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Naturally occurring enolethers

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Abstract

Enolethers are a group of reactive compounds also occurring in the nature and displaying different kinds of activities, such as antifungal, antibacterial, nematocidal, cytostatic, cytotoxic, phytotoxic, nematicidal, antipyretic, hypotensive, analgesic, antitussive, depresant, anticancerogenic and antiviral.

Keywords: enolether, fungicide, antibiotic, strobilurine, oudemansin, rhyncophylline, mitragynine, corynoxine

Introduction

Enolethers are a large group of organic compounds having oxygen atom conjugated through lone electron pairs with the double bond. Thus the double bond becomes more reactive. Even more reactive is the double bond when it is activated in β-position with one or two electron-withdrawing groups, thus giving rise to "activated enolethers". In the latter compounds the alkoxygroup can, under very mild conditions, be replaced by suitable nucleophile in nucleophilic vinylic substitution running with inversion of configuration, as compared to other types of nucleophilic vinylic substitutions running with retention of configuration (Saloň 2005).

Enolethers have been reviewed in (Houben-Weyl) and updated this year by us (Milata et al. 2008,in press). In this latest paper the part about naturally occurring enolethers have been left out, therefore the summarizing treatment of this group of compounds in nature seems to be very useful and complemental (Table 1). Naturally occurring enolethers are closely connected with synthetic enolethers used as antifungals, but they are beyond the scope of this review.

Biologically active enolethers

The strobilurins and oudemansins are produced by a number of saprotrophic higher fungal species. These include the ascomycete *Bolinia (Camarops) lutea*, a basidiomycete from the family Crepidotaceae (*Crepidotus fulvotomentosus*), and several members of the basidiomycete family Tricholomataceae from the genera *Oudemansiella*, *Xerula* (formerly a subgenus of *Oudemansiella*), and *Strobilurus* (*Pseudohiatula*) (Clough 1993).

The high fungicidal activity of the new antibiotic mucidin as a first β-methoxyacrylate antibiotic (MOA) isolated from the cultural medium and mycelium of the fungus *Oudemansiella mucida* was first discovered by Musilek et al. (1969) in the mid-1960's. Two fungicidal antibiotics called strobilurins A and B were isolated from mycelium of the basidiomycete *Strobilurus tenacellus* in 1977 (Anke et al. 1977). Structural elucidation of these compounds revealed that strobilurin A and mucidin are identical and represent methyl (2*E*,3*Z*,5*E*)-2-methoxymethylene-3-methyl-6-phenylhexa-3,5-dienoate (Sedmera et al. 1981; von Jagow et al. 1986). The *E,Z,E*-configuration of the double bonds of strobilurins was confirmed by chemical and spectroscopic studies (Anke et al. 1984) as well as by stereospecific synthesis. The spectral properties of a synthetic *E,E,E*-isomer of strobilurin A differed from those of the natural compound (Beautement and Clough 1987).

3-Methoxy-prop-2-enoic acid (or amide) unit is present in many naturally occurring biologically active substances such as strobilurines (mucidines), 9-methoxy-strobilurines, oudemansines, “folines”, “mitra, rhyncophylline, corynox”-derivatives and some other types of compounds, generally bearing terminal methoxygroup (no ethoxy or carbethoxy group in all compounds is presented). From another point of view, the unique triene moiety includes two-electron rich and acid-sensitive methyl enolethers as common substructures. Metoxystrobilurines have two methoxy groups attached to double bonds, thus being dienedienolethers. The alkaloids of Mitragyna with special reference to those of *Mitragyna speciosa*, Korth. are reviewed at www.coffeshop.pl/dokumenty/Shellard_Mitragyna.pdf. A link between strobilurins and oudemansins are 9-methoxystrobilurins. The oudemansins differ from the strobilurins in that the 9,10 double bond of the triene system in the side chain is reduced and bears a methoxy substituent (Zapf et al.1995b).

3-Methoxy-prop-2-enoic acid derivative skeleton, namely (*E*)-methyl-β-methoxyacrylate group as a common pharmacophore responsible for biological activity of these types of compounds, beside bridge group (such as 1,2-phenylene spacer) and side chain (phenoxy group). Natural strobilurins, e.g. A, B, C, D, F, G, H and 8 synthetic ones including azoxystrobin and picoxystrobin were submitted to QASAR. On the bridge group often ring

hydroxylation followed by conjugation occurred, from pharmacophore ester group could be hydrolyzed, ether bridge cleaved and double bond biotically reduced and oxidized or photolytic reactions including isomerization to (*Z*)-isomer could take place (Balba 2007). Strobilurin A is degraded to its inactive acid by hydrolyzing by *P. urticae* ATCC 48165 within 24 h (Kettering et al. 2004). Hirsuteine and hirsutine both are hydroxylated to position 11 and glycosylated to corresponding 11-*O*-β-D-glucuronide when metabolized by rats (Nakazawa et al. 2006). On the basis of these results has a set of 13 new strobilurine analogs designed and synthesized (Huang et al. 2007), from which 3 seems to be promising fungi in tests.

Strobilurin A was first isolated by Anke et al. in 1977. 9-Methoxystrobilurin A was isolated by Anke and Steglich in 1995 (Zapf et al. 1995a). The strobilurins, also named Q_o inhibitors or QoIs for short, were introduced in the mid-1990s. They exhibit efficacy against a broad-spectrum of fungal diseases, possess significant post-infective activity, and have a unique mode of action (1). Several pathogens have developed qualitative resistance to the strobilurins as a new and potent analogue of antifungal β-methoxyacrylates caused by a G143A mutation of the cytochrome *b* target site (Bartlett et al. 1995a,b). Structurally complicated strobilurin K and L were also isolated in 1996. Strobilurins are metabolites isolated from basidiomycetes which inhibit mitochondrial respiration and as a result, have fungicidal activity. Interestingly, this 9-methoxystrobilurin family was found to exhibit potent cytostatic activity toward human-derived tumor cell lines in addition to the originally reported antifungal activity. As an example, 9-methoxystrobilurin A and K inhibited the growth of HeLa S3 cell at very low concentration (the IC_{50} value reached 8.5 nM) without showing any significant cytotoxity. 9-Methoxystrobilurins K, L and strobilurin E exhibit interesting biological activity among them remarkable cytostatic activity toward human Burkitt´s lymphoma derived cell lines or strong antifungal activities toward several typical fungi by inhibiting a mitochondrial respiration pathway (Aiba et al. 2001).

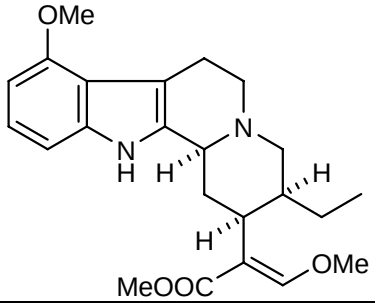
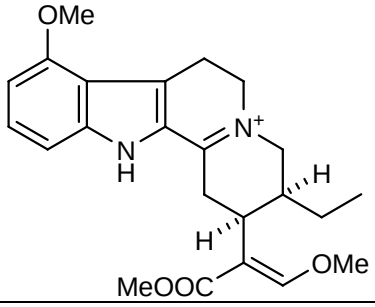
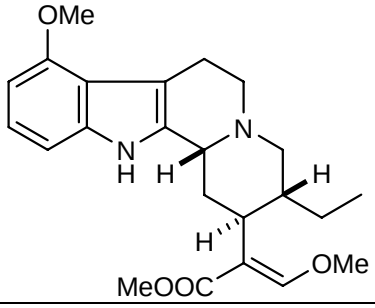
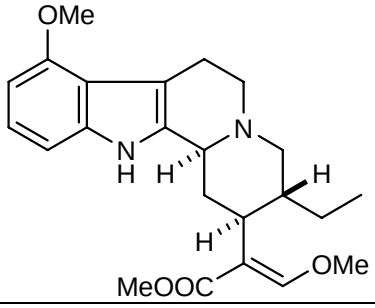
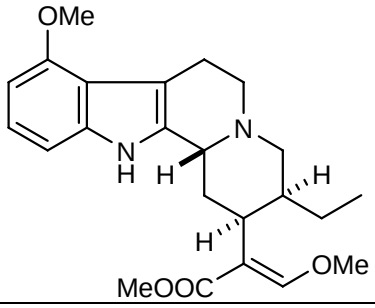
The evolution of strobilurins such as a new class of active substances has been collected by Anke in 1999 (Sauter et al. 1999 and references therein, especially 45). A review about natural and synthetic strobilurin fungicides, their analogues, fumoxadone and fenamidone, focused onto biochemical mode of action, synthesis, biokinetics, biology, resistance, human and environmental safety has been published in 2002. The strobilurins are an outstanding new class of agricultural fungicides demonstrating excellent properties in areas above. They are extremely successful because of the benefits that they bring and are clearly one of the most valuable classes of single-site fungicide ever discovered by the agrochemical

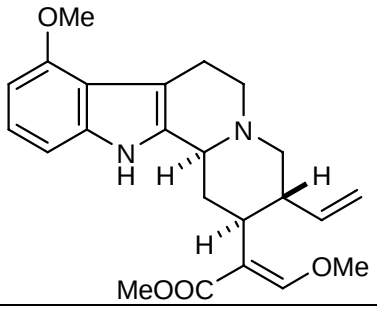
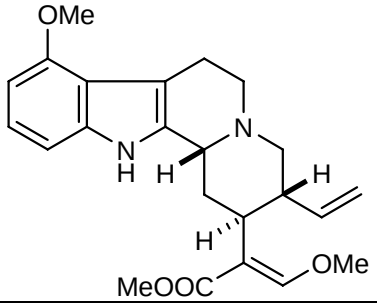
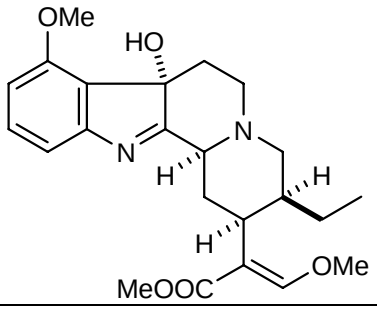
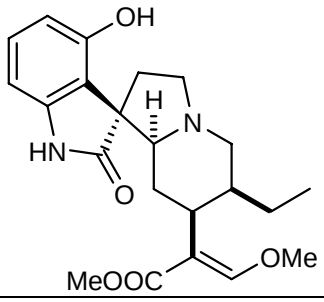
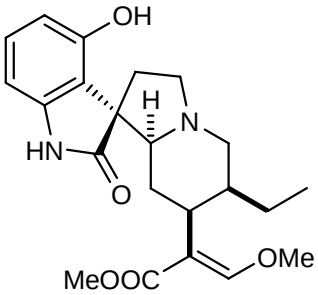
industry. If recommended use-patterns continue to be followed, the dependence of crop protection on the stobilurins is likely to continue for many years into the future (Bartlett et al. 2002, 1995b).

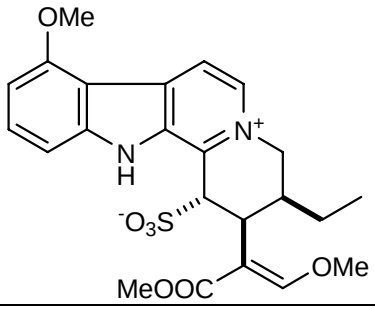
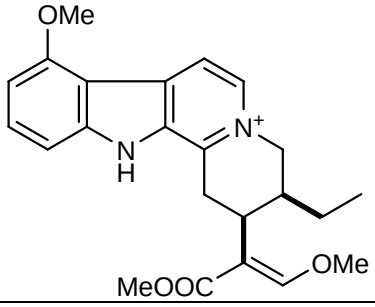
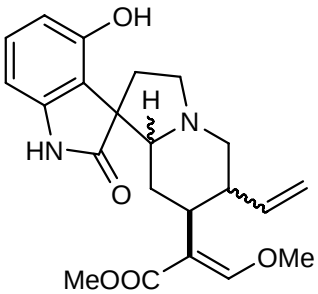
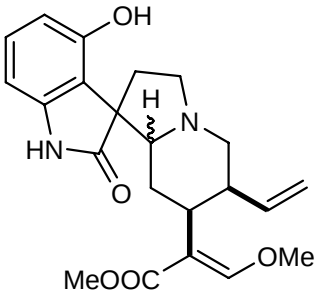
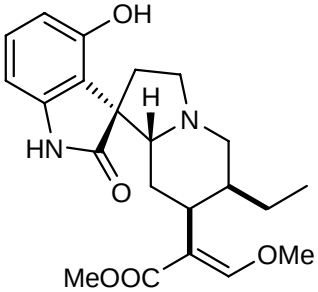
The fungicidal activity of strobilurins, oudemansins, and myxothiazols is based on the suppression of cell respiration of fungi in the bc_1-complex of cytochromes. They also manifest other biological activities that are not always coupled with inhibition of respiration. Studies of the structure of the natural methoxyacrylates have made it possible to create a novel class of synthetic agricultural fungicides with enhanced stability, high activity, and a broad spectrum of action. The main regularities of the structure - activity relationship and methods of synthesis of these compounds are discussed in review including the bibliography with 159 references (Zakharychev and Kovalenko 1998). Antifungal, antibacterial (Anke et al. 1989), cytotoxic (Zapf et al. 1995a), phytotoxic or nematicidal (Stadler et al. 1993; Anke et al. 1995), activities were assayed as described previously (Kettering et al. 2004). *Uncaria rhynchophylla* and related species (i.e. Gouteng of the Pharmacopoeia of the People´s Republic of China) have antihypertensive, sedative and anticonvulsant activities, containing isirhynchophylline, rhynchophylline, isocorynoxeine, corynoxine A and B, dihydrocorynantheine, corynantheine, hirsutine, hirsuteine, epiallo-corynantheine and other 13 indentified, mainly pentacyclic indole alkaloids (Zhu et al. 1997).

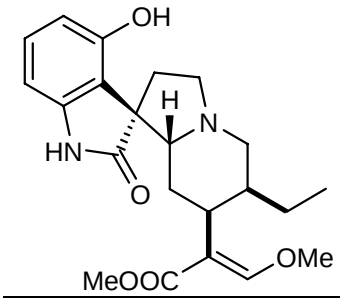
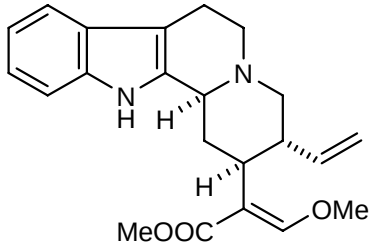
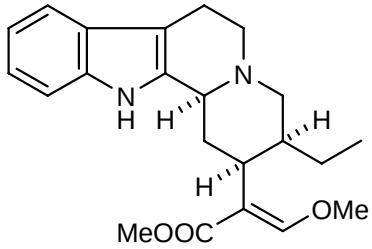
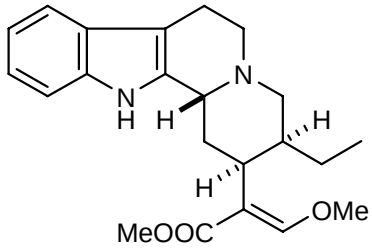
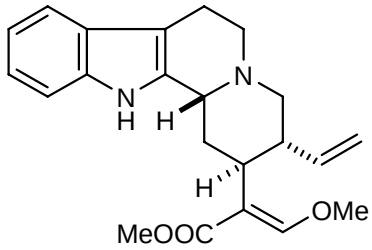
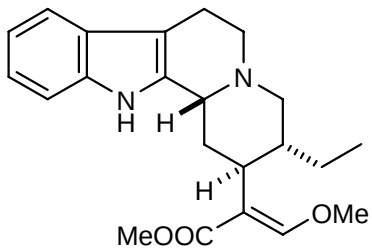
Hirsutine and its derivatives potently inhibited the replication of several strains of Fluv-A (H3N2) at concentrations that were significantly lower than their cytotoxic concentrations. Its 50% effective concentration ranged from 0.28 μg mL^{-1} to 0.57 μg mL^{-1} while the 50 % cytotoxic concentration was 48.7 μg/mL. The mechanism of antiviral activity is similar to ribavirin (Konno et al. 1997). 9-Methoxystrobilurin A and K inhibited the growth of HeLa S3 cell at very low concentration (the IC_{50} value reached 8.5 nM) without showing any significant cytotoxity (Uchiro et al. 2000).

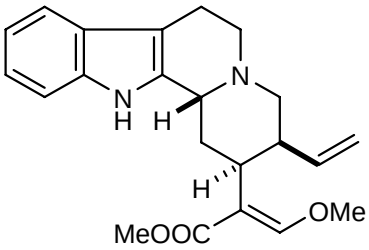
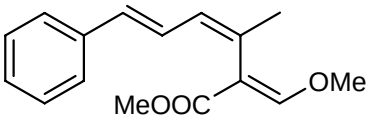
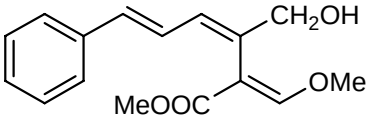
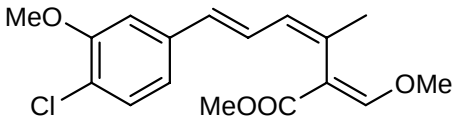
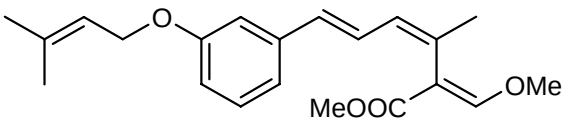
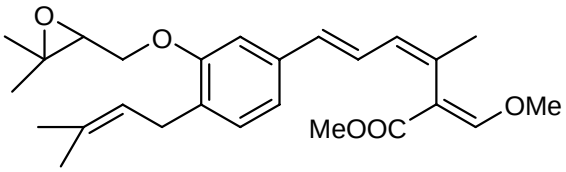
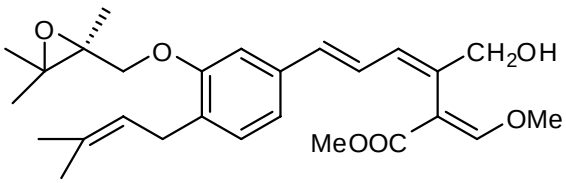
Table 1. Interesting naturally occurring enolethers

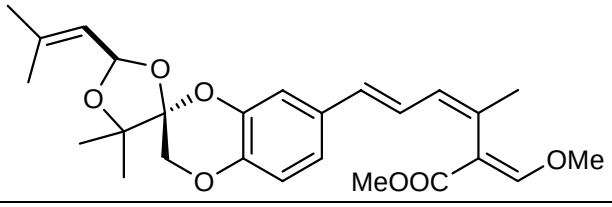
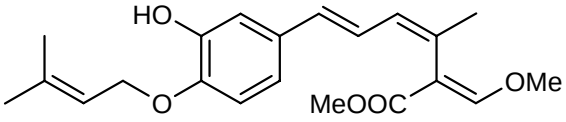
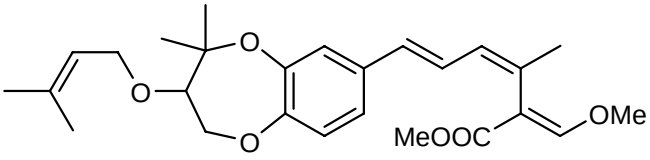
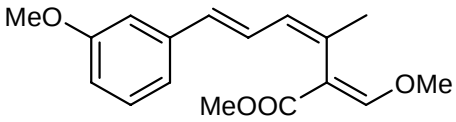
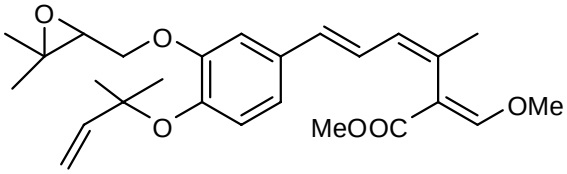
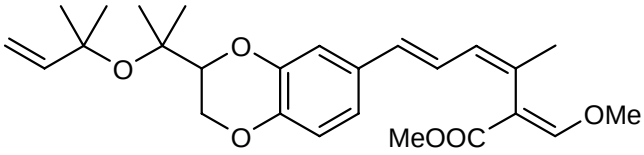
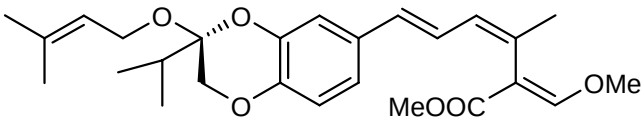
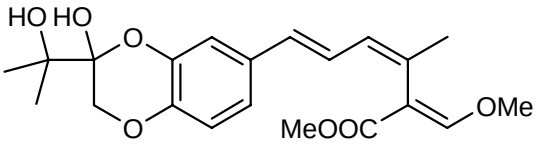
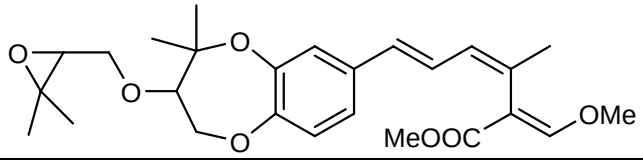
Formula	Name / Source	Properties / Reference
	Mitragynine Mitragyna speciosa Konth. Uncaria spp. (Naucleaceae)	Analgesic, Antitussive, depresant Phillipson 1975; Ma 2007
	3-Dehydromitragynine Mitragyna speciosa (Naucleaceae)	Alkaloid Houghton 1986; Takayama 1998
	Mitraciliatine Mitragyna ciliata, Mitragyna tubulosa, Mitragyna speciosa, Uncaria spp. (Nauleaceae)	Alkaloid Beckett 1963
	Speciogynine Mitragyna speciosa Konth.	Alkaloid Beckett 1966
	Speciociliatine Mitragyna speciosa Konth.	Alkaloid Beckett 1966

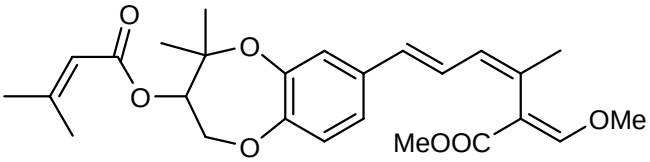
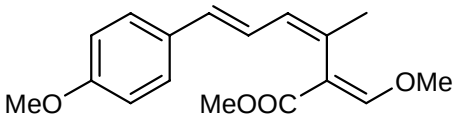
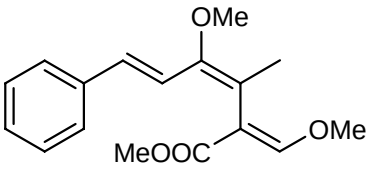
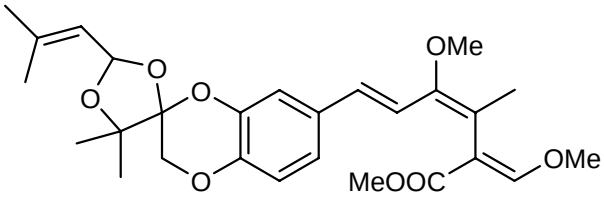
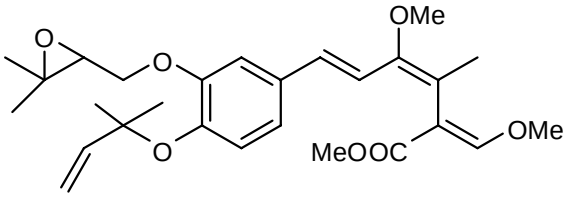
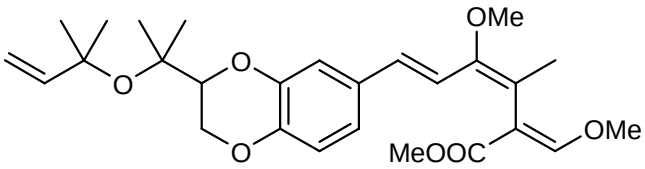
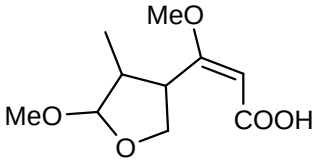
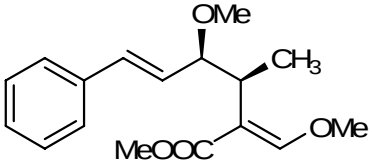
	Paynantheine Mitragyna speciosa Konth. (Naucleaceae)	Alkaloid Ponglux 1994
	3-Isopyanantheine Mitragyna speciosa Konth. (Naucleaceae)	Alkaloid Shellard 1978
	7□-Hydroxy-7*H*-mitragynine Mitragyna speciosa Konth.	Alkaloid Ponglux 1994
	Mitrafoline Mitragyna speciosa Konth.	Alkaloid Hemingway 1975
	Isomitrafoline Mitragyna speciosa Konth.	Alkaloid Hemingway 1975

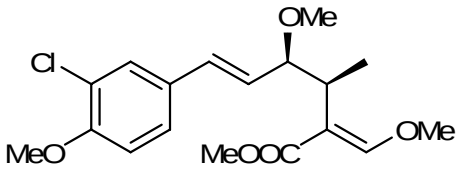
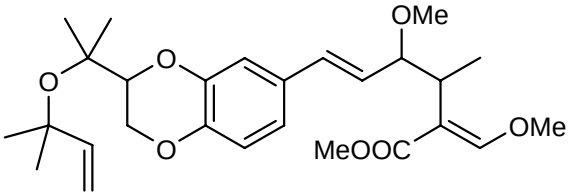
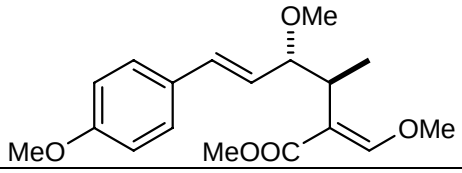
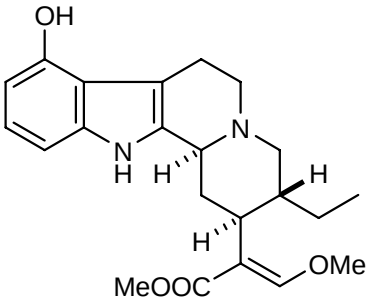
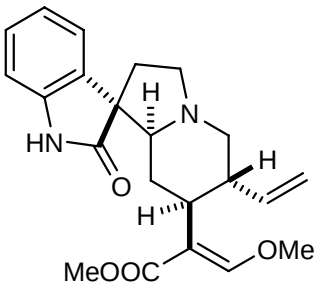
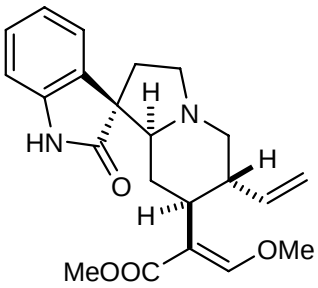
	Mitrasulgynine	Alkaloid
	Mitragyna speciosa Konth.	Takayama 1998
	No name	Alkaloid
	Mitragyna speciosa Konth.	Takayama 1998
	Rotundifoline	Alkaloid
	Mitragyna speciosa Konth.	Barger 1939; Hemingway 1975
	Isorotundifoline	Alkaloid
	Mitragyna speciosa Konth.	Hemingway 1975
	Speciofoline	Alkaloid
	Mitragyna speciosa Konth.	Hemingway 1975

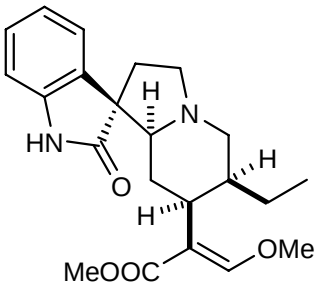
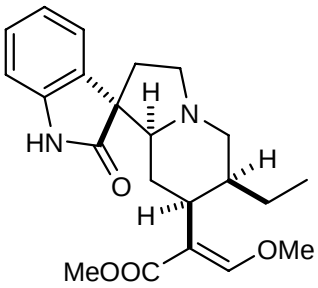
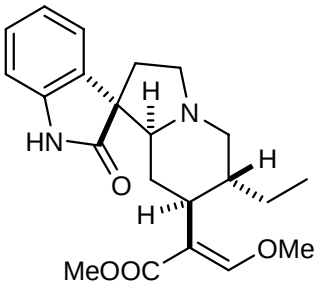
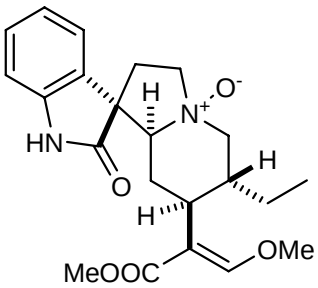
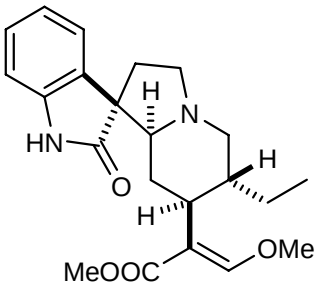
	Isospeciofoline Mitragyna speciosa Konth.	Alkaloid Hemingway 1975
	Corynantheine Pseudocinchoa Africana A.Chev., Mitragyna parvifolia, Uncaria rhyncophylla (Rubiaceae, Naucleaceae)	Alkaloid Janot 1944; Lewis 1974
	Corynantheidine Demetoxymitragyne, obsolete synonym for □-Yohimbine Pseudocinchona africana A.Chev., Mitragyna speciosa, Uncaria spp. (Rubiaceae, Naucleaceae)	Alkaloid Janot 1953
	3-Isocorynantheidine Mitragyna speciosa, Uncaria spp. (Naucleaceae)	Alkaloid Phillipson 1975a
	Hirsuteine Mitragyna parvifolia, Mitragyna hirsuta, Uncaria sp. (Naucleaceae)	Alkaloid Shellard 1972
	Hirsutine Mitragyna parvifolia, Mitragyna hirsuta, Uncaria sp. (Naucleaceae)	Natural alkaloid Haginiwa 1973

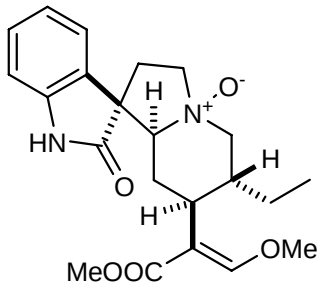
	Epiallocorynantheine Uncaria attenuata subsp. bulusanensis (Naucleaceae)	Alkaloid Phillipson 1975b
	Strobilurin A, Mucidin, Mucidermin Strobilurus tenacellus, Oudemansiella mucida, Bolinea lutea, other fungi	Fungicide (Mucidernin "Spofa"), antibiotic, potent inhibitor of respiration Anke 1977
	Hydroxystrobilurin A Pterula sp.	Fungicide Engler 1995
	Strobilurin B Strobilurus tenacellus, Bolinea lutea	Fungicide, antibiotic, respiration inhibitor Anke 1977
	Strobilurin C Xerula longipes, Xerula melanotricha	Fungicide, respiration inhibitor Anke 1983
	Strobilurin D, Basidiomycete Favolaschia calocera, Cyphellopsis anomala	Cytostatic, fungicide,Weber 1990a; revised in: Nicholas 1997
	Hydroxystrobilurin D Basidiomycete Favolaschia calocera, Mycena sanguinolenta	Fungicide Backens 1988; revised in: Nicholas 1997

	Strobilurin E	cytostatic, fungicide	
	mycelial cultures of agaric Crepidotus fulvotomentosus	Weber 1990b	
	Strobilurin F	cytostatic, fungicide	
	Cyphellopsis anomala (F1), Bolinea (Camarops) lutea (F2)	Weber 1990a; Fredenhagen 1990a,b	
	Strobilurin G	Fungicide	
	ascomycete Bolinea (Camarops) lutea	Fredenhagen 1990a,b	
	Strobilurin H	Fungicide	
	Bolinea (Camarops) lutea	Fredenhagen 1990a	
	Strobilurin K	Fungicide	
	Mycena tintinnabulum, Favolaschia Art.	Zapf 1995b	
	Strobilurin L	Fungicide, cytostatic	
	basidomycete Favolaschia pustulosa	Wood 1996	
	Strobilurin M	antibacterial	
	Mycenae sp.	Daferner 1998	
	Strobilurin N	Biologically inactive	
	Mycena crocata	Buchanan 1999	
	Strobilurin O	nematocidal	
	Mushroom	Hosokawa 2000	

	Strobilurin P Mushroom	nematocidal Hosokawa 2000
	Strobilurin X, 4′-Methoxymucidin Oudemansiella mucida	Antifungal Vondracek 1983
	9-Methoxystrobilurin A Favolaschia sp.	Fungicide, cytostatic Zapf 1995b,c
	9-Methoxystrobilurin E Favolaschia pustulosa	cytostatic Wood 1996
	9-Methoxystrobilurin K mycelial culture of Favolashia sp.	Fungicide, cytostatic, antibiotics Wood 1996; revised in: Nicholas 1997
	9-Methoxystrobilurin L basidomycete Favolaschia pustulosa	Fungicide, cytostatic Wood 1996; revised in: Nicholas 1997
	3-Methoxy-3-(tetrahydro-5-methoxy-4-methyl-3-furanyl)-2-propenoic acid Aspergillus terreus	Natural product Arai 1983
	Oudemansin A Oudemansiella mucida	Antibiotics, antifungal, slightly antitumors, Anke 1979

	Oudemansin B Xerula longipes, Xerula melanotricha	Antifungal, inhibitor of eucaryotic respiration Anke 1983
	Oudemansin L Favolaschia pustulosa	Natural product Wood 1996
	Oudemansin X Oudemansiella radicata	Antifungal Anke 1990
	Gambirine Uncaria Gambier, Uncaria Callophylla, Neonauclea schlechteri (Naucleaceae)	Alkaloid Beckett 1966
	Corynoxeine Pseudocinchona africana, Mitragyna rotundifolia, Mitragyna speciosa, Uncaria attenuata (Rubiaceae, Naucleaceae)	Alkaloid Cu 1957
	Isocorynoxeine Mitragyna rotundifolia, Uncaria attenuata, U. guianensis (Rubiaceae, Naucleaceae)	Alkaloid Hough 1974

	Corynoxine A Pseudocinchona africana, Uncaria macrophylla, Mitragyna speciosa (Rubiaceae, Naucleaceae)	Alkaloid Cu 1957
	Corynoxine B, Isocorynoxine Uncaria macrophylla (Naucleaceae)	Alkaloid Phillipson 1973
	Rhynchophylline, Mitrinermine Uncaria rhyncophylla, Mitragyna sp., Cephalanthus occidentalis (Naucleaceae)	Alkaloid, Antipyretic, hypotensive Seaton 1957
	Rhynchophylline *N*-oxide Mitragyna inermis, Cephalanthus occidentalis (Naucleaceae)	Alkaloid Shellard 1971
	Isorhynchophylline Uncaria sp., Mitragyna sp. (Naucleaceae)	Alkaloid Seaton 1957

	Isorhynchophylline *N*-oxide	Alkaloid	Shellard 1971
	Mitragyna inermis, Mitragyna rotundifolia, Cephalanthus occidentalis (Naucleaceae)		

Conclusion

Strobilurin and oudemansinsins analogues also provide an illustrative example of how bioisosterism can be applied for directed enhancement of properties of natural compounds. They manifest nearly identical high activity in vitro against a wide array of fungi (with exception of stobilurin F1), but are inactive against bacteria (Zakharychev and Kovalenko 1998 and citation therein). Owing to its antimycotic activity, strobilurin A has been used in clinical and veterinary medicine under the commercial name of Mucidermin Spofa (Clough 1993). Despite high biological and particularly fungicidal activity of methoxyacrylate-type antibiotics, their application for plant protection is impeded due to their high sensitivity to light. Nevertheless, it is on the basis of the natural methoxyacrylates that synthetic agrochemical preparations with a basically new mechanism of action have been obtained. Analogues of the natural MOA-inhibitors have indisputable advantages over other systemic fungicides because of the lack of natural resistant microbial strains. Thus, ICI-A5504 efficiently inhibits fungi that are resistant to inhibitors of C-14-demethylase, phenylamides, dicarboxyimides, and benzimidazoles (Godwin et al. 1992).

Antibiotics were studied in connection with the chemical communication of fungi. In dual cultures *Oudemansiella mucida* and *Xerula melanotricha* (basidiomycetes) react to the presence of living *Penicillium notatum* or *P. turbatum* with an increased production of strobilurin A or X. *P. notatum* in turn reacts to the two basidiomycetes or their antibiotic strobilurin A alone with the production of *N*-(2-hydroxypropanoyl)-2-aminobenzoic acid amide or chrysogine. *P. melinii* and *P. urticae* overgrow *O. mucida* due to complete resistance to strobilurin A. *P. brevicompactum*, *P. citrinum*, *P. janczewskii* and the other *Penicillium* strains are all sensitive but apparently do not induce *O. mucida* to produce the amounts of strobilurin A needed to inhibit their growth (Kettering et al. 2004).

Strobilurins and their analogues constitute a large group of compounds that are hardly inferior to triazole fungicides in structural diversity. They represent a new class of plant-protecting agents that meet all the demands that are made nowadays for pesticides. Intensive studies aimed at a search for novel biologically active pesticides are currently under way by different manufacturers. However, these studies are still in their infancy and so far only three fungicides have been produced by ICI, BASF, and Shionogi. Probably, original products will be offered very soon by Bayer and Roussel UCLAF. Interest in this group of compounds is increasing with every passing year as can be evidenced from the number of patent applications. The place occupied by strobilurin analogues on the world pesticide market will be evident in due course (Zakharychev and Kovalenko 1998).

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References

Aiba Y, Hasegawa D, Marunouchi T, Nagasawa K, Uchiro H, Kobayashi S (2001) Bioorganic and Medicinal Chemistry Letters 11: 2783–2786.

Anke H, Bergendorff O, Sterner O (1989) Food Chemistry and Toxicology 27: 393–397.

Anke H, Stadler M, Mayer A, Sterner O, (1995) Canadian Journal of Botany 73: 932–939.

Anke T, Oberwinkler F, Steglich W, Scharmm G (1977) Journal of Antibiotics 30: 806–810.

Anke T, Hecht HJ, Schramm G, Steglich W (1979) Journal of Antibiotics 32: 1112–1117.

Anke T, Besl H, Mocek U, Steglich W (1983) Journal of Antibiotics 36: 661–666.

Anke T, Schramm G, Schwalge B (1984) Liebigs Annalen der Chemie 9: 1616–1625.

Anke T, Werle A, Bross M, Steglich W (1990) Journal of Antibiotics 43: 1010–1011.

Arai K, Yoshimura T, Itatani Y, Yamamoto Y (1983) Chemical and Pharmaceutical Bulletin 31: 925–933.

Balba H, (2007) Journal of Environmental Science and Health Part B 42: 441–451.

Backens S, Steglich J, Bäuerle J, Anke T (1988) Liebigs Annalen der Chemie 405–409.

Barger G, Dyer E, Sargent LJ (1939) Journal of Organic Chemistry 4: 418–427.

Bartlett DW, Clough JM, Godwin JR, Hall AA, Hamer M, Parr-Dobrzanski B (1995a) Angewandte Chemie International Edition in English 34: 196–198.

Bartlett DW, Clough JM, Godwin JR, Hall AA, Hamer M, Parr-Dobrzanski B (1995b) Angewandte Chemie 107: 255–257.

Bartlett DW, Clough JM, Godwin JR, Hall AA, Hamer M, Parr-Dobrzanski B (2002) Pesticide Management Science 58: 649–662.

Beautement K, Clough JM (1987) Tetrahedron Letters 28: 475–478.

Beckett AH, Shellard EJ, Tachie AN (1963) Journal of Pharmacy and Pharmacology Suppl. 15: 166T and 267T.

Beckett AH, Shellard EJ, Phillipson JD, Calvin ML (1966) Planta Medica 14: 277.

Buchanan MS, Steglich W, Anke T (1999) Zeitschrift für Naturforschung 54c: 463–468.

Clough JM (1993) Natural Products Report 10: 565–574.

Cu NA, Goutarel R, Janot MM (1957) Bulletin de la Société Chimique de France 1292–1294.

Daferner M, Anke T, Hellwig V, Steglich W, Sterner O (1998) Journal of Antibiotics 51: 816–822.

Engler M, Anke T, Klostermeyer D, Steglich W (1995) Journal of Antibiotics 48: 884–885

Fredenhagen A, Kuhn A, Peter HH, Cuomo V, Giuliano U (1990a) Journal of Antibiotics 43: 655–660.

Fredenhagen A, Hug P, Peter HH (1990b) Journal of Antibiotics 43: 661–667.

Godwin JR, Anthony VM, Clough JM, Godfrey CRA (1992) In: Brighton Crop Protection Conference - Pests and Diseases, Vol 1 (pp 435–442) British Crop Protection Council, Farnham, UK.

Haginiwa J, Sakai S, Aimi N, Yamanaka E, Shinma N (1973) Yakugaku Zasshi 93: 448–452.

Hemingway SR, Houghton PJ, Phillipson JD, Shellard EJ (1975) Phytochemistry 14: 557–563.

Hosokawa N, Momose I, Sekigawa R, Naganawa H, Iinuma H, Takeuchi T (2000) Journal of Antibiotics 53: 297–300.

Houben-Weyl (1993): modified from Frauenrath H. In: Kropf H, Schaumann E (Ed) Houben-Weyl Vol. E 15 (pp 140-305), VI/1d (p 136) and VI/3 (p 90). Georg Thieme Verlag, Stuttgart.

Hough PJ (1974) Planta Medica 26: 104.

Houghton P, Said IM (1986) Phytochemistry 25: 2910–2912.

Huang W, Zhao PL, Liu CL, Chen Q, Liu ZM, Yang GF (2007) Agriculture and Food Chemistry 55: 3004–3010.

Von Jagow G, Gribble GW, Trumpower BL (1986) Biochemistry 25: 775–780.

Janot MM, Goutarel R (1944) Comptes Rendus de l'Académie des Sciences. 218: 852–854.

Janot MM, Goutarel R, Chabasse-Massonneau J (1953) Bulletin de la Société Chimiques de France 1033–1038.

Kettering M, Sterner O, Anke T (2004) Zeitschrift für Naturforschung 59c: 816–823.

Konno K, Inoue H, Fujiwara M, Mizuta T, Takayama H, Limura Y, Aimi N, Tokuhisa K, Hanasaki Y, Katsuura K, Shigeta S, Yokota T (1997) Antiviral Research 34: 88–88.

Ma J, Yin W, Zhou H, Cook JM (2007) Organic Letters 9: 3491–3494.

Milata V, Rádl S, Voltrová S (2008) 32.5.3. Product Subclass: Enol Ethers (acyclic, cyclic, i.e. endocyclic C=C-O- unit). Science of Synthesis. Georg Thieme Verlag, Stuttgart (in press).

Musílek V, Černá J, Šašek M, Semerdžieva M, Vondráček M (1969) Folia Microbiologica 14: 377–387.

Nakazawa T, Banba K, Hata K, Nihei Y, Hoshikawa A, Ohsawa K (2006) Biological and Pharmaceutical Bulletin 29: 1671–1677.

Nicholas GM, Blunt JW, Cole ALJ, Munro MHG (1997) Tetrahedron Letters 38: 7465–7468.

Phillipson JD, Hemingway SR (1975a) Journal of Chromatography A 105: 163–178.

Phillipson JD, Hemingway SR (1975b) Phytochemistry 14: 1855–1865.

Phillipson JD, Rungsiyakul D, Shellard EJ (1973) Phytochemistry 12: 2043-2048.

Ponglux D, Wongseripipatana S, Takayama H, Kikuchi M, Kurihara M, Kitajima M, Aimi N, Sakai S (1994) Planta Medica 60: 580.

Saloň J, Milata V, Gatial A, Prónayová N, Leško J, Černuchová P, Vo-Thanh G, Loupy A (2005) European Journal of Organic Chemistry 22: 4870–4878.

Sauter H, Steglich W, Anke T (1999) Angewandte Chemie International Edition in English 38: 1328–1349.

Seaton JC, Marion L (1957) Canadian Journal of Chemistry 35: 1102–1108.

Sedmera P, Musílek V, Nerud F, Vondráček M (1981) Journal of Antibiotics 34: 1069.

Seto H, Lewis W, Tanabe C, Tanabe M (1974) Tetrahedron Letters 15: 4491–4494.

Shellard EJ, Houghton PJ (1972) Planta Medica 21: 382.

Shellard EJ, Houghton PJ, Resha M (1978) Planta Medica 34: 253.

Shellard EJ, Phillipson JD, Sarpong K (1971) Phytochemistry 10: 2505–2511.

Stadler M, Anke H, Berquist KE, Sterner O (1993) Journal of Antibiotics 46: 961–967.

Takayama H, Kurihara M, Kitajima M, Said IM, Aimi N (1998) Tetrahedron 54: 8433–8440.

Uchiro H, Nagasawa k, Aiba Y, Kobayashi S (2000) Tetrahedron Letters 41: 4165–4168.

Vondracek M, Vondrackova J, Sedmera P, Musilek V (1983) Collection of Czechoslovak Chemical Communication 48: 1508–1512.

Weber W, Anke T, Bross M, Steglich W (1990a) Planta Medica 56: 446–450.

Weber W, Anke T, Steffan B, Steglich W (1990b) Journal of Antibiotics 43: 207–212.

Wood KA, Kau DA, Wrigley SK, Beneyto R, Reuno DV, Ainsworth AM, Penn J, Hill D, Killacky J, Depledge P (1996) Journal of Natural Products 59: 646–649.

Zakharychev VV, Kovalenko LV (1998) Russian Chemical Reviews 67: 535–544.

Zapf S, Hoßfeld M, Anke H, Velten R, Steglich W, (1995a) Journal of Antibiotics 48: 36–41.

Zapf S, Werle A, Anke T, Klostermeyer D, Steffan B, Steglich W (1995b) Angewandte Chemie International Edition in English 34: 196–198.

Zapf S, Werle A, Anke T, Klostermeyer D, Steffan B, Steglich W (1995c) Angewandte Chemie 107: 255–257.

Zhu M, Phillipson JD, Yu H, Greengrass PM, Norman NG (1997) Phytotherapy Research 11: 231–236.