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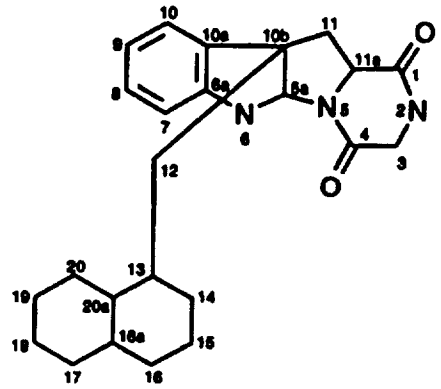
(57) Abstract

Described is the isolation of drimentines comprising the structural elements shown under formula (A). These novel antibiotics can be used in a wide range of therapeutic applications which include but are not limited to the treatment of bacteria, fungi, endoparasites and ectoparasites infections, cancer and other malignant diseases in human and animal health.



(A)

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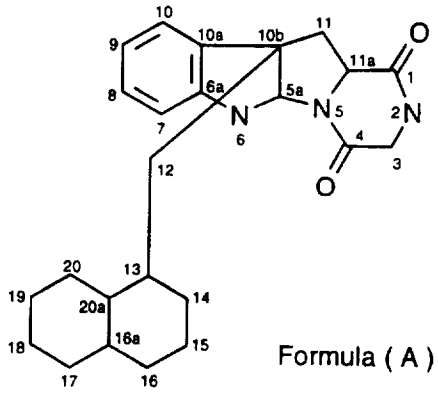
TERPENYLATED DIKETOPIPERAZINES, (DRIMENTINES)

The present invention relates to a novel class of antibiotics, the drimentines, and to structural and functional derivatives thereof. The chemical structure of drimentines is presented below. The present invention further relates to a process for producing said drimentines, to the use of this novel class of antibiotics in a wide range of therapeutic applications which include but are not limited to the treatment of bacteria, fungi, endoparasite and ectoparasite infections, cancer and other malignant diseases in human and animal health. Last not least, the present invention relates to microoganisms capable of producing a drimentine.

The present invention is based on the isolation of a soil-borne microorganism that produces the drimentines as a novel class of antibiotics. Said microorganism is an *Actinomycete* strain which was isolated from under an *Acacia sp.* tree in a dry creek bed near the township of Dungog, New South Wales, Australia.

Formula (A) below, shows the basic structural elements of a drimentine:

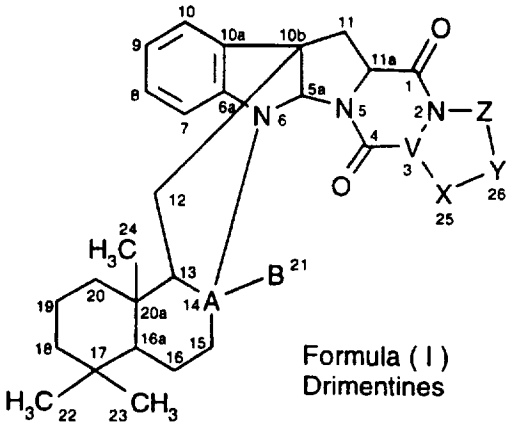


Formula (A)

These elements consist basically of the shown condensed ring systems which are connected to each other in position 10b and 13 through a methylene bridge. If not otherwise specified, the term 'drimentine' used throughout the present patent application circumscribes a natural or synthetic molecule showing this characteristic chemical substructure.

After purification said *Actinomycete* strain was cultured in the proper culture medium. In the mycelia of the strain an antibiotic complex of said drimetines is produced. This novel class of compounds exhibits activity against Gram positive bacteria and mammalian tumor cell lines as well as a pronounced activity against a wide range of ectoparasites and endoparasites.

Within the present invention drimentines showing the advantageous substitution pattern in accordance with formula (I)

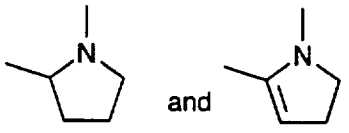


Formula (I)
Drimentines

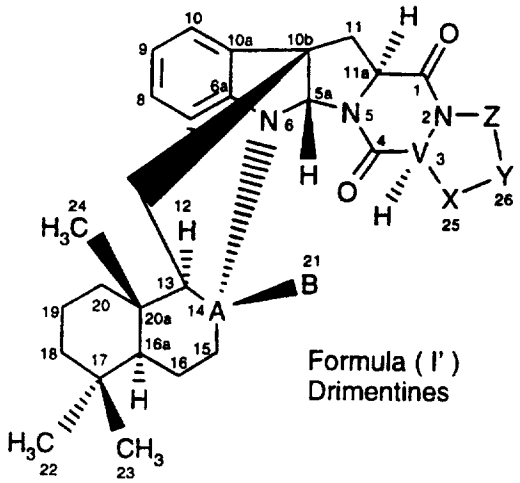
wherein

(a) the bond A-N is either absent or present, and if the bond A-N is absent, A is a carbon ring atom, N in position 6 carries a hydrogen atom, and A-B represents the group $=C=CH_2$; whereas if tne bond A-N is present, A is a carbon ring atom, and A-B stands for the group $=C(-CH_3)-$; and

(b) the bond Y-Z is either absent or present, and if the bond Y-Z is absent, Z is hydrogen, and V-X-Y represent together the group $=CH-CH_2-CH(CH_3)_2$; whereas if the bond Y-Z is present, V-X-Y-Z-N form together one of the five-membered rings selected from the group consisting of

 and are preferred.

Due to their pronounced biological activity drimentines of the formula I'



Formula (I')
Drimentines

wherein the substituents A, B, V, X, Y and Z are defined as under formula I above are especially preferred.

The above mentioned *Actinomycete* strain produces a complex of substances which after purification could be resolved into five individual components, named: drimentines A, B, C, D and E.

The chemical formulae of said antibiotics are shown in detail below. The correspondence between the name and the formula are as follows:

NAME	FORMULA
Drimentine A	formula (Ia)
Drimentine B	formula (Ib)
Drimentine C	formula (Ic)
Drimentine D	formula (Id)
Drimentine E	formula (Ie)
3,25-Dihydrodrimentine E*	formula (If)

* 3,25-Dihydrodrimentine E is a chemically modified drimentine E

The physico-chemical and biological properties of the drimentines compared with known antibiotics confirmed the drimentines to be a novel class of antibiotics possessing a new

terpenylated diketopiperazine structure which is not similar to any chemical structure of any known class of antibiotics.

The structures of the individual drimentines A to E are presented below. Their physico-chemical properties are listed in tables 1 to 6. These physico-chemical data include Appearance, Melting point (M.p.), Molecular formula and data accumulated using the following techniques: High resolution electron impact mass spectrometry (HREIMS), Ultra-violet spectrophotometry (UV), Infra-red spectrophotometry (IR), Optical rotatory analysis ([α]), Circular dichroism analysis (CD), ^{13}C and ^{1}H Nuclear magnetic resonance spectrometry (NMR).

The present invention is based on: (1) the discovery of a microorganism that provides the drimentines as a novel class of antibiotics, (2) the drimentines per se as well as structural derivatives and functional analogues, (3) a process for their production which comprises culturing a microorganism capable of producing drimentines, preferably a drimentine-producing bacterial, more preferably a drimentine-producing *Actinomycete* strain, most preferably *Actinomycete* strain MST-8651 or an optimized strain derived therefrom, (4) isolation of a drimentine from the culture product, (5) the use of a drimentine in a broad range of therapeutic applications and (6) the conversion of a drimentine into a structural derivative thereof or to another therapeutically useful compound by chemical or biological means as exemplified below by the preparation of the derivative 3,25-dihydrodrimentine E of formula If and by the conversion of one drimentine into a different one.

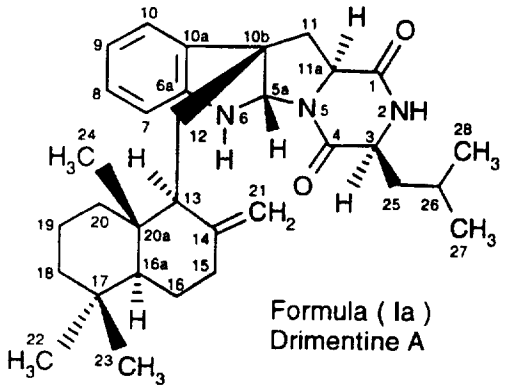
A structural derivative of a drimentine is a molecule that still contains the basic structural elements shown under formula (A) but may contain one or more substituents. A functional derivative may show greater structural modifications but displays still a similar spectum of activity.

The term 'chemical means' embraces but is not limited to chemical manipulations such as exposing the drimentine-producing strain to chemical stress (e.g. culturing in the presence of a chemical mutating agent), or to the incorporation of one or more chemical substituents at one or more reactive positions of the molecule by suitable chemical reactions such as halogenation, alkylation, halo-alkylation, acylation, halo-acylation, hydrogenation, hydroxylization, esterification, etherification, etc. Such reactions are widely used in chemistry and well known to the skilled artisan.

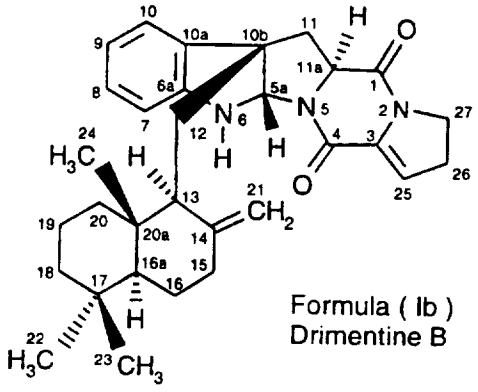
The term 'biological means' embraces but is not limited to biological or microbiological manipulations such as fusion of a producing strain with a non-producing strain, the isolation of the gene or gene cluster responsible for the production of a drimentine and the incorporation of said gene or gene cluster into a different strain or microorganism or even into a cell of a higher organism by means of genetic engineering.

Deposition of biological material: A pure sample of the *Actinomycete* strain which produces the drimentines A, B, C, D and E has been deposited under the Budapest Treaty as *Actinomycete* strain MST-8651 with the Australian Government Analytical Laboratory (AGAL) on 22 August 1996 under Accession No. N96/101825.

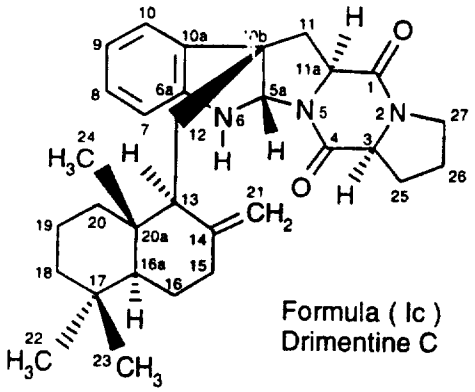
The drimentines A to E and 3,25-dihydrodrimentine E of the present invention show the following chemical structures:



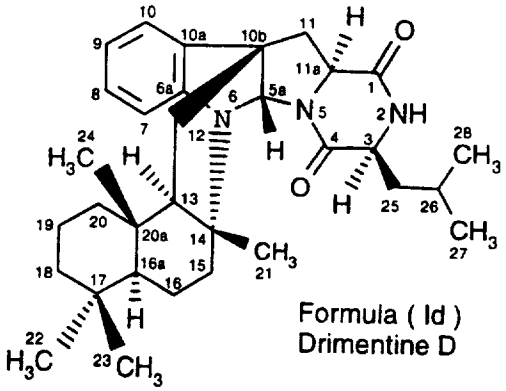
Formula (Ia)
Drimentine A



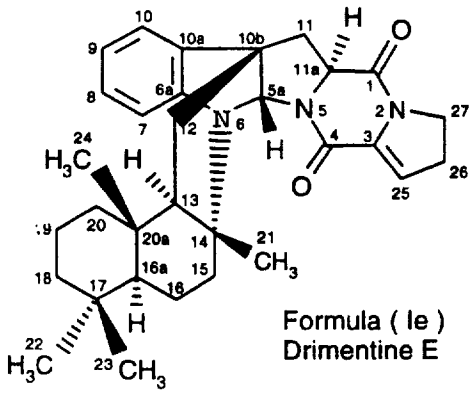
Formula (Ib)
Drimentine B



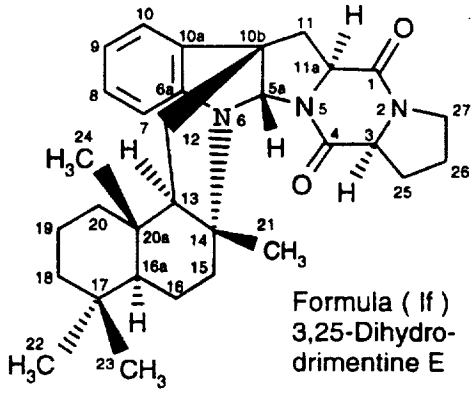
Formula (Ic)
Drimentine C



Formula (Id)
Drimentine D



Formula (Ie)
Drimentine E



Formula (If)
3,25-Dihydro-
drimentine E

The drimentines can be produced by culturing an appropriate microorganism, preferably a drimentine-producing microorganism, more preferably a drimentine-producing bacterial strain, even more preferably a drimentine-producing *Actinomycete* strain, most preferably *Actinomycete* strain MST-8651 or any optimized strain derived therefrom, in an suitable culture medium. Suitable culture media are those containing nutrients which are commonly utilized by said microorganism. In the case of *Actinomycetes*, culture media are used which are commonly utilized by *Actinomycetes*. For instance, as the carbon sources, there may be used glucose, glycerol, sucrose, dextrin, starch, etc. As the nitrogen sources, there may be employed soybean meal, wheat embryo, peptone, meat extract, yeast extract, corn steep liquor, an ammonium salt, etc. Further, if necessary, inorganic salts such as calcium carbonate, potassium chloride, magnesium sulfate and phosphates may be used. As a culturing method, a liquid or solid phase fermentation is suitable. The culturing conditions such as the cultivation temperature, time, etc. are selected so that they are suitable for the growth of the microorganism used, and for the production of the antibiotic at the maximum yield. The production of the antibiotics reaches the maximum when the cultivation with aeration-agitation is conducted at a cultivation temperature from 25 to 35°C for 92 to 144 h. The drimentines are produced and accumulated in the mycelia and may be isolated and purified by means of conventional methods. For example, a method utilizing the differing partitioning behavior of the antibiotics and impurities between organic and aqueous solutions, a method of utilizing the difference in the solubility between the antibiotic and impurities, and a method of utilizing the difference in the adsorption may be used individually or in combination, or repeatedly.

The drimentines of the invention have broad therapeutic activity, for example, antibacterial activity against Gram positive and Gram negative bacteria; antifungal activity against fungi and yeasts; anthelmintic activity against nematodes, cestodes and trematodes, and other endoparasites; activity against a broad range of important accarina, insecticidal activity against a range of ectoparasites; anticancer activity against a range of malignant cells types. The compounds of the invention are therefore of use in treating animals and humans with a broad range of therapeutic needs.

Ectoparasites and endoparasites infect humans and a variety of animals and are particularly prevalent in farm animals such as pigs, sheep, cattle, goats and poultry (for example, chickens and turkeys), horses, rabbits, game-birds, caged birds, and domestic animals such as dogs, cats, guinea pigs, gerbils and hamsters. Parasitic infection of livestock, leading to anaemia, malnutrition and weight loss is a major cause of economic loss throughout the world. Examples of genera of endoparasites infecting such animals and/or humans are *Ancylostoma, Ascaridia, Ascaris, Aspicularis, Brugia, Bunostomum, Capillaria, Chabertia, Cooperia, Dictyocaulus, Dirofilaria, Dracunculus, Enterobius, Haemonchus, Heterakis, Loa, Necator, Nematodirus, Nematospiroides (Heligomoroides), Nippostrongylus, Oesophagostomum, Onchocerca, Ostertagia, Oxyuris, Parascaris, Strongylus, Strongyloides, Syphacia, Toxascaris, Toxocara, Trichonema, Trichostrongylus, Trichinella, Trichuris, Triodontophorus, Uncinaria* and *Wuchereria.*

Examples of ectoparasites infecting animals and/or humans, without being limiting, are arthropod ectoparasites such as biting insects, blowfly, fleas, lice, mites, sucking insects, ticks and other dipterous pests. Examples of genera of such ectoparasites infecting animals and/or humans are *Ambylomma, Boophilus, Ctenocephalides, Chorioptes, Calliphora, Demodex, Damalinia, Dermatobia, Gastrophilus, Haematobia, Haematopinus, Haemaphysalis, Hyaloma, Hypoderma, Ixodes, Linognathus, Lucilia, Melophagus, Oestrus, Otobius, Otodectes, Psorergates, Psoroptes, Rhipicephalus, Sarcoptes, Stomoxys and Tabanus.*Compounds of the invention are also of use as anti-fungals, for example, against strains of *Candida sp.* such as *Candida albicans* and *Candida glabrata* and against yeast such as *Saccharomyces carlsbergensis.*

Compounds of the invention are also of use in combating insect, acarine and nematode pests in agriculture, horticulture, forestry, public health and stored products. Pests of soil and plant crops, including cereals (for example, wheat, barley, maize and rice), cotton, tobacco, vegetables (for example, soya), fruit (for example, apples, vines and citrus) as well as root crops (for example, sugarbeet, potatoes) may usefully be treated. Particular examples of such pests are fruit mites and aphids such as *Aphis fabae, Aulacorthum circumflexum, Myzus persicae, Nephotettix cincticeps, Nilparvats lugens, Panonychus ulmi, Photodon humuli, Phyllocoptruta oleivora, Tetranychus urticae* and members of the genera *Trialeuroides*; nematodes such as members of the genera *Aphelencoides, Globodera, Heterodera, Meloidogyne* and *Panagrellus;* Lepidoptera such as *Heliothis, Plutella* and *Spodoptera; g*rain weevils such as *Anthonomus grandis* and *Sitophilus granarius;* flour beetles such as *Tribolium castaneum;* flies such as *Musca domestica;* fire ants; leaf miners; *Pear psylla; Thrips tabaci;* cockroaches such as *Blatella germanica* and *Periplaneta americana* and mosquitoes such as *Aedes aegypti.*

Accordingly, the present invention provides the drimentines as a novel class of antibiotics. They may be formulated for administration purposes in any convenient way for use in human or veterinary medicine and the invention therefore includes within its scope pharmaceutical compositions comprising as active ingredient a drimentine or a derivative thereof. Depending on the medical indication the compounds and pharmaceutical compositions in accordance with the invention can be adapted for the specific use in human or veterinary medicine. Such compositions may be presented for use in conventional manner with the aid of one or more suitable carriers or excipients. Suitable carriers or excipients are those which are physiologically acceptable to the organism to which the drimentine has to be administered. Carriers or excipients that cause no undesirable side-effects are preferred. The compositions of the invention include those in a form especially formulated for parenteral (including intramammary administration), oral, rectal, topical, transdermal, implant, ophthalmic, nasal or genito-urinary use.

The drimentines according to the invention may be formulated for use in human or veterinary medicine by injection and may be presented in unit dose form, in ampoules, or other unit-dose containers, or in multi-dose containers, if necessary with an added preservative. The compositions for injection may be in the form of suspensions, solutions, or

emulsions, in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing, solubilising and/or dispersing agents. Alternatively the active ingredient may be in sterile powder form for reconstitution with a suitable vehicle, for example, sterile, pyrogen-free water, before use. Oily vehicles include polyhydric alcohols and their esters such as glycerol esters, fatty acids, vegetable oils such as arachis oil or cottonseed oil, mineral oils such as liquid paraffin, and ethyl oleate and other similar compounds. Other vehicles such as propylene glycol may also be used. Compositions for veterinary medicine may also be formulated as intramammary preparations in either long acting or quick-release bases and may be sterile solutions or suspensions in aqueous or oily vehicles optionally containing a thickening or suspending agent such as soft or hard paraffins, beeswax, 12-hydroxy stearin, hydrogenated castor oil, aluminum stearates, or glyceryl monostearate. Conventional non-ionic, cationic or anionic surface active agents may be used alone or in combination in the composition.

The drimentines of the invention may also be presented for human or veterinary use in a form suitable for oral administration, for example in the form of solutions, syrups or suspensions, or a dry powder for constitution with water or other suitable vehicle before use, optionally with flavouring and coloring agents. Solid compositions such as tablets, capsules, lozenges, pills, boluses, powder, pastes, granules, pellets or premix preparations may also be used. Solid and liquid compositions for oral use may be prepared according to methods well known in the art. Such compositions may also contain one or more pharmaceutically acceptable carriers and excipients which may be in solid or liquid form. Examples of suitable pharmaceutically acceptable carriers for use in solid dosage forms include binding agents (for example, pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (for example, lactose, micro-crystalline cellulose or calcium phosphate); lubricants (for example, magnesium stearate, talc or silica); disintegrants (for example, potato starch or sodium starch glycollate); or wetting agents (for example, sodium lauryl sulphate). Tablets may be coated by methods well known in the art.

Examples of suitable pharmaceutically acceptable additives for use in liquid dosage forms include suspending agents (for example, sorbitol syrup, methyl cellulose or hydrogenated *edible* fats); emulsifying agents (for example, lecithin or acacia); non-aqueous vehicles (for example, almond oil, oily esters or ethyl alcohol); and preservatives (for example, methyl or

propyl p-hydroxybenzoates or sorbic acid); stabilizing and solubilising agents may also be included. Pastes for oral administration may be formulated according to methods well known in the art. Examples of suitable pharmaceutically acceptable additives for use in paste formulations include suspending or gelling agents for example, aluminum distearate or hydrogenated castor oil; dispersing agents for example, polysorbates, non-aqueous vehicles for example, arachis oil or oily esters; stabilizing and solubilising agents. The compounds of the invention may also be administered in veterinary medicine by incorporation thereof into animals' daily solid or liquid dietary intake, for example, as part of the daily animal feed or drinking water.

The compounds of the invention may also be administered orally in veterinary medicine in the form of a liquid drench such as a solution, suspension or dispersion of the active ingredient together with a pharmaceutically acceptable carrier or excipient.

The drimentines of the invention may also, for example, be formulated as suppositories for example, containing conventional suppository bases for use in human or veterinary medicine or as pessaries for example, containing conventional pessary bases.
Drimentines according to the invention may be formulated for topical administration, for use in veterinary and human medicine, as ointments, creams, lotions, shampoos, powders, pessaries, sprays, dips, aerosols, drops (for example, eye or nose drops) or pour-ons. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilized components. Pour-ons may, for example, be formulated for veterinary use in oils containing organic solvents, optionally with formulatory agents for example, stabilizing and solubilising agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Powders may be formed with the aid of any suitable powder base. Drops may be formulated with an aqueous or non aqueous base also comprising one or more dispersing agents, stabilizing agents, solubilising agents or suspending agents. They may also contain a preservative.

For topical administration by inhalation the drimentines according to the invention may be delivered for use in human or veterinary medicine in the form of an aerosol spray presentation or an insufflator.

The drimentines of the present invention may be administered in combination with other pharmaceutically active ingredients to broaden the spectrum of activity. The total daily dosages of drimentines of the invention employed in both veterinary and human medicine will suitably be in the range 0,01-2000 mg/kg body-weight, preferably from 0,1-1000 mg/kg body-weight, preferably from 1-100 mg/kg and these may be administered as single or divided doses. However, they can also be administered as depot preparations (implants, slow-release formulations, etc.) weekly, monthly or at even longer intervals. In such cases the dosage will be much higher than the daily one and has to be adapted to the administration form, the body weight and the concrete indication. The appropriate dosage can be determined by conducting model tests, preferably via animal models.

The drimentines according to the invention may be formulated in any convenient way for horticultural or agricultural use and the invention therefore includes within its scope compositions comprising a compound according to the invention adapted for horticultural or agricultural use. Such formulations include dry or liquid types, for example dusts, including dust bases or concentrates, powders, including soluble or wettable powders, granulates, including microgranules and dispersible granules, pellets, flowables, emulsions such as dilute emulsions or emulsifiable concentrates, dips such as root dips and seed dips, seed dressings, seed pellets, oil concentrates, oil solutions, injections for example, stem injections, sprays, smokes and mists.

Generally such formulations will include the compound in association with a suitable carrier or diluent. Such carriers may be liquid or solid and designed to aid the application of the compound either by way of dispersing it where it is to be applied or to provide a formulation which can be made by the user into a dispersible preparation. Such formulations are well known in the art and may be prepared by conventional methods such as, for example, by blending and/or grinding of the active ingredient(s) together with the carrier or diluent, for example, solid carrier, solvent or surface active agent.

Suitable solid carriers, for use in formulations such as dusts, granulates and powders may be selected from, for example, natural mineral fillers, such as diatomite, talc, kaolinite, montmorillonite, prophyllite or attapulgite. Highly dispersed acid or highly dispersed absorbent polymers may, if desired, be included in the composition. Granulated adsorptive carriers which may be used may be porous (such as pumice, ground brick, sepiolite or bentonite) or non-porous (such as calcite or sand). Suitable pregranulated materials which may be used may be organic or inorganic including dolomite and ground plant residues. Suitable solvents for use as carriers or diluents include but are not limited to: aromatic hydrocarbons, aliphatic hydrocarbons, alcohols and glycols or ethers thereof, esters, ketones, acid amides, strongly polar solvents, optionally epoxidized vegetable oils and water. Conventional non ionic, cationic or anionic surface-active agents, for example, ethoxylated alkyl phenols and alcohols, alkali metal or alkaline earth metal salts of alkyl benzene sulphonic acids, lignosulphonic acids or sulphosuccinic acids or sulphonates of polymeric phenols which have good emulsifying, dispersing and/or wetting properties may also be used either alone or in combination in the compositions.

Stabilizers, anti-caking agents, anti-foaming agents, viscosity regulators, binders and adhesives, photostabilisers, as well as fertilisers, feeding stimulants or other active substances may, if desired, be included in the compositions. The compounds of the invention may also be formulated in admixture with other therapeutically active compounds. In the formulations, the concentration of active material is generally from 0.01 to 99% and more preferably between 0.01% and 40% by weight. Commercial products are generally provided as concentrated compositions to be diluted to an appropriate concentration, for example from 0.001 to 0.0001% by weight, for use.

If *Actinomycetes* are used for the production, the compounds of the invention can be prepared by the processes described in detail below. If other producing microorganisms are used the culture medium and the culturing condition have to be adapted to the corresponding microorganism. The following examples exemplify the production of drimentines but do not limit the scope of the present invention to these specific examples.

Example 1: Fermentation and isolation of the drimentines

Agar slope cultures (ISP-2 agar comprising: Yeast Extract 0.4%, Malt Extract 1%, Glucose 0.4%, Agar 2% made up to volume, adjusted to pH 7.3 and sterilized by autoclaving prior to

use) of *Actinomycete* strain MST-8651 are grown for 5 days, covered with sterile distilled water, and the surface is gently scraped to produce a suspension of the organism. The suspension is dispensed into baffled Erlenmeyer flasks (250 ml) containing seed medium (ISP-2 broth comprising ISP-2 agar without Agar, 100 ml), using one slope for two flasks, and incubated at 28°C for 2 days with shaking (200 rpm). The resulting inoculum is dispensed into production medium (ISP-2 broth) in baffled Erlenmeyer flasks (10 ml inoculum, 100 ml medium per 250 ml flask), which are then incubated with shaking (200 rpm) at 28°C for 4 days. The fermentation (3 l) at harvest is adjusted from pH 8.5 to 5.5 with concentrated hydrochloric acid, and the cell mass is separated by centrifugation and filtration. The culture filtrate is extracted with ethyl acetate (3 x 650 ml), and the combined extracts after drying over anhydrous sodium sulphate are evaporated to give the crude medium extract (234 mg). The cell mass is extracted by stirring gently for 1 h with acetone (2 x 500 ml). The combined acetone extracts are concentrated on a rotary evaporator to an aqueous residue (20 ml, pH 5.5), which is extracted with ethyl acetate (3 x 20 ml) to give after drying the crude cell extract (700 mg).

Example 2: Purification of drimentines A to E

Chromatography of the crude cell extract (700 mg) on silica gel (48 g), eluting with acetone/dichloromethane (increasing from 3% to 20%), gives piericidin A1 (250 mg), which can be identified by comparison of ^{1}H and ^{13}C NMR and EI-MS spectra with literature data (S.Yoshida, K.Yoneyama, S.Shiraishi, A.Watanabe and N.Takahashi, *Agricultural and Biological Chemistry*, 1977, **41**, 855), followed by fractions 1 (18 mg), 2 (70 mg), 3 (45 mg) and 4 (26 mg). Further chromatography of these fractions on silica gel yields pure drimentines. Fraction 1 with ethyl acetate/hexane (20%) gives drimentine A (10 mg). Fraction 2 with ethyl acetate/hexane (35%) gives drimentine B (13 mg), drimentine C (15 mg), and a mixture of drimentines B and C (42 mg). Fraction 3 with ethyl acetate/hexane (40%) gives drimentine D (30 mg), and fraction 4 with ethyl acetate/hexane (70%) gives drimentine E (20 mg).

Example 3: Physico-chemical properties of the drimentines

The physico-chemical properties, HREIMS of molecular ions, UV, IR, and CD data of drimentines A, B, C, D and E are presented in Table 1, ^{13}C and ^{1}H NMR data in Tables 2-6.

Table 1. Physico-chemical properties of drimentines A-E

Drimentine	A	B	C	D	E
Appearance	crystals	crystals	crystals	crystals	crystals
M.p. (°C)	130-132	158-160	108-110	141-145	260-262
Molecular formula	$C_{32}H_{45}N_3O_2$	$C_{31}H_{39}N_3O_2$	$C_{31}H_{41}N_3O_2$	$C_{32}H_{45}N_3O_2$	$C_{31}H_{39}N_3O_2$
EI-MS	M^+	M^+	M^+	M^+	M^+
Found (*m/z*)	503.3512	485.3043	487.3195	503.3489	485.3042
Calcd (*m/z*)	503.3512	485.3042	487.3199	503.3512	485.3042
UV (EtOH)	240 (9445)	243 (12420)	240 (6078)	235_{infl} (3146)	226_{infl} (8235)
λ nm (ε)	297 (4167)	273_{infl} (6667)	297 (2157)	273 (1326)	268_{infl} (5441)
		295_{infl} (4091)		280_{infl} (1236)	
IR (KBr)	3300, 3080	3345, 3080	3340, 3080	3345, 1680	1670
ν_{max}	1675, 1608	1680, 1640	1665, 1608		1640
		1608			
$[\alpha]^{25,D}$	-209.6_	-195.2_	-275.9_	-24.2_	+17.6_
($CHCl_3$)	(c. 6.2×10^{-3})	(c. 7.5×10^{-3})	(c. 5.8×10^{-3})	(c. 6.0×10^{-3})	(c. 1.1×10^{-2})
CD	(c. 1.8×10^{-2})	(c. 1.6×10^{-2})	(c. 2.5×10^{-2})	(c. 4.5×10^{-2})	(c. 9.7×10^{-3})
nm Δε	326 -0.13	342 0	317 0	342 0	316 0
(EtOH)	296 -3.10	303 -0.38	294 -3.00	276_{infl} +0.22	288 -0.38
	267 -0.77	287 -0.24	267 -0.95	267_{infl} +0.33	275_{infl} -0.17
	242 -8.73	268 -0.36	243 -8.86	236 +1.53	267_{infl} -0.04
	223 0	260 -0.35	217 -1.96	218 +1.02	263 0
	217 +1.99	232 -1.60			245 +1.09
	213 0	217 -0.83			233 0
					227 -0.67
					219 0

Table 2. NMR data for drimentine A

Position	δC ($CDCl_3$)	Type	δH ($CDCl_3$)[a]
1	169.7	C	
2	–	NH	5.80, s (br)
3	53.3	CH	3.93, m (overlapping)
4	166.8	C	
5	–	–	
5a	79.0	CH	5.38, s
6	–	NH	5.05, s (br)
6a	148.9	C	
7	109.6	CH	6.60, dd, J 1.0, 7.5
8[b]	123.2	CH	7.10, m
9	119.4	CH	6.78, dt, J 1.0, 7.5
10[b]	128.7	CH	7.10, m
10a	132.1	C	
10b	55.51	C	
11	37.9	CH_2	2.56 (11α), dd, J 5.5, 12.5;
			2.17 (11β), dd, J 11.0, 12.5
11a	59.0	CH	3.92, m (overlapping)
12	29.4	CH_2	1.88, d, J 5.0
13	52.3	CH	1.53, m
14	149.5	C	
15	38.2	CH_2	2.40 (15α[c]), ddd, J 2.5, 4.0, 12.5;
			1.97 (15β[c]), dt, J 4.0, 12.5
16	24.3	CH_2	1.71, m; 1.28, m
16a	55.45	CH	1.02, dd, J 2.5, 12.5
17	33.6	C	
18	41.9	CH_2	1.34, m; 1.12, dt, J 4.5, 13.0
19	19.2	CH_2	1.45, m
20	38.8	CH_2	1.69, m; 0.81, m (overlapping)
20a	40.1	C	
21	107.2	CH_2	4.88, s; 4.72, s

Continuation of Table 2. NMR data for drimentine A

Position	δC ($CDCl_3$)	Type	δH ($CDCl_3$)[a]
22	33.1	CH_3	0.84, s
23	21.7	CH_3	0.75, s
24	14.5	CH_3	0.60, s
25	38.6	CH_2	2.02, ddd, J 3.5, 10.0, 14.5;
			1.55,m
26	24.6	CH	1.74, m
27[d]	23.3	CH_3	0.98, d J 7.0
28[d]	21.0	CH_3	0.91, d J 7.0

a Multiplicity indicated by s singlet, d doublet, t triplet, m multiplet; J in Hz.

b, c, d Assignments within these pairs may be reversed.

Table 3. NMR data for drimentine B

Position	δC ($CDCl_3$)	Type	δH ($CDCl_3$)[a]
1	162.5	C	
2	–	–	
3	135.0	C	
4	155.7	C	
5	–	–	
5a	78.6	CH	5.50, s
6	–	NH	4.87, s (br)
6a	148.9	C	
7	109.6	CH	6.59, d, J 8.0
8[b]	123.2	CH	7.10, m
9	119.4	CH	6.78, dt, J 1.0, 7.5
10[b]	128.7	CH	7.10, m
10a	131.8	C	
10b	56.0	C	

Continuation of Table 3. NMR data for drimentine B

Position	δC ($CDCl_3$)	Type	δH ($CDCl_3$)[a]
11	39.3	CH_2	2.55 (11α), dd, J 5.5, 12.5;
			2.07 (11β), dd, J 12.5, 12.5
11a	61.3	CH	4.07, dd, J 5.5, 12.5
12	29.6	CH_2	1.88, d, J 5.0
13	52.3	CH	1.53, m
14	149.4	–	
15	38.3	CH_2	2.40 (15α[c]), ddd, J 2.5, 4.0, 12.5;
			1.98 (15β[c]), dt, J 5.0, 12.5
16	24.3	CH_2	1.71, m; 1.28, m
16a	55.5	CH	1.02, dd, J 3.0, 12.5
17	33.6	–	
18	41.9	CH_2	1.34, m; 1.12, dt, J 4.5, 13.0
19	19.2	CH_2	1.47, m
20	38.8	CH_2	1.71, m; 0.83, m (overlapping)
20a	40.1	–	
21	107.5	CH_2	4.89, s; 4.74, s
22	33.5	CH_3	0.84, s
23	21.7	CH_3	0.76, s
24	14.5	CH_3	0.60, s
25	118.9	CH	6.16, t, J 3.0
26	28.3	CH_2	2.76, m
27	45.1	CH_2	3.99, ddd, J 7.5, 9.5, 12.5; 3.89, td, J 10.0,
			12.5

a Multiplicity indicated by s singlet, d doublet, t triplet, m multiplet; J in Hz.

b,c Assignments within these pairs may be reversed.

Table 4. NMR data for drimentine C

Position	δC ($CDCl_3$)	Type	δH ($CDCl_3$)[a]
1	165.9	C	
2	–	–	
3	60.6	CH	4.07, t, J 7.5
4	167.1	C	
5	–	–	
5a	78.6	CH	5.34, s
6	–	NH	5.05, s (br)
6a	148.6	C	
7	109.6	CH	6.60, dd, J 1.0, 7.5
8[b]	123.2	CH	7.10, m
9	119.4	CH	6.78, dt, J 1.0, 7.5
10[b]	128.7	CH	7.10, m
10a	132.3	C	
10b	56.0	C	
11	39.3	CH_2	2.56 (11α), dd, J 5.5, 12.5;
			2.07 (11β), dd, J 11.0, 12.5
11a	60.4	CH	3.96, dd, J 5.5, 11.0
12	29.6	CH_2	1.85, d, J 5.0
13	52.2	CH	1.53, m
14	149.5	C	
15	38.2	CH_2	2.40 (15α[c]), ddd, J 2.5, 4.0, 12.5;
			1.98 (15β[c]), dt, J 5.0, 12.5
16	24.3	CH_2	1.70, m; 1.27, m
16a	55.4	CH	1.02, dd, J 3.0, 12.5
17	33.6	C	
18	41.9	CH_2	1.34, m; 1.12, dt, J 4.5, 13.0
19	19.2	CH_2	1.48, m
20	38.7	CH_2	1.71, m; 0.83, m (overlapping)
20a	40.0	C	

21	107.1	CH_2	4.86, s; 4.70, s

Continuation of Table 4. NMR data for drimentine C

Position	δC ($CDCl_3$)	Type	δH ($CDCl_3$)[a]
22	33.5	CH_3	0.84, s
23	21.7	CH_3	0.76, s
24	14.5	CH_3	0.60, s
25	27.7	CH_2	2.12, m
26	23.1	CH_2	1.87, m
27	45.1	CH_2	3.50, m

a Multiplicity indicated by s singlet, d doublet, t triplet, m multiplet; J in Hz.

b,c Assignments within these pairs may be reversed.

Table 5. NMR data for drimentine D

Position	δC ($CDCl_3$)	Type	δH ($CDCl_3$)[a]
1	170.7	C	
2	–	NH	5.72, s (br)
3	52.4	CH	3.83, dd, J 4.0, 10.5
4	167.6	C	
5	–	–	
5a	87.0	CH	5.27, s
6	–	–	
6a	150.0	C	
7[b]	126.3	CH	7.21, m
8	127.5	CH	7.23, m
9[b]	123.2	CH	7.22, m
10	120.6	CH	7.14, m
10a	142.3	C	
10b	51.8	C	

Continuation of Table 5. NMR data for drimentine D

Position	δC ($CDCl_3$)	Type	δH ($CDCl_3$)[a]
11	34.1	CH_2	2.75 (11α), dd, J 6.0, 12.5;
			2.10 (11β), dd, J 10.5, 12.5
11a	60.4	CH	3.97, dd, J 6.0, 10.5
12	28.1	CH_2	1.88, dd, J 4.0, 12.5;
			1.58, m (overlapping)
13	50.4	CH	0.54, dd, J 4.0, 12.5
14	62.1	C	
15	38.8	CH_2	1.83, m; 1.37, m
16	19.7	CH_2	1.61, m; 1.44, dd, J 3.0, 12.5
16a	56.8	CH	0.38, dd, J 3.0, 12.5
17	33.14	C	
18	41.8	CH_2	1.25, m; 0.96, dt, J 4.0, 13.5
19	18.4	CH_2	1.53, m; 1.31, m
20	39.2	CH_2	1.38, m; 0.46, dt, J 3.5, 13.5
20a	37.4	C	
21	24.6	CH_3	1.68, s
22	33.08	CH_3	0.73, s
23	21.1	CH_3	0.75, s
24	16.8	CH_3	0.86, s
25	38.1	CH_2	1.96, ddd, J 4.0, 10.5,14.0;1.36, m
26	24.4	CH	1.74, m
27[c]	23.0	CH_3	0.92, d, J 7.0
28[c]	21.0	CH_3	0.85, d, J 7.0

a Multiplicity indicated by s singlet, d doublet, t triplet, m multiplet; J in Hz.

b,c Assignments within these pairs may be reversed.

Table 6. NMR data for drimentine E

Position	δC ($CDCl_3$)	Type	δH ($CDCl_3$)[a]
1	162.6	C	
2	-	–	
3	134.8	C	
4	157.9	C	
5	–	–	
5a	87.0	CH	5.37, s
6	–	–	
6a	150.0	C	
7[b]	126.3	CH	7.21, m
8	127.5	CH	7.23, m
9[b]	123.2	CH	7.22, m
10	120.6	CH	7.14, m
10a	142.3	C	
10b	51.8	C	
11	35.1	CH_2	2.80 (11α), dd, J 5.5, 12.5;
			2.05 (11β), dd, J 12.5, 12.5
11a	62.9	CH	4.11, dd, J 5.5, 12.5
12	28.2	CH_2	1.86, dd, J 4.5, 12.5;1.59, m (overlapping)
13	50.6	CH	0.58, dd, J 4.0, 12.5
14	62.5	C	
15	38.8	CH_2	1.82, m; 1.36, m
16	19.7	CH_2	1.61, m; 1.44, dd, J 3, 12.5
16a	56.8	CH	0.39, dd, J 3.0, 12.5
17	33.2	C	
18	41.8	CH_2	1.23, m; 0.96, dt, J 3.5, 12.5
19	18.4	CH_2	1.53, m; 1.31, m
20	39.2	CH_2	1.38, m; 0.47, dt, J 3.5, 12.5
20a	37.4	C	
21	24.7	CH_3	1.67, s
22	33.1	CH_3	0.73, s

Continuation of Table 6. NMR data for drimentine E

Position	δC ($CDCl_3$)	Type	δH ($CDCl_3$)[a]
23	21.7	CH_3	0.74, s
24	16.8	CH_3	0.84, s
25	118.2	CH	6.06, t, J 4.0
26	28.2	CH_2	2.70, m
27	45.2	CH_2	3.97, dt, J 12.5, 8.5;
			3.85, dt, J 12.5, 10.0

a Multiplicity indicated by s singlet, d doublet, t triplet, m multiplet; J in Hz.

b Assignments may be reversed.

Example 4: Conversion of drimentine D into drimentine A

Drimentine D (6 mg) in chloroform (1 ml) is stirred with hydrochloric acid (2N, 0.1 ml) for 58 h. After adding dichloromethane (15 ml) and saturated aqueous sodium carbonate (2 ml), the organic layer is separated, dried over anhydrous sodium sulphate, and evaporated under vacuum. Chromatography of the residue on silica gel in ethyl acetate/hexane afforded drimentine A (2.6 mg, 43%), identified by R_f value on TLC and ^1H NMR spectrum in comparison with authentic material, together with starting material (3.4 mg).

Example 5: Conversion of drimentine E into drimentine B

Treatment of drimentine E (6 mg) with hydrochloric acid as for drimentine D gives drimentine B (2.8 mg, 47%), identified similarly, together with recovered material (3.2 mg).

Example 6: Conversion of drimentine E into 3,25-dihydrodrimentine E

Drimentine E (5 mg) in ethanol (2 ml) is stirred with 10% palladium on charcoal catalyst (5 mg) under hydrogen for 1.5 h. The catalyst is removed by filtration and the solvent evaporated under vacuun· to give 3,25-dihydrodrimentine E (5 mg, 100%), mp 180-182°C; Found; M^+, *m/z* 487.3196. Calc. for $C_{31}H_{41}N_3O$ *m/z* 487.3199.

Example 7: Conversion of 3,25-dihydrodrimentine E into drimentine C

3,25-Dihydrodrimentine E (4.5 mg) treated with hydrochloric acid as for drimentine D for 65 h gives drimentine C (1.6 mg, 36%), purified by chromatography on silica gel in acetone/dichloromethane and identified by R_f value on TLC and ^1H NMR spectrum in comparison with authentic material, together with recovered material (2.8 mg).

Example 8: Antitumor activity of the drimentines: [^3H] thymidine uptake test:

Stock solutions of drimentines A to E (1 mg/ml, 200 µl) are individually serially diluted with methanol (100 µl) to provide a range of 12 concentrations from 1000 µg/ml to 0.45 µg/ml. An aliquot (10 µl) of each dilution is then transferred to the appropriate wells of a 96-well microtitre plate and evaporated to dryness.

NS-1 murine myeloma cells suspended in RMPI 1640 media (50,000 cells/ml, 190 µl) and [^3H]thymidine (ICN 2406601, 10 µl) are added to each well and the plates are incubated for 6 h before the cells are harvested onto glass fibre mats and the tritium content of the cells is measured by liquid scintillation spectroscopy. The percent inhibition of cell growth is determined by:

100 - [100 x (counts per minute in the test well/ counts per minute in control wells)]

The results are tabulated in Table 7.

Table 7: Percentage inhibition of [^3H] thymidine uptake in NS-1 murine beta lymphocyte myeloma cells by drimentines A to E.

Compound	Concentration (µg/ml)						
	100	50	25	12.5	6.25	3.12	1.56
Drimentine A	NI^	NI	NI	NI	NI	NI	NI
Drimentine B	59	41	32	20	2	NI	NI
Drimentine C	98	95	91	63	34	NI	NI
Drimentine D	82	76	59	77	5	2	NI
Drimentine E	98	71	71	27	4	NI	NI
Control	NI	NI	NI	NI	NI	NI	NI

^ NI: No inhibition

Example 9: Antibacterial activity of drimentines

A stock solution of drimentine E (1 mg/ml, 200 µl) is serially diluted with methanol (100 µl) to provide a range of 12 concentrations from 1000 µg/ml to 0.45 µg/ml. An aliquot (10µl) of each dilution is then transferred to the appropriate wells of a 96-well microtitre plate, evaporated to dryness then reconstituted in 10% (v/v) dimethyl sulfoxide (DMSO) in water (10 µl). Nutrient agar (100 µl) is added to each well prior to testing. The cooled agar is inoculated with a dilute suspension of *Bacillus subtilis* (5 µl) and incubated at 28°C for 24 h after which the wells are inspected for bacterial growth. Drimentine E shows antibacterial activity against *Bacillus subtilis* down to 50 µg/ml.

Alternatively, application of a paper disc containing 100 µg/ml also inhibits growth of *B. subtilis*.

Pharmaceutical compositions

The pharmaceutical compositions of the present invention are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture and processing the mixture of granules, if desired or necessary after the addition of suitable excipients, to form tablets or dragée cores.

The following formulation examples illustrate the invention described above, but do not imply any limitation of the scope thereof.

Pharmaceutical compositions for the use in human health:

Example 10: Tablets each comprising 20 mg of active ingredient (drimentine A) are prepared in the customary manner, for example in the following composition:

Composition:

active ingredient	20 mg
wheat starch	60 mg
lactose	50 mg
colloidal silica	5 mg
talc	9 mg
magnesium stearate	1 mg
	145 mg

Preparation: The active ingredient is mixed with a portion of the wheat starch, with lactose and colloidal silica and the mixture is forced through a sieve. A further portion of the wheat starch is made into a paste with 5 times the amount of water on a water bath and the powder mixture is kneaded with the paste until a slightly plastic mass is obtained. The plastic mass is pressed through a sieve of about 3 mm mesh size and dried, and the resulting dry granules are forced through a sieve once more. Then, the remainder of the wheat starch, the talc and the magnesium stearate are admixed and the mixture is pressed to form tablets each weighing 145 mg and having a breaking notch.

Example 11: Tablets each comprising 1mg of active ingredient (drimentine A) are prepared in the customary manner in the following composition:

Composition:

active ingredient	1 mg
wheat starch	60 mg
lactose	50 mg
colloidal silica	5 mg
talc	9 mg
magnesium stearate	1 mg
	126 mg

Preparation: The active ingredient is mixed with a portion of the wheat starch, with lactose and colloidal silica and the mixture is forced through a sieve. A further portion of the wheat starch is made into a paste with 5 times the amount of water on a water bath and the powder mixture is kneaded with the paste until a slightly plastic mass is obtained. The plastic mass is pressed through a sieve of about 3 mm mesh size and dried, and the resulting dry granules are forced through a sieve once more. Then, the remainder of the wheat starch, the talc and the magnesium stearate are admixed and the mixture is pressed to form tablets each weighing 126 mg and having a breaking notch.

Example 12: Capsules each comprising 10mg of active ingredient (drimentine A) are prepared in the customary manner as follows:

Composition:

active ingredient	2500 mg
talc	200 mg
colloidal silica	50 mg

Preparation: The active ingredient is homogeneously mixed with talc and colloidal silica, and the mixture is forced through a sieve of 0.5 mm mesh size and introduced in portions of 11 mg into hard gelatine capsules of a suitable size.

Example 13: Capsules, each comprising 25 mg of active ingredient, for example one of the compounds of the formula I described in the preceding examples, are prepared as follows:

Composition: active ingredient, gelucire 44/14 (gelucire 44/14 is an admixture of esters of saturated C_8-C_{18}-fatty acids with glycerol and polyethylene glycol having a molecular weight of approximately 1500; produced by Gatte-fossé, F-69800 Saint Priest, France).

Preparation: A portion of gelucire 44/14 is melted at a temperature of from 50°C to 100°C. The active ingredient is mixed with the liquid gelucire 44/14 in a heated mortar to form a paste. The remainder of the gelucire 44/14 is then also melted and is added to the paste. The mixture is stirred at 50°C until a solution is obtained. This is introduced into the capsules while warm and is cooled. The wax so obtained comprises 12 % by weight active ingredient. The wax-like dispersion can also be processed in water by ultrasound treatment to form a milky liquid that can be administered orally.

Pharmaceutical compositions for the use in animal health:

Example 14: Tablets comprising 25 mg of active ingredient (drimentine A) can be prepared as follows:

Constituents (for 1000 tablets)

active ingredient	25.0 g
lactose	100.7 g
wheat starch	7.5 g
polyethylene glycol 6000	5.0 g
talcum	5.0 g
magnesium stearate	1.8 g
demineralised water	q.s.

Preparation: All the solid ingredients are first forced through a sieve having a mesh size of 0.6 mm. Then the active ingredient, the lactose, the talcum and half the starch are mixed together. The other half of the starch is suspended in 40 ml of water and the suspension is added to a boiling solution of the polyethylene glycol in 100 ml of water. The resulting starch paste is added to the main batch and the mixture is granulated, if necessary with the addition of water. The granules are dried overnight at 35°C, forced through a sieve having a mesh size of 1.2 mm, mixed with the magnesium stearate and compressed to form tablets having a diameter of about 6 mm which are concave on both sides.

Example 15: Tablets comprising 0.02 g of active ingredient (drimentine A) are prepared as follows:

Composition (for 10 000 tablets)

active ingredient	200.00 g
lactose	290.80 g
potato starch	274.70 g
stearic acid	10.00 g
talcum	200.00 g
magnesium stearate	2.50 g
colloidal silica	32.00 g
ethanol	q.s.

A mixture of the active ingredient, the lactose and 194.70g of potato starch is moistened with an ethanolic solution of the stearic acid and granulated through a sieve. After drying, the remaining potato starch, the talcum, the magnesium stearate and the colloidal silica are mixed in and the mixture is compressed to form tablets each weighing 0.1 g, which may, if desired, be provided with dividing notches for finer adaptation of the dose.

Example 16: Tablets comprising 25 mg of active ingredient (drimentine A) can be prepared as follows using a direct compression process:

Constituents (for 1000 tablets)

active ingredient	25.0 g
lactose, spray-dried	46.0 g
microcrystalline cellulose	20.0g
corn starch	5.0 g
talcum	3.5 g
magnesium stearate	0.5 g

Preparation: All the solid ingredients are first forced through a sieve having a mesh size of 0.6 mm. Then the active ingredient, the lactose, the microcrystalline cellulose, talcum are thoroughly mixed for 20 minutes. Finally the magnesium stearate is added and mixed in for 3 minutes. The mixture is compressed to form tablets having a diameter of about 6 mm which are concave on both sides.

Example 17: Capsules comprising 0.025 g of active ingredient (drimentine A) can be prepared as follows:

Composition (for 1000 capsules)

active ingredient	25.00 g
lactose	249.80 g
gelatin	2.00 g
corn starch	10.00 g
talcum	15.00 g
water	q.s.

The active ingredient is mixed with the lactose, the mixture is moistened uniformly with an aqueous solution of the gelatin and granulated through a sieve having a mesh size of 1.2-1.5 mm. The granules are mixed with the dried corn starch and the talcum and introduced in 300 mg portions into hard gelatin capsules.

Example 18: Premix (food additive)

0.25 part by weight of active ingredient (drimentine A) and

4.75 parts by weight of secondary calcium phosphate, alumina, Aerosil, carbonate or chalk are mixed until homogeneous with

95 parts by weight of an animal food.

Example 19: Premix (food additive)

0.40 part by weight of active ingredient (drimentine A) and

5.00 parts by weight of Aerosil/chalk (1:1) are mixed until homogeneous with

94.6 parts by weight of a commercial dry food.

Example 20: Emulsifiable concentrate

20 parts by weight of active ingredient (drimentine A) are mixed with

20 parts by weight of the emulsifier, e.g. a mixture of alkylarylpolyglycol ether with alkylarylpolysulfonates, and with

60 parts by weight of a solvent, until the solution has been completely homogenised. Emulsions of the desired concentration are obtained by dilution with water.

Example 21: Solutions (e.g. for use as a drink additive)

15 percent by weight active ingredient (drimentine A) in 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane,

10 percent by weight active ingredient in diethylene glycol monoethyl ether,

10 percent by weight in polyethylene glycol 300, and

5 percent by weight in glycerol.

Example 22: Soluble powder

25 parts by weight of active ingredient (drimentine A)

1 part by weight of sodium lauryl sulfate,

3 parts by weight of colloidal silica gel, and

71 parts by weight of urea.

The ingredients are mixed together and ground with one another until homogeneous.

Other biologically active compounds or adjuvants that are neutral towards the active ingredients and that have no adverse effect on the host animal to be treated, as well as mineral salts or vitamins, can be added to the compositions described.

Pest control composition for use in plant protection:

The pesticides (pest control compositions) according to the invention are, depending on the intended aims and the prevailing circumstances, emulsifiable concentrates, suspension concentrates, ready-to-spray or ready-to-dilute solutions, spreadable pastes, dilute emulsions, soluble powders, dispersable powders, wettable powders, dusts, granules or encapsulations in polymeric substances, all of these comprising the compound of the formula (I) (drimentine A).

In these compositions, the active ingredient is employed in pure form, for example the solid active ingredients in a specific particle size, or, preferably, together with - at least - one of the auxiliaries conventionally used in the art of formulation, such as extenders, for example solvents or solid carriers, or surface-active compounds (surfactants).

Examples of solvents which are suitable are: unhydrogenated or partially hydrogenated aromatic hydrocarbons, preferably the fractions C_8 to C_{12} of alkylbenzenes, such as xylene mixtures, alkylated naphthalene or tetrahydronaphthalene, aliphatic or cycloaliphatic hydrocarbons, such as paraffins or cyclohexane, alcohols, such as ethanol, propanol or butanol, glycols and their ethers and esters, such as propylene glycol, dipropylene glycol ether, ethylene glycol, ethylene glycol monomethyl ether or ethylene glycol monoethyl ether, ketones, such as cyclohexanone, isophorone or diacetone alcohol, strongly polar solvents, such as N-methylpyrrolid-2-one, dimethyl sulfoxide or N,N-dimethylformamide, water, unepoxidized or epoxidized vegetable oils, such as unepoxidized or epoxidized rapeseed, castor, coconut or soya oil, and silicone oils.

Solid carriers which are used for example for dusts and dispersable powders are, as a rule, ground natural minerals, such as calcite, talc, kaolin, montmorillonite or attapulgite. Highly-disperse silicas or highly-disperse absorptive polymers may also be used to improve the physical properties. Suitable particulate, adsorptive carriers for granules are porous types, such as pumice, brick grit, sepiolite or bentonite, and suitable non-absorptive carrier

materials are calcite or sand. Moreover, a large number of granulated materials of inorganic or organic nature, in particular dolomite or comminuted plant residues, may be used.

Suitable surface-active compounds are, depending on the nature of the active ingredient to be formulated, non-ionic, cationic and/or anionic surfactants or surfactant mixtures having good emulsifying, dispersing and wetting properties. The surfactants listed below are only given by way of example; a large number of other surfactants conventionally used in the art of formulation and suitable according to the invention are described in the relevant literature.

Suitable non-ionic surfactants are mainly polyglycol ether derivatives of aliphatic or cycloaliphatic alcohols, saturated or unsaturated fatty acids and alkylphenols, which can have 3 to 30 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon radical and 6 to 18 carbon atoms in the alkyl radical of the alkylphenols. Also suitable are water-soluble polyethylene oxide adducts with polypropylene glycol, ethylene diaminopolypropylene glycol and alkyl polypropylene glycol having 1 to 10 carbon atoms in the alkyl chain and comprising 20 to 250 ethylene glycol ether groups and 10 to 100 propylene glycol ether groups. The above-mentioned compounds conventionally have 1 to 5 ethylene glycol units per propylene glycol unit. Examples which may be mentioned are nonylphenol polyethoxyethanols, castor oil polyglycol ether, polypropylene/polyethylene oxide adducts, tributylphenoxypolyethoxyethanol, polyethylene glycol and octylphenoxypolyethoxyethanol. Also suitable are fatty acid esters or polyoxyethylene sorbitan, such as polyoxyethylene sorbitan trioleate.

The cationic surfactants are mainly quaternary ammonium salts which have, as substituents, at least one alkyl radical having 8 to 22 carbon atoms and as further substituents lower, halogenated or unhalogenated alkyl, benzyl or lower hydroxyalkyl radicals. The salts are preferably in the form of halides, methylsulfates or ethylsulfates. Examples are stearyl-trimethyl-ammonium chloride and benzyl di-(2-chloroethyl)ethylammonium bromide.

Suitable anionic surfactants can be water-soluble soaps and also water-soluble synthetic surface-active compounds. Soaps which are suitable are the alkali metal salts, alkaline earth metal salts and substituted or unsubstituted ammonium salts of higher fatty acids (C_{10}-C_{22}), such as the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid

mixtures which can be obtained, for example, from coconut or tall oil; fatty acid methyltaurinates should furthermore be mentioned. However, so-called synthetic surfactants are used more frequently, in particular fatty sulfonates, fatty sulfates, sulfonated benzimidazole derivatives or alkylarylsulfonates. The fatty sulfonates and fatty sulfates are, as a rule, in the form of alkali metal salts, alkaline earth metal salts or substituted or unsubstituted ammonium salts and have, as a rule, an alkyl radical of 8 to 22 carbon atoms, even if alkyl is the alkyl moiety of acyl radicals, for example the sodium salt or calcium salt of lignosulfonic acid, of the dodecylsulfuric ester or of a fatty alcohol sulfate mixture prepared from natural fatty acids. This group also includes the salts of the sulfuric esters and sulfonic acids of fatty alcohol/ethylene oxide adducts. The sulfonated benzimidazole derivatives comprise preferably 2 sulfonyl groups and a fatty acid radical having approximately 8-22 carbon atoms. Alkylarylsulfonates are, for example, the sodium salts, calcium salts or triethanolammonium salts of dodecylbenzenesulfonic acid or of a naphthalenesulfonic acid/formaldehyde condensate. Suitable phosphates, for example salts of the phosphoric ester of a p-nonylphenol/(4-14)-ethylene oxide adduct, or phospholipids, are also suitable.

As a rule, the compositions comprise 0.1 to 99 %, in particular 0.1 to 95 %, of a mixture of the active ingredient of the formula (I) (e,g. drimentine A), and 1 to 99.9 %, in particular 5 to 99.9 %, of - at least - one solid or liquid auxiliary, it being possible, as a rule, for 0 to 25 %, in particular 0.1 to 20 %, of the compositions to be surfactants (% in each case meaning percent by weight). While concentrated compositions are more preferred as commercially available goods, the end consumer uses, as a rule, dilute compositions which have considerably lower concentrations of active ingredient. Preferred compositions are composed, in particular, as follows (% = percent by weight):

Emulsifiable concentrates [active ingredient (drimentine A)]:

Mixture of active ingredient :	1 to 90 %, preferably 5 to 20 %
Surfactant:	1 to 30 %, preferably 10 to 20 %
Solvent:	5 to 98 %, preferably 70 to 85 %

Dusts [active ingredient (drimentine A)]:

Mixture of active ingredients:	0.1 to 10 %, preferably 0.1 to 1 %
Solid carrier:	99.9 to 90 %, preferably 99.9 to 99 %

Suspension concentrates [active ingredient (drimentine A)]:

Mixture of active ingredients:	5 to 75 %, preferably 10 to 50 %
Water:	94 to 24 %, preferably 88 to 30 %
Surfactant:	1 to 40 %, preferably 2 to 30 %

Wettable powders [active ingredient (drimentine A)]:

Mixture of active ingredients:	0.5 to 90 %, preferably 1 to 80 %
Surfactant:	0.5 to 20 %, preferably 1 to 15 %
Solid carrier:	5 to 99 %, preferably 15 to 98 %

Granules [active ingredient (drimentine A)]:

Mixture of active ingredients:	0.5 to 30 %, preferably 3 to 15 %
Solid carrier:	99.5 to 70 %, preferably 97 to 85 %

The compositions according to the invention can also comprise other solid or liquid auxiliaries, such as stabilizers, for example epoxidized or unepoxidized vegetable oils (for example epoxidized coconut oil, rapeseed oil or soya oil), antifoams, for example silicone oil, preservatives, viscosity regulators, binders and/or adhesives, and also fertilizers or other active ingredients for achieving specific effects, for example bactericides, fungicides, nematicides, molluscicides or herbicides.

The compositions according to the invention are prepared in a known manner, for example in the absence of auxiliaries by grinding, screening and/or compressing a solid active ingredient or mixture of active ingredients, for example to a specific particle size, and, in the presence of at least one auxiliary, for example by intimately mixing and/or grinding the

active ingredient or mixture of active ingredients with the auxiliary (auxiliaries). The process for the preparation of the compositions is therefore a further subject-matter of the invention.

The compound of the formula (I) is preferably employed with the auxiliaries conventionally used in the art of formulation and are therefore processed in a known manner to give, for example, emulsifiable concentrates, ready-to-spray or ready-to-dilute solutions, dilute emulsions, wettable powders, soluble powders, dusts, granules, and also encapsulations, for example in polymeric substances. The methods of application, such as spraying, atomizing, dusting, wetting, scattering or pouring, and the type of composition are selected to suit the intended aims and the prevailing circumstances.

The methods of application for the compositions, i.e. the methods of controlling pests of the abovementioned type, such as spraying, atomizing, dusting, brushing on, seed dressing, scattering or pouring, which are to be selected to suit the intended aims and the prevailing circumstances, and also the use of the compositions for controlling pests of the above-mentioned type are further subject-matters of the invention. Typical rates of application are between 0.1 and 1000 ppm, preferably between 0.1 and 500 ppm, of active ingredient. The rate of application can vary within wide limits and depends on the nature of the soil, the type of application (foliar application; seed treatment; use in the seed furrow), the crop plant, the pest to be controlled, the respective climate prevailing, and other factors determined by type of application, timing of application and target crop. The rates of application per hectare are generally 1 to 2000 g of active ingredient per hectare, in particular 10 to 1000 g/ha, preferably 20 to 600 g/ha.

A preferred method of application in the field of crop protection is application to the foliage of the plants (foliar application), it being possible to adjust frequency and rate of application depending on the risk of infestation of the pest in question. Alternatively, the active ingredients can reach the plants via the root system (systemic action), by drenching the locus of the plants with a liquid composition or by incorporating the active ingredients in solid form into the locus of the plants, for example the soil, for example in the form of granules (soil application). In the case of paddy rice, such granules can be metered into the flooded paddy-field.

The compositions according to the invention are also suitable for protecting plant propagation material, for example seed, such as fruits, tubers or kernels, or nursery plants, against animal pests. The propagation material can be treated with the composition before planting, for example seed can be dressed before sowing. The active ingredients according to the invention can also be applied to seed kernels (coating), either by soaking the kernels in a liquid composition or by coating them with a solid composition. Alternatively, the composition can be applied to the planting site when planting the propagation material, for example into the seed furrow during sowing. These treatment methods for plant propagation material and the resulting treated plant propagation material are other subject-matters of the invention.

The following examples are intended to illustrate the invention. They do not impose any limitation on the invention.

Formulation examples

(% = percent by weight, ratios of active ingredients = weight ratios) containing as active ingredient e.g. drimentine A:

Example 23: Emulsion concentrates	a)	b)	c)
Mixture of active ingredients (1 : 1)	25 %	40 %	50 %
Calcium dodecylbenzenesulfonate	5 %	8 %	6 %
Castor oil polyethylene glycol ether (36 mol of EO)	5 %	-	-
Tributylphenol polyethylene glycol ether (30 mol of EO)	-	12 %	4 %
Cyclohexanone	-	15 %	20 %
Xylene mixture	65 %	25 %	20 %

Emulsions of any desired concentration can be prepared from such concentrates by dilution with water.

Example 24: Solutions	a)	b)	c)	d)
Mixture of active ingredients (1 : 3)	80 %	10 %	5 %	95 %
Ethylene glycol monomethyl ether	20 %	-	-	-
Polyethylene glycol MW 400	-	70 %	-	-
N-Methyl-2-pyrrolidone	-	20 %	-	-
Epoxidized coconut oil	-	-	1 %	5 %
Petroleum ether (boiling range 160-190°C)	-	-	94 %	-

The solutions are suitable for use in the form of microdrops.

Example 25: Granules	a)	b)	c)	d)
Mixture of active ingredients (3 : 1)	5 %	10 %	8 %	21 %
Kaolin	94 %	-	79 %	54 %
Highly-disperse silica	1 %	-	13 %	7 %
Attapulgite	-	90 %	-	18 %

The active ingredients are dissolved together in dichloromethane, the solution is sprayed onto the carrier, and the solvent is subsequently evaporated in vacuo.

Example 26: Dusts	a)	b)
Mixture of active ingredients (1 : 1)	2 %	5 %
Highly-disperse silica	1 %	5 %
Talc	97 %	-
Kaolin	-	90 %

Ready-to-use dusts are obtained by intimately mixing the carriers with the active ingredients.

Example 27: Wettable powders	a)	b)	c)
Mixture of active ingredients (4 : 1)	25 %	50 %	75 %
Sodium lignosulfonate	5 %	5 %	-
Sodium lauryl sulfate	3 %	-	5 %
Sodium diisobutylnaphthalene-sulfonate	-	6 %	10 %
Octylphenol polyethylene glycol ether (7-8 mol of EO)	-	2 %	-
Highly-disperse silica	5 %	10 %	10 %
Kaolin	62 %	27 %	-

The active ingredients are mixed with the additives and ground thoroughly in a suitable mill. This gives wettable powders which can be diluted with water to give suspensions of any desired concentration.

Example 28: Emulsion concentrate

Mixture of active ingredients (1 : 2)	10 %
Octylphenol polyethylene glycol ether (4-5 mol of EO)	3 %
Calcium dodecylbenzenesulfonate	3 %
Castor oil polyglycol ether (36 mol of EO)	4 %
Cyclohexanone	30 %
Xylene mixture	50 %

Emulsions of any desired concentration can be prepared from this concentrate by dilution with water.

Example 29: Dusts	a)	b)
Mixture of active ingredients (5 : 2)	5 %	8 %
Talc	95 %	-
Kaolin	-	92 %

Ready-to-use dusts are obtained by mixing the active ingredients with the carrier and grinding the mixture in a suitable mill.

Example 30: Extruder granules

Mixture of active ingredients (2 : 1)	10 %
Sodium lignosulfonate	2 %
Carboxymethylcellulose	1 %
Kaolin	87 %

The active ingredients are mixed with the additives, and the mixture is ground and moistened with water. This mixture is extruded, granulated and subsequently dried in a stream of air.

Example 31: Coated granules

Mixture of active ingredients (1 : 1)	3 %
Polyethylene glycol (MW 200)	3 %
Kaolin	94 %

In a mixer, the finely ground active ingredients are applied uniformly to the kaolin which has been moistened with polyethylene glycol. In this manner, dust-free coated granules are obtained.

Example 32: Suspension concentrate

Mixture of active ingredients (1 : 1)	40 %
Ethylene glycol	10 %
Nonylphenol polyethylene glycol ether (15 mol of EO)	6 %
Sodium lignosulfonate	10 %
Carboxymethylcellulose	1 %
37 % aqueous formaldehyde solution	0.2 %
Silicone oil in the form of a 75 % aqueous emulsion	0.8 %
Water	32 %

The active ingredient is mixed intimately with the additives. This gives a suspension concentrate from which suspsensions of any desired concentration can be prepared by dilution with water.

Biological Tests:

In the agricultural field the biological activity of the compounds of the present invention can be determined by conducting one or more of the following tests or any other appropriate tests.

Example B1: Action against *Bemisia tabaci*

Dwarf bean plants are placed into gauze cages and populated with *Bemisia tabaci* adults. After oviposition, all adults are removed. 10 days later, the plants and the nymphs thereon are sprayed with an aqueous suspension spray mixture comprising 50 ppm of the active ingredient. After a further 14 days, the percentage hatching rate of the eggs is evaluated in comparison with untreated control batches.

Example B2: Action against *Spodoptera littoralis* caterpillars

Young soya plants are sprayed with an aqueous emulsion spray mixture comprising 360 ppm of the active ingredient. After the spray coating has dried on, the soya plants are populated with 10 third-instar *Spodoptera littoralis* caterpillars and placed in a plastic container. The test is evaluated 3 days later. The percentage reduction in population or the percentage reduction of feeding damage (% action) is determined by comparing the number of dead caterpillars and the feeding damage on the treated plants with those on the untreated plants.

Example B3: Ovicidal action against *Lobesia botrana*

Lobesia botrana eggs deposited on filter paper are immersed briefly into a test solution comprising 400 ppm of the active ingredient to be tested in acetone/water. After the test solution has dried on, the eggs are incubated in Petri dishes. After 6 days, the percentage hatching rate of the eggs is evaluated in comparison with untreated control batches (% reduction in hatching rate).

Example B4: Ovicidal action against *Heliothis virescens*

Heliothis virescens eggs deposited on filter paper are immersed briefly into a test solution comprising 400 ppm of the active ingredient to be tested in acetone/water. After the test solution has dried on, the eggs are incubated in Petri dishes. After 6 days, the percentage hatching rate of the eggs is evaluated in comparison with untreated control batches (% reduction in hatching rate).

Example B5: Action against *Plutella xylostella* caterpillars

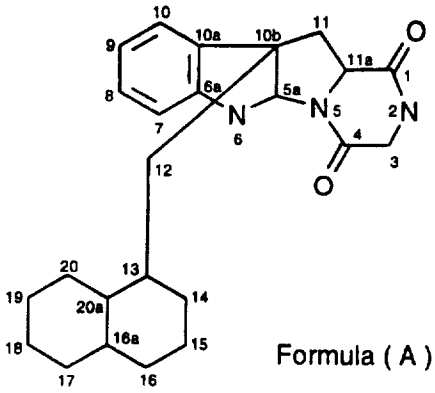
Young cabbage plants are sprayed with an aqueous emulsion spray mixture comprising 440 ppm of the active ingredient. After the spray coating has dried on, the cabbage plants are populated with 10 third-instar *Plutella xylostella* caterpillars and placed in a plastic container. The test is evaluated 3 days later. The percentage reduction in population or the percentage reduction in feeding damage (% action) is determined by comparing the number of dead caterpillars and the feeding damage on the treated plants with those on the untreated plants.

Example B6: Action against *Ctenocephalides felis* (cat flea)

20 adult fleas of the species *Ctenocephalides felis* are introduced into a flat round cage closed off at both ends with gauze. A vessel sealed at the bottom with a parafilm membrane is then placed on the cage. The vessel contains blood comprising 1.0 ppm of active ingredient and is heated to a constant temperature of 37°C. The fleas take up the blood through the membrane. Evaluation is effected 24 and 48 hours after the start of the test. The percentage reduction in population (% activity) is determined from a comparison of the number of dead fleas given treated blood with those given untreated blood (control group). 24 hours after treatment the blood is replaced with fresh blood that has likewise been treated and the test is continued with the surviving fleas. The untreated blood for the control group is also replaced after 24 hours.

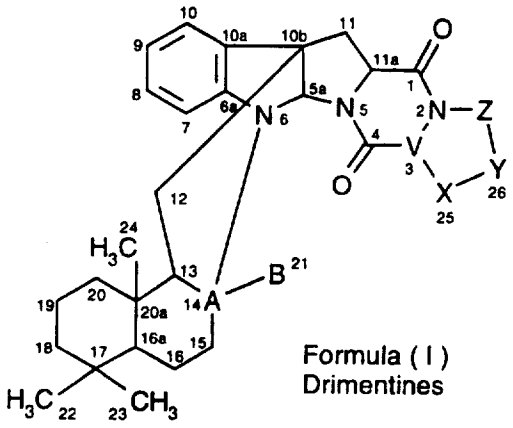
What is claimed is:

1. An antibiotically active drimentine comprising the structural elements shown in formula A



Formula (A)

2. A drimentine according to claim 1 that shows the formula I



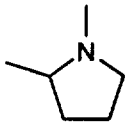
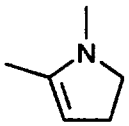
Formula (I)
Drimentines

wherein

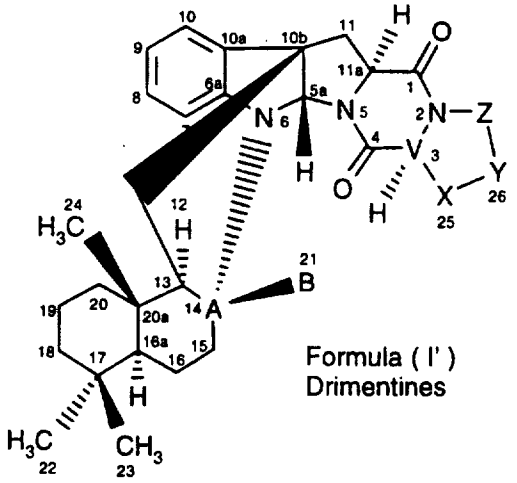
(a) the bond A-N is either absent or present, and if the bond A-N is absent, A is a carbon ring atom, N in position 6 carries a hydrogen atom, and A-B represents the group $=C=CH_2$; whereas if the bond A-N is present, A is a carbon ring atom, and A-B stands for the group $=C(-CH_3)-$; and

(b) the bond Y-Z is either absent or present, and if the bond Y-Z is absent, Z is hydrogen, and V-X-Y represent together the group $=CH-CH_2-CH(CH_3)_2$; whereas if the bond Y-Z is

present, V-X-Y-Z-N form together one of the five-membered rings selected from the group consisting of

 and  or a structural or functional derivative thereof.

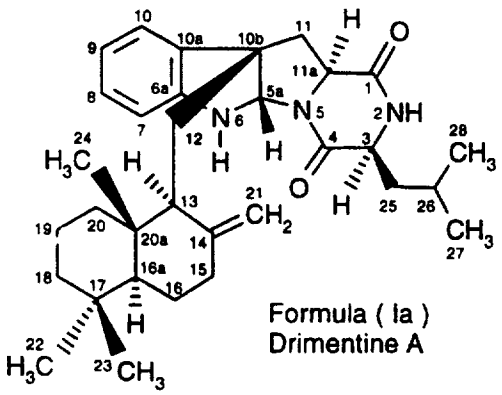
3. A drimentine according to any one of claims 1 and 2 that displays the conformation which is shown under the following formula I'



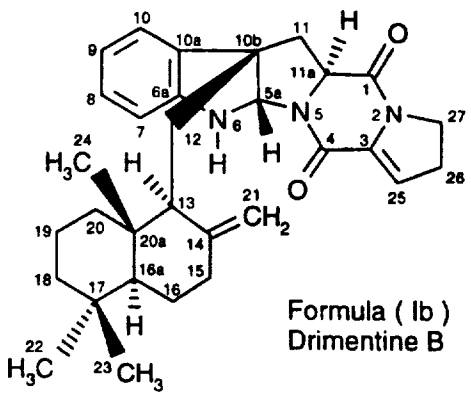
Formula (I')
Drimentines

wherein the substituents A, B, V, X, Y and Z are defined as under formula I or a structural or functional derivative thereof.

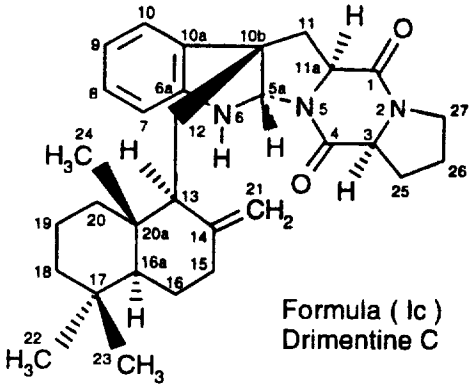
4. A drimentine according to claim 3, selected from the group of drimentines consisting of



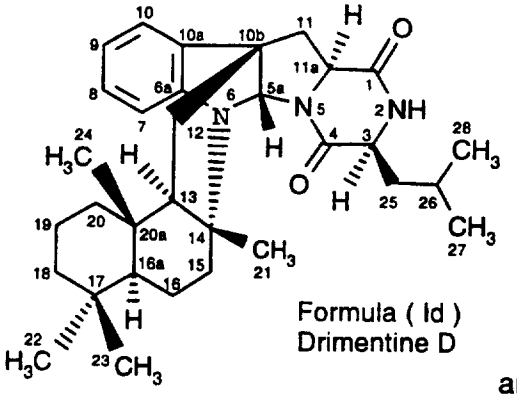
Formula (Ia)
Drimentine A



Formula (Ib)
Drimentine B

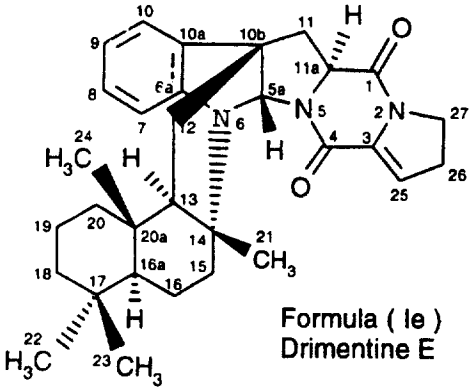


Formula (Ic)
Drimentine C



Formula (Id)
Drimentine D

and

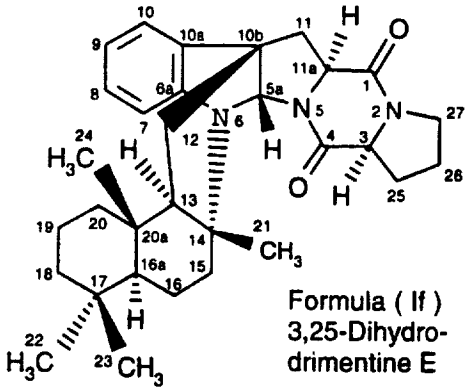


Formula (Ie)
Drimentine E

or a structural or functional derivative thereof.

5. A compound according to any one of claims 1 to 4, wherein said compound is a chemically modified drimentine.

6. A compound according to claim 5, wherein said chemically modified drimentine is 3,25-dihydrodrimentine of the following formula (If)



Formula (If)
3,25-Dihydro-
drimentine E

or a structural or functional derivative thereof.

7. A microorganism capable of producing a drimentine according to any one of claims 1 to 5.

8. A microorganism according to claim 7, wherein said microorganism is a bacterium.

9. A microorganism according to claim 7, wherein said microorganism is an *Actinomycete* strain.

10. An *Actinomycete* strain according to claim 8 that is the *Actinomycete* strain MST-8651 as deposited with the Australian Government Analytical Laboratory (AGAL) on 22 August 1996 under Accession No. N96/101825.

11 A pharmaceutical composition comprising a drimentine according to any one of claims 1 to 6 and a pharmaceutical carrier.

12. A pharmaceutical composition according to claim 11 adapted to parenteral, oral, rectal, topical, transdermal, implant, ophthalmic, nasal or genito-urinary use.

13. The use of a drimentine according to any one of claims 1 to 6 for the preparation of a pharmaceutical composition to be used for the treatment of bacteria, fungi, endoparasites and ectoparasites infections, cancer and other malignant diseases in human and animal health.

14. The use of a drimentine according to claim 13, wherein said therapeutic conditions embrace but are not limited to cancer or conditions caused by pathogenic organisms embracing bacteria, fungi, nematodes, cestodes, trematodes, accarina and insects.

15. A method for the treatment of warm-blooded animals, including humans, suffering from a disease caused by pathogenic organisms embracing bacteria, fungi, nematodes, cestodes, trematodes, accarina and insects, which method comprises the administration of a therapeutically effective amount of a drimentine according to any one of claims 1 to 6 or the administration of a pharmaceutical composition of claim 11 or 12 to a warm-blooded animal, including a human being.

16. A method for combatting ectoparasites on warm-blooded animals, including humans, comprising the administration ectoparasiticidally effective amount of a drimentine according to any one of claims 1 to 6 to the parasite or its habitat.

17. A method according to claim 16, wherein a drimentine according to any one of claims 1 to 6 is administered systemically to the host of the parasite.

18. A pest control composition comprising a pesticidally effective amount of a drimentine according to any one of claims 1 to 6 together with a suitable carriers and/or excipient.

19. A method for combating pests in agriculture, horticulture or forestry, or in stores, buildings or other public places or locations of the pests, which comprises applying to plants or other vegetation or to the pests themselves or a location thereof an effective amount of one or more drimentines according of any one of claims 1 to 6.

20. A process for the preparation of a drimentine according to any one of claims 1 to 6 which comprises culturing a microorganism capable of producing one or more drimentines, isolation of a drimentine from the culture product and optionally converting the drimentine by chemical or biological means in a structural or functional derivative.

21. A drimentine or a structural or functional derivative thereof according to any one of claims 1 to 6 for use in a method for the therapeutic treatment of the human or animal body.

H-21027/A/MST 1

PCT/IB 97 01425

05. 09. 97

BUDAPEST TREATY ON THE INTERNATIO
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS
FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

TO
Microbial Screening Technologies P/L.
P.O. Box 57
Kemps Creek 2171
Dr. Ernest Lacey
NAME AND ADDRESS OF DEPOSITOR

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified at the bottom of this page

RECEIVED
22 AUG 1996

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:
Actinomycete MST-8651

Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:
N96/101825

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I above was accompanied by:

[X] a scientific description

[ ] a proposed taxonomic designation

(Mark with a cross where applicable)

III. RECEIPT AND ACCEPTANCE

This International Depositary Authority accepts the microorganism identified under I above, which was received by it on 22/8/96 (date of the original deposit)[1]

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I above was received by this International Depositary Authority on (date of the original deposit) and a request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion)

V. INTERNATIONAL DEPOSITARY AUTHORITY

Name: AUSTRALIAN GOVERNMENT ANALYTICAL LABORATORIES

Address: PO Box 385 Pymble, 2073
Phone (02)449 0111
Facsimile (02)449 1653

Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s):

Date: 28/8/96

1 Where Rule 6.4(d) applies, such date is the date on which the status of international depositary authority was acquired.

Form BP/4 (sole page)

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/IB 97/01425

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: C07D 487/14, 487/22, 471/22 A61K 31/395 A01N 43/90 C12N 1/20 // (C12N 1/20, C12R 1:04)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Chemical Abstracts; substructure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts 123:246080 Barrow et al.:"Structure-activity studies of the natural product substance P antagonist WIN 64821". & Bioorg. Med. Chem. Lett. (1995), 5(4), 377-80	1-2

☐ Further documents are listed in the continuation of Box C

☐ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 1997	19 DEC 1997
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer **G. HEARDER** Telephone No.: (02) 6283 2553