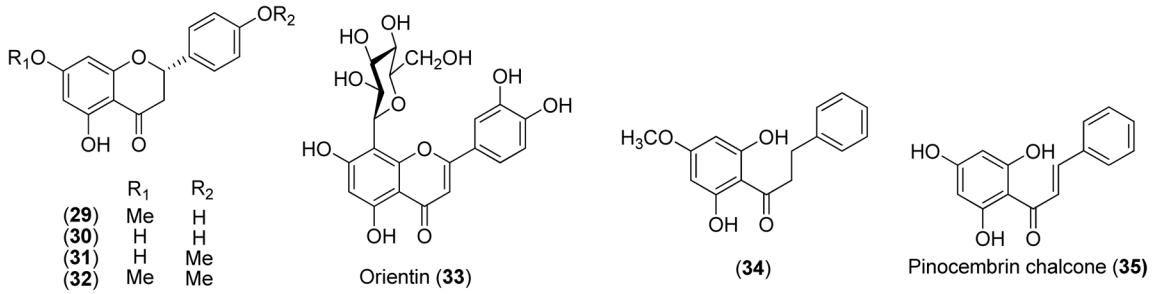


Fig. 2.
Antifungal flavonoids from *Piper* spp.

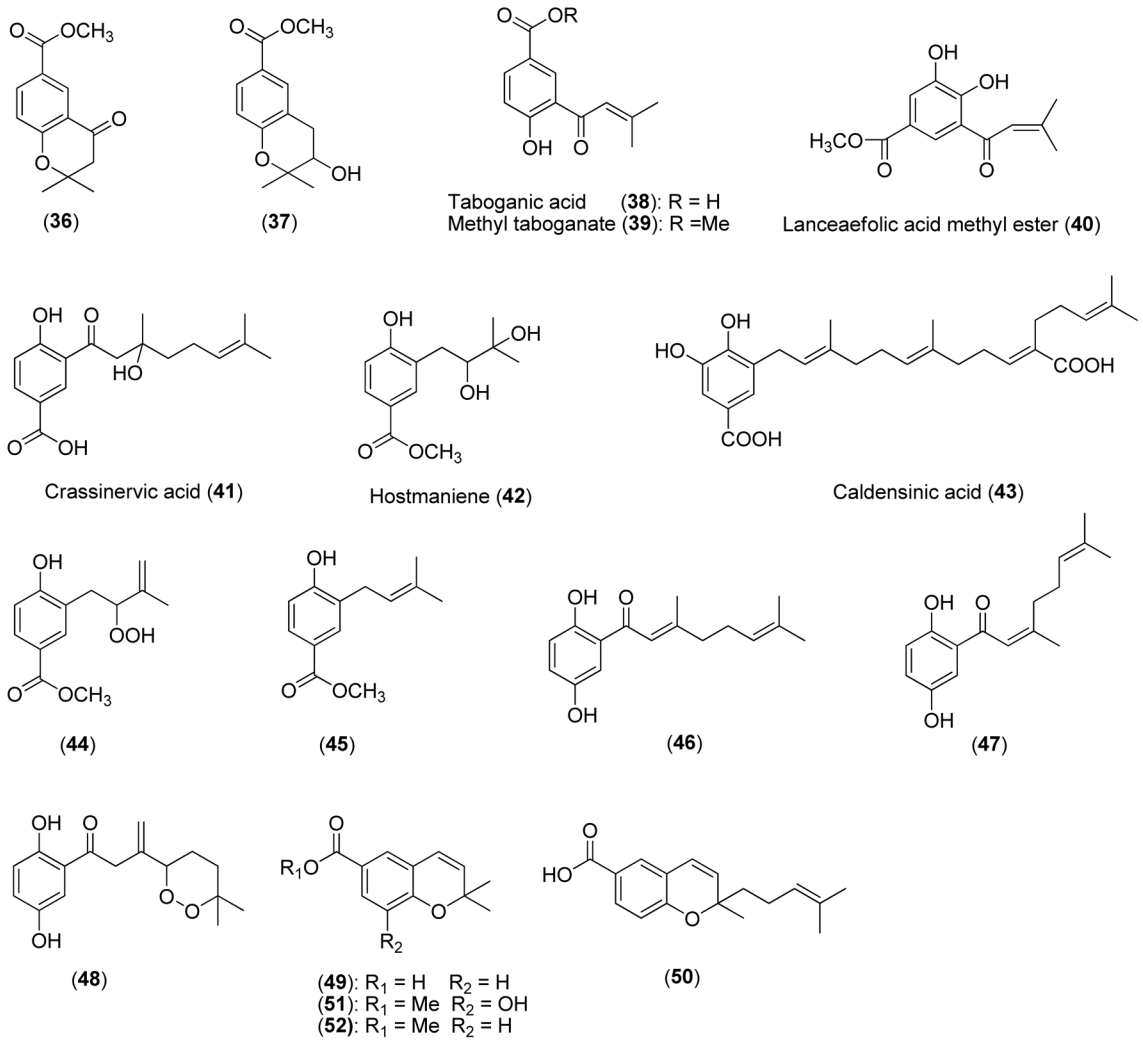


Fig. 3.
Antifungal prenylated benzoic acid derivatives from *Piper* spp.

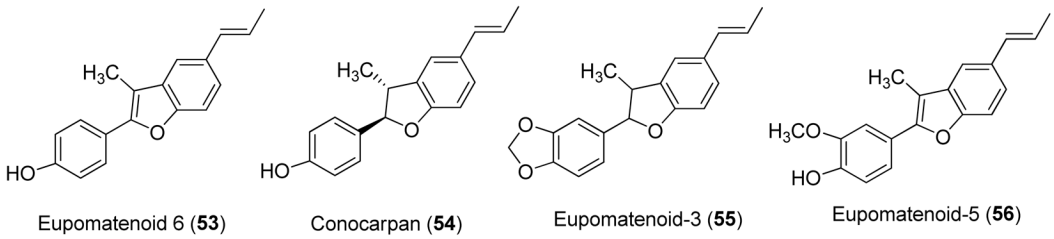


Fig. 4.
Antifungal lignans from *Piper* spp.

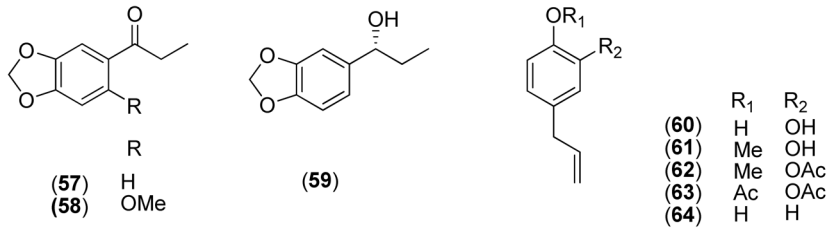
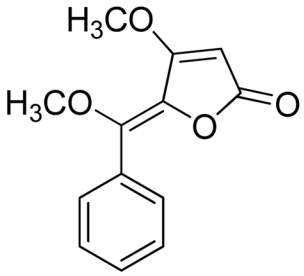
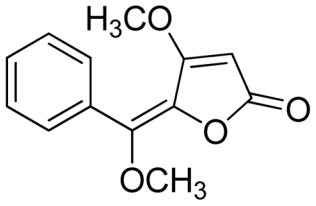


Fig. 5.
Antifungal phenylpropanoids from *Piper* spp.

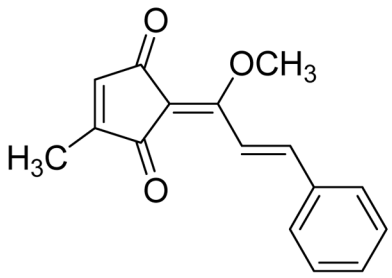


(**65**)

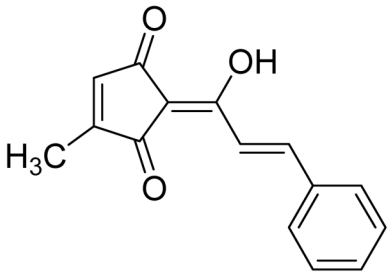


(**66**)

Fig. 6.
Antifungal butenolides from *Piper* spp.



Coruscanone A (**67**)



Coruscanone B (**68**)

Fig. 7.
Antifungal cyclopentenones from *Piper* spp.