

ANTICANCER STEROIDAL LACTONES UNSATURATED IN POSITION 7 (8)

FIELD OF THE INVENTION

5 The present invention relates to new anticancer compounds, pharmaceutical compositions containing them, and their use as anticancer agents.

BACKGROUND OF THE INVENTION

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 The present invention relates to compounds with some structural similarities to bufadienolide compounds disclosed in the prior art. For a review of bufadienolides see Huimin Gao et al in Nat. Prod. Rep., 2011, 28, 953.

15

 The bufadienolide compounds reported in the prior art are natural steroids, originally isolated from terrestrial natural sources such as plants of the families Crassulaceae, Hyacinthaceae, Iridaceae, Melianthaceae, Ranunculaceae, and Santalaceae, and animals of the
20 genus *Bufo* (toads), *Photinus* (fireflies), and *Rhabdophis* (snakes) (Steyn et al. Nat. Prod. Rep. 1998, 15, 397-413; Krenn et al. Phytochemistry, 1998, 48(1), 1-29).

 Among these bufadienolide compounds, Scilliroside and other
25 Scilla compounds have been isolated from the red squill, *Urginea maritima*, and are disclosed to be highly toxic, specially Scilliroside which affects the cardiovascular and central nervous systems, causing convulsions and death (Verbiscar et al. J. Agric. Food Chem. 1986, 34, 973-979; Kopp et al. Phytochemistry, 1996, 42(2), 513-522). Majinda et
30 al. also isolated bufadienolide compounds from *Urginea sanguinea*, which make the plant unsafe to be used as a medicinal plant (Planta Med. 1997, 63, 188-190).

The antiviral activity against a series of rhinoviruses and the anti-herpetic activity of several bufadienolide compounds were evaluated by Kamano et al. (Chem. Pharm. Bull. 1988, 36(1), 326-332) and Takechi
5 et al. (Phytochemistry, 1996, 41(1), 125-127), respectively, and they found that most of the compounds displayed some inhibitory activity.

Additionally, the cytotoxic activity of several bufadienolide compounds has been evaluated by several authors. Specifically, Jing et
10 al. reported that bufalin has a potent growth-inhibitory effect on human cancer cells of leukaemia (HL-60, ML1, U937, and K562 cell lines), epithelioid carcinoma (HeLa cell line), hepatoma (PLC/PRF/5 cell line), and epidermoid carcinoma (A431 cell line), but it is less potent on mouse leukaemia M1, melanoma B16, and lymphoid neoplasm P388
15 cell lines and rat hepatoma AH66 and chromaffin cell PC12 cell lines. They also found that bufalin induces typical apoptosis in human leukaemia HL-60 cell line but not in human leukocytes (Jpn. J. Cancer Res. 1994, 85(6), 645-651).

20 Kupchan et al. disclosed several bufadienolide compounds isolated from *Bersama abyssinica* which showed inhibitory activity against human carcinoma of the nasopharynx (KB) cell line (Bioorg. Chem. 1971, 1, 13-31; J. Org. Chem. 1971, 36(18), 2611-2616).

25 Kamano et al. evaluated the cytotoxic activity of 80 bufadienolide and cardenolide compounds, isolated from the Chinese drug Ch'an Su (obtained from the skin glands of toads such as *Bufo gargarizans*), against a primary liver carcinoma PLC/PRF/5 cell line and the colchicine-resistant cell line of PLC/PRF/5. Of them, 16 were shown to
30 have potent cytotoxicities ($IC_{50} < 10^{-3}$ μ g/mL) against PLC/PRF/5 cell line (Bioorg. Med. Chem. 1998, 6, 1103-1115; J. Med. Chem. 2002, 45, 5440-5447). Additional bufadienolide compounds were isolated by

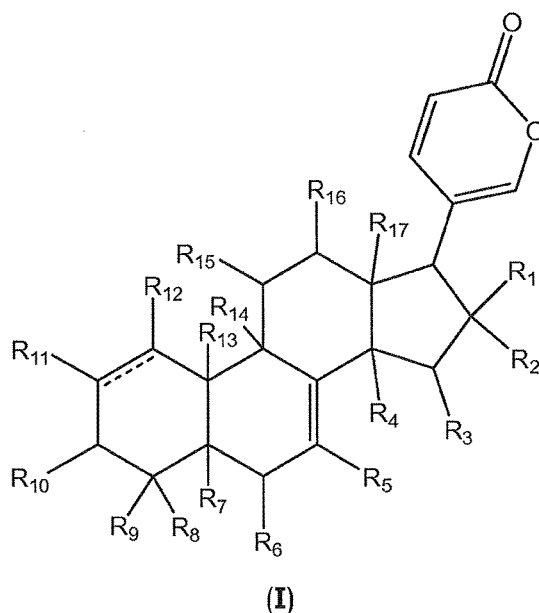
Nogawa et al. from the same source, which were tested against human carcinoma of the nasopharynx (KB), human leukaemia (HL-60), murine leukaemia (MH60), pancreas adenocarcinoma (BXPC3), breast adenocarcinoma (MCF7), CNS glioblastoma (SF268), lung NSC
5 (NCIH460), colon carcinoma (KM20L2), and prostate cancer (DU145) cell lines (J. Nat. Prod. 2001, 64, 1148-1152).

Ye et al. prepared novel bufadienolide compounds from bufalin by microbial hydroxylation. The compounds were tested against human
10 hepatoma Bel-7402, human gastric cancer BGC-823, human cervical carcinoma HeLa, and human leukaemia HL-60 cell lines, showing some of them potent cytotoxicities comparable to that of bufalin (J. Steroid. Biochem. Mol. Biol. 2004, 91, 87-98; J. Nat. Prod. 2005, 68, 626-628).

15 Since cancer is a leading cause of death in animals and humans, several efforts have been and are still being undertaken in order to obtain an anticancer therapy active and safe to be administered to patients suffering from a cancer. The problem to be solved by the present invention is to provide compounds that are useful in the
20 treatment of cancer.

SUMMARY

Disclosed are compounds of general formula **I** or
25 pharmaceutically acceptable salts, prodrugs or stereoisomers thereof



wherein

- 5 each R_1 and R_2 is independently selected from hydrogen, halogen, OR_a , $OCOR_a$, and $OCOOR_a$, or R_1 and R_2 together are $=O$;

- each R_3 , R_{15} , and R_{16} is independently selected from hydrogen, OR_a , $OCOR_a$, $OCOOR_a$, and $=O$, with the proviso that when a $=O$ group exists
 10 the hydrogen of the C atom to which the $=O$ is attached is absent;

each R_4 , R_5 , R_6 , R_7 , R_{11} , R_{12} , and R_{14} is independently selected from hydrogen, OR_a , $OCOR_a$, and $OCOOR_a$;

- 15 each R_8 , R_9 , and R_{17} is independently selected from hydrogen, OR_a , $OCOR_a$, $OCOOR_a$, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, and substituted or unsubstituted C_2 - C_{12} alkynyl;

- 20 R_{10} is selected from hydrogen, OR_b , $OCOR_a$, $OCOOR_a$, and $=O$, with the proviso that when a $=O$ group exists the hydrogen of the C atom to which the $=O$ is attached is absent;

R_{13} is selected from hydrogen, COR_a , substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, and substituted or unsubstituted C_2 - C_{12} alkynyl;

5

each R_a is independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

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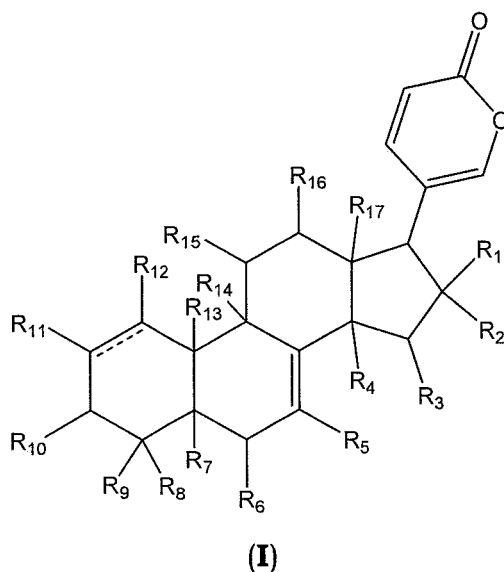
each R_b is independently selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, substituted or unsubstituted C_2 - C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and substituted or unsubstituted sugar; and

15

the ----- line represents an additional bond, an epoxy group, or is absent.

20

In one aspect, there is provided a compound of general formula **I**



wherein

R₁ is selected from hydrogen and halogen;

R₂ is halogen;

5

each R₃, R₁₅, and R₁₆ is independently selected from hydrogen, OR_a, OCOR_a, OCOOR_a, and =O, with the proviso that when a =O group exists the hydrogen of the C atom to which the =O is attached is absent;

10 each R₄, R₅, R₆, R₇, R₁₁, R₁₂, and R₁₄ is independently selected from hydrogen, OR_a, OCOR_a, and OCOOR_a;

each R₈, R₉, and R₁₇ is independently selected from hydrogen, OR_a, OCOR_a, OCOOR_a, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl;

R₁₀ is selected from hydrogen, OR_b, OCOR_a, OCOOR_a, and =O, with the proviso that when a =O group exists the hydrogen of the C atom to which the =O is attached is absent;

R₁₃ is selected from hydrogen, COR_a, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl;

25

each R_a is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

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each R_b is independently selected from hydrogen, substituted or unsubstituted C_1-C_{12} alkyl, substituted or unsubstituted C_2-C_{12} alkenyl, substituted or unsubstituted C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group,
5 and substituted or unsubstituted sugar; and

the ----- line represents an additional bond, an epoxy group, or is absent;

10 or a pharmaceutically acceptable salt or stereoisomer thereof.

Disclosed is a compound of formula **I**, or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof, for use as a medicament, in particular as a medicament for treating cancer.

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In another aspect, there is provided a compound as described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, for use as a medicament.

20 Disclosed is the use of a compound of formula **I**, or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof, in the treatment of cancer, or in the preparation of a medicament, preferably for the treatment of cancer. Other embodiments of the disclosure are methods of treatment, and compounds for use in these
25 methods. Therefore, the present disclosure

further provides a method of treating any mammal, notably a human, affected by cancer which comprises administering to the affected individual a therapeutically effective amount of a compound as defined above.

5 Disclosed is a compound of formula **I**, or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof, for use as an anticancer agent.

In another aspect, there is provided use of a compound as described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, in
10 the preparation of a medicament for the treatment of cancer.

Disclosed are pharmaceutical compositions comprising a compound of formula **I**, or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof, together with a pharmaceutically acceptable carrier or diluent.

15 In another aspect, there is provided a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier or diluent.

20 **DETAILED DESCRIPTION OF THE INVENTION**

The present invention relates to compounds of general formula **I** as defined above.

In these compounds the groups can be selected in accordance
25 with the following guidance:

Alkyl groups may be branched or unbranched, and preferably have from 1 to about 12 carbon atoms. One more preferred class of alkyl groups has from 1 to about 6 carbon atoms. Even more preferred are alkyl groups having 1, 2, 3 or 4 carbon atoms. Methyl, ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and
30 isobutyl are particularly preferred alkyl groups in the compounds of the present invention. As used herein, the term alkyl, unless otherwise stated, refers to both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members.

Preferred alkenyl and alkynyl groups in the compounds of the present invention may be branched or unbranched, have one or more unsaturated linkages and from 2 to about 12 carbon atoms. One more preferred class of alkenyl and alkynyl groups has from 2 to about 6 carbon atoms. Even more preferred are alkenyl and alkynyl groups having 2, 3 or 4 carbon atoms. The terms alkenyl and alkynyl as used herein refer to both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members.

10

Suitable aryl groups in the compounds of the present invention include single and multiple ring compounds, including multiple ring compounds that contain separate and/or fused aryl groups. Typical aryl groups contain from 1 to 3 separated or fused rings and from 6 to about 18 carbon ring atoms. Preferably aryl groups contain from 6 to about 10 carbon ring atoms. Specially preferred aryl groups include substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted biphenyl, substituted or unsubstituted phenanthryl, and substituted or unsubstituted anthryl.

20

Suitable heterocyclic groups include heteroaromatic and heteroalicyclic groups containing from 1 to 3 separated and/or fused rings and from 5 to about 18 ring atoms. Preferably heteroaromatic and heteroalicyclic groups contain from 5 to about 10 ring atoms. Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolyl including 8-quinolyl, isoquinolyl, pyridyl, pyrazinyl, pyrazolyl, pyrimidinyl, furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, isoxazolyl, oxazolyl, imidazolyl, indolyl, isoindolyl, indazolyl, indolizinyl, phthalazinyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, pyridazinyl, triazinyl, cinnolinyl, benzimidazolyl,

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benzofuranyl, benzofurazanyl, benzothienyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl and furopyridyl. Suitable heteroalicyclic groups in the compounds of the present invention contain one, two or three heteroatoms selected from
 5 N, O or S atoms and include, e.g., pyrrolidinyl, tetrahydrofuryl, dihydrofuryl, tetrahydrothienyl, tetrahydrothiopyranyl, piperidyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, azetidyl, oxetanyl, thietanyl, homopiperidyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridyl, 2-pyrrolinyl, 3-
 10 pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxolanyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexyl, 3-azabicyclo[4.1.0]heptyl, 3H-indolyl, and quinolizinyl.

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The term sugar includes monosaccharides, disaccharides, trisaccharides, polysaccharides, oligosaccharides, and saccharide derivatives. Preferably the saccharide is selected from rhamnose, glucose, digitoxose, digitalose, digginose, sarmentose, vallarose, and
 20 fructose. Derivatives thereof, including sugar glycosides, N-glycosylamines, O-acyl derivatives, O-methyl derivatives, sugar alcohols, sugar acids, deoxy sugars, and related groups, are also preferred sugar groups.

25 Suitable halogen groups in the compounds of the present invention include F, Cl, Br and I.

The groups above mentioned may be substituted at one or more available positions by one or more suitable groups such as OR', =O, SR',
 30 SOR', SO₂R', NO₂, NHR', N(R')₂, =N-R', NHCOR', N(COR')₂, NHSO₂R', NR'C(=NR')NR'R', CN, halogen, COR', COOR', OCOR', OCONHR', OCON(R')₂, CONHR', CON(R')₂, substituted or unsubstituted C₁-C₁₂

alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group, wherein each of the R' groups is independently selected from the group consisting of hydrogen, OH, NO₂, NH₂, SH, CN, halogen, COH, COalkyl, COOH, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group. Where such groups are themselves substituted, the substituents may be chosen from the foregoing list.

The term "pharmaceutically acceptable salts and prodrugs" refers to any pharmaceutically acceptable salt, ester, solvate, hydrate or any other compound which, upon administration to the patient is capable of providing (directly or indirectly) a compound as described herein. However, it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the invention since those may be useful in the preparation of pharmaceutically acceptable salts. The preparation of salts and prodrugs can be carried out by methods known in the art.

For instance, pharmaceutically acceptable salts of compounds provided herein are synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent or in a mixture of both. Generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol or acetonitrile are preferred. Examples of the acid addition salts include mineral acid addition salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulphate, nitrate, phosphate, and organic acid addition salts such as, for example,

acetate, trifluoroacetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulfonate and *p*-toluenesulfonate. Examples of the alkali addition salts include inorganic salts such as, for example, sodium, potassium, calcium and ammonium salts, and
5 organic alkali salts such as, for example, ethylenediamine, ethanolamine, *N,N*-dialkyl ethanolamine, triethanolamine and basic aminoacids salts.

The compounds of the invention may be in crystalline form either
10 as free compounds or as solvates (e.g. hydrates) and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art.

Any compound that is a prodrug of a compound of formula **I** is
15 within the scope of the invention. The term "prodrug" is used in its broadest sense and encompasses those derivatives that are converted in vivo to the compounds of the invention. Examples of prodrugs include, but are not limited to, derivatives and metabolites of the compounds of formula **I** or **II** that include biohydrolyzable moieties such as
20 biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Preferably, prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by
25 esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by Burger "Medicinal Chemistry and Drug Discovery 6th ed. (Donald J. Abraham ed., 2001, Wiley) and "Design and Applications of Prodrugs" (H. Bundgaard ed., 1985, Harwood Academic Publishers).

30

Any compound referred to herein is intended to represent such specific compound as well as certain variations or forms. In particular,

compounds referred to herein may have asymmetric centres and therefore exist in different enantiomeric or diastereoisomeric forms. Thus any given compound referred to herein is intended to represent any one of a racemate, one or more enantiomeric forms, one or more
5 diastereomeric forms, and mixtures thereof. Likewise, stereoisomerism or geometric isomerism about the double bond is also possible, therefore in some cases the molecule could exist as (*E*)-isomer or (*Z*)-isomer (*trans* and *cis* isomers). If the molecule contains several double bonds, each double bond will have its own stereoisomerism, that could
10 be the same as, or different to, the stereoisomerism of the other double bonds of the molecule. Furthermore, compounds referred to herein may exist as atropoisomers. All the stereoisomers including enantiomers, diastereoisomers, geometric isomers and atropoisomers of the compounds referred to herein, and mixtures thereof, are considered
15 within the scope of the present invention.

Furthermore, any compound referred to herein may exist in isotopically-labelled forms i.e. compounds which differ in the presence of one or more isotopically-enriched atoms. For example, compounds
20 having the present structures except for the replacement of at least one hydrogen atom by deuterium or tritium, or the replacement of at least one carbon by ^{13}C - or ^{14}C -enriched carbon, or the replacement of at least one nitrogen atom by ^{15}N -enriched nitrogen are within the scope of this invention.

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To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about". It is understood that, whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value,
30 and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art,

including equivalents and approximations due to the experimental and/or measurement conditions for such given value.

In compounds of general formula **I**, each R_1 and R_2 is preferably
5 and independently selected from hydrogen, halogen, OR_a , and $OCOR_a$,
wherein R_a is selected from hydrogen and substituted or unsubstituted
 C_1 - C_{12} alkyl. Particularly preferred R_a is hydrogen and substituted or
unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl,
ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-
10 butyl and isobutyl. More preferably, R_1 and R_2 are each independently
selected from hydrogen and halogen, being Cl the most preferred
halogen.

Particular preferred R_3 , R_5 , R_6 , R_{14} , and R_{15} are each
15 independently selected from hydrogen, OR_a , and $OCOR_a$, wherein R_a is
selected from hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl.
Particularly preferred R_a is hydrogen and substituted or unsubstituted
 C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl, ethyl, n-
propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and
20 isobutyl. More preferably R_3 , R_5 , R_6 , R_{14} , and R_{15} are hydrogen.

R_4 is preferably selected from hydrogen and OR_a , wherein R_a is
selected from hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl.
Particularly preferred R_a is hydrogen and substituted or unsubstituted
25 C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl, ethyl, n-
propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and
isobutyl. More preferably, R_4 is OR_a and R_a is hydrogen.

R_7 is preferably selected from hydrogen, OR_a , and $OCOR_a$,
30 wherein R_a is selected from hydrogen and substituted or unsubstituted
 C_1 - C_{12} alkyl. Particularly preferred R_a is hydrogen and substituted or
unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl,

ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl. More preferably, R₇ is hydrogen.

Particularly preferred R₈ and R₉ are each independently selected
 5 from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, OR_a, and
 OCOR_a, wherein R_a is selected from hydrogen and substituted or
 unsubstituted C₁-C₁₂ alkyl. Particularly preferred R_a is hydrogen and
 substituted or unsubstituted C₁-C₆ alkyl; and even more preferred is
 10 hydrogen, methyl, ethyl, n-propyl, isopropyl and butyl, including n-
 butyl, *tert*-butyl, *sec*-butyl and isobutyl. More preferably R₈ and R₉ are
 each a substituted or unsubstituted C₁-C₆ alkyl; and even more
 preferred are methyl, ethyl, n-propyl, isopropyl and butyl, including n-
 butyl, *tert*-butyl, *sec*-butyl and isobutyl; being methyl the most
 preferred.

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R₁₀ is preferably selected from OR_b, OCOR_a, and =O, with the
 proviso that when R₁₀ is =O the hydrogen of the C atom to which R₁₀ is
 attached is absent, and wherein R_a is selected from hydrogen and
 substituted or unsubstituted C₁-C₁₂ alkyl and R_b is selected from
 20 hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, and substituted or
 unsubstituted sugar. Particularly preferred R_a is hydrogen and
 substituted or unsubstituted C₁-C₆ alkyl; and even more preferred is
 hydrogen, methyl, ethyl, n-propyl, isopropyl and butyl, including n-
 butyl, *tert*-butyl, *sec*-butyl and isobutyl. Particularly preferred R_b is
 25 hydrogen, substituted or unsubstituted C₁-C₆ alkyl, monosaccharide,
 disaccharide, and trisaccharide; and even more preferred is hydrogen,
 methyl, ethyl, n-propyl, isopropyl, n-butyl, *tert*-butyl, *sec*-butyl,
 isobutyl, rhamnose, glucose, digitoxose, digitalose, digginose,
 sarmentose, vallarose, and fructose. More preferably, R₁₀ is =O or OR_b,
 30 wherein R_b is methyl.

In one preferred class of the compounds of the invention wherein the ----- line is absent, particularly preferred R_{11} and R_{12} are each independently selected from hydrogen, OR_a , and $OCOR_a$, wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl.

5 Particularly preferred R_a is hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl, ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl.

10 In another preferred class of compounds of the invention wherein either an additional bond or an epoxy group is present in the place indicated with the ----- line, particularly preferred R_{11} and R_{12} are hydrogen.

15 R_{13} is preferably selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, and COR_a , wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl, ethyl, n-propyl, isopropyl
20 and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl. More preferably R_{13} is substituted or unsubstituted C_1 - C_6 alkyl and COR_a , wherein R_a is hydrogen and substituted or unsubstituted C_1 - C_6 alkyl. Even more preferred R_{13} is a substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted
25 propyl, and COR_a , wherein R_a is hydrogen. Preferred substituents of methyl, ethyl, and propyl are OR' wherein R' is hydrogen or $COalkyl$, being hydrogen the most preferred R' .

R_{16} is preferably selected from hydrogen, OR_a , and $OCOR_a$,
30 wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl,

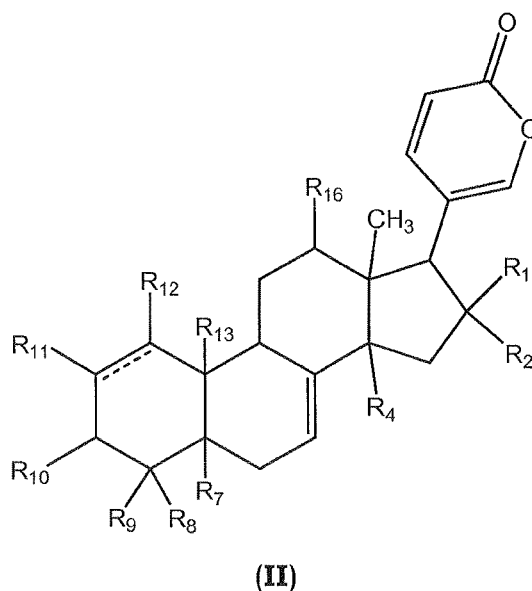
ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl. More preferably R_{16} is hydrogen or OR_a , wherein R_a is hydrogen.

5 Particularly preferred R_{17} is substituted or unsubstituted C_1 - C_{12} alkyl. More preferably is a substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred is methyl, ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl. Methyl is the most preferred R_{17} .

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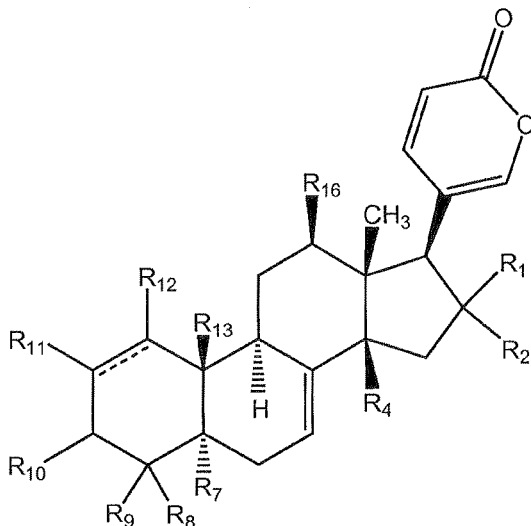
Particularly preferred is the presence of an additional bond or an epoxy group in the place indicated with the ----- line.

More particularly, the invention provides compounds of general
15 formula **II** or pharmaceutically acceptable salts, prodrugs or stereoisomers thereof



20 wherein R_1 , R_2 , R_4 , R_7 , R_8 - R_{13} , R_{16} and the ----- line have the same meaning given above.

Particularly preferred stereochemistry of said compounds of general formula **II** is the following:



- 5 In compounds of general formula **II**, each R₁ and R₂ is preferably and independently selected from hydrogen, halogen, OR_a, and OCOR_a, wherein R_a is selected from hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C₁-C₆ alkyl; and even more preferred is hydrogen, methyl,
10 ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl. More preferably, R₁ and R₂ are each independently selected from hydrogen and halogen, being Cl the most preferred halogen.
- 15 R₄ is preferably selected from hydrogen and OR_a, wherein R_a is selected from hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C₁-C₆ alkyl; and even more preferred is hydrogen, methyl, ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and
20 isobutyl. More preferably, R₄ is OR_a and R_a is hydrogen.

R₇ is preferably selected from hydrogen, OR_a, and OCOR_a, wherein R_a is selected from hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C₁-C₆ alkyl; and even more preferred is hydrogen, methyl, ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl. More preferably, R₇ is hydrogen.

Particularly preferred R₈ and R₉ are each independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, OR_a, and OCOR_a, wherein R_a is selected from hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C₁-C₆ alkyl; and even more preferred is hydrogen, methyl, ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl. More preferably R₈ and R₉ are each a substituted or unsubstituted C₁-C₆ alkyl; and even more preferred are methyl, ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl; being methyl the most preferred.

R₁₀ is preferably selected from OR_b, and OCOR_a, and =O, with the proviso that when R₁₀ is =O the hydrogen of the C atom to which R₁₀ is attached is absent, and wherein R_a is selected from hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl and R_b is selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, and substituted or unsubstituted sugar. Particularly preferred R_a is hydrogen and substituted or unsubstituted C₁-C₆ alkyl; and even more preferred is hydrogen, methyl, ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl. Particularly preferred R_b is hydrogen, substituted or unsubstituted C₁-C₆ alkyl, monosaccharide, disaccharide, and trisaccharide; and even more preferred is hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, *tert*-butyl, *sec*-butyl, isobutyl, rhamnose, glucose, digitoxose, digitalose, digginose,

sarmentose, vallarose, and fructose. More preferably, R_{10} is $=O$ or OR_b , wherein R_b is methyl.

In one preferred class of the compounds of the invention wherein
5 the ----- line is absent, particularly preferred R_{11} and R_{12} are each independently selected from hydrogen, OR_a , and $OCOR_a$, wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl, ethyl, n-
10 propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl.

In another preferred class of compounds of the invention wherein either an additional bond or an epoxy group is present in the place
15 indicated with the ----- line, particularly preferred R_{11} and R_{12} are hydrogen.

R_{13} is preferably selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, and COR_a , wherein R_a is selected from
20 hydrogen and substituted or unsubstituted C_1 - C_{12} alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C_1 - C_6 alkyl; and even more preferred is hydrogen, methyl, ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl. More preferably R_{13} is substituted or unsubstituted C_1 - C_6 alkyl and COR_a ,
25 wherein R_a is hydrogen and substituted or unsubstituted C_1 - C_6 alkyl. Even more preferred R_{13} is a substituted or unsubstituted methyl, substituted or unsubstituted ethyl, substituted or unsubstituted propyl, and COR_a , wherein R_a is hydrogen. Preferred substituents of methyl, ethyl, and propyl are OR' wherein R' is hydrogen or $COalkyl$,
30 being hydrogen the most preferred R' .

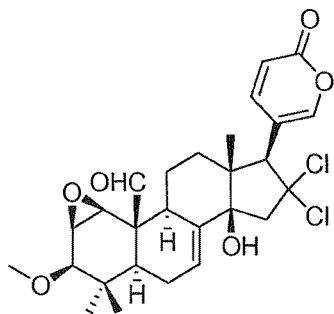
R₁₆ is preferably selected from hydrogen, OR_a, and OCOR_a, wherein R_a is selected from hydrogen and substituted or unsubstituted C₁-C₁₂ alkyl. Particularly preferred R_a is hydrogen and substituted or unsubstituted C₁-C₆ alkyl; and even more preferred is hydrogen, methyl, ethyl, n-propyl, isopropyl and butyl, including n-butyl, *tert*-butyl, *sec*-butyl and isobutyl. More preferably R₁₆ is hydrogen or OR_a, wherein R_a is hydrogen.

Particularly preferred is the presence of an additional bond or an epoxy group in the place indicated with a ----- line.

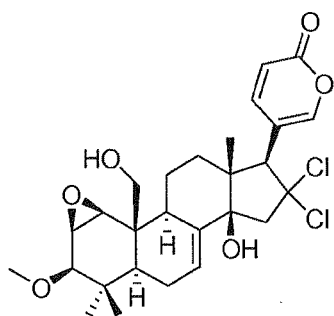
In the present description and definitions, when there are several substituents R_a present in the compounds of the invention, and unless it is stated explicitly so, it should be understood that they can be each independently different within the given definition, i.e. R_a does not represent necessarily the same group simultaneously in a given compound of the invention.

In the previous paragraphs preferences for the substituent groups R₁ to R₁₇ and the dotted line are defined. It should also be understood that the different combinations of these preferences are also preferred within the compounds of the invention.

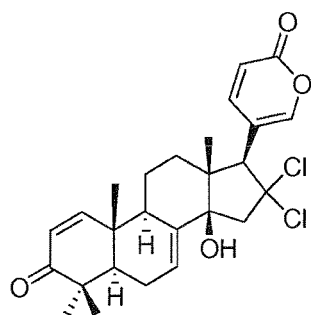
Particularly preferred compounds of the invention are the following:



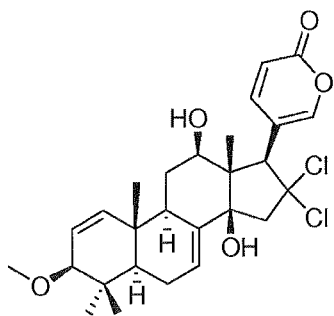
Aegomycin A



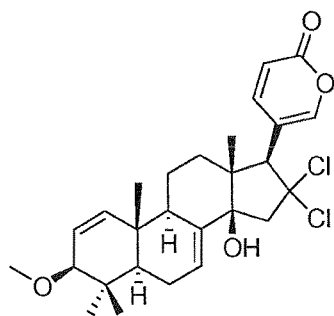
Aegomycin B



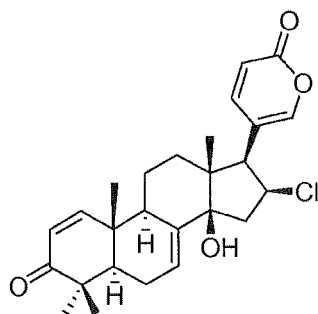
Aegomycin C



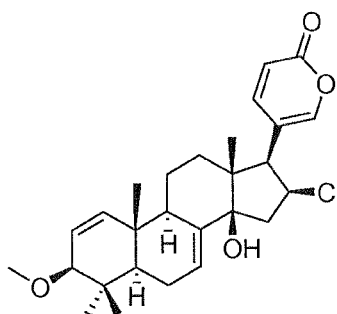
Aegomycin D



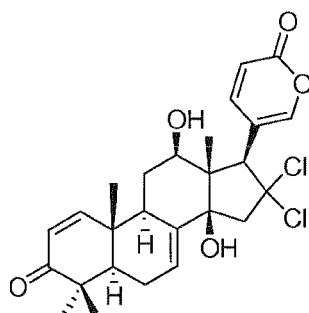
Aegomycin E



Aegomycin F



Aegomycin G



Aegomycin H

- 5 or pharmaceutically acceptable salts, prodrugs or stereoisomers thereof.
The stereochemistry indicated here for Aegomycins A-H is relative.

Aegomycins A-H were isolated from a porifera of the family Mycalidae, genus *Mycale*, subgenus *Aegogropila*, species *Mycale*
10 (*Aegogropila*) *crassissima* (Dendy, 1905). A sample of *Mycale* (*Aegogropila*) *crassissima* (Dendy, 1905) was deposited at the Institute of Marine Sciences and Limnology of the Universidad Nacional Autónoma of Mexico, with the reference code MFIA-399. This sponge
15 S / 39° 55.043' E) at depths ranging between 5 and 31.4 m.

The description of the sponge is the following: The specimens examined were thinly encrusting growing on rocks. The colour of live specimens was brown, although they have also been described as orange or ochre. Spicule complement: Megascleres were straight
5 subtylostyles, often with hardly perceptible tyle, and usually slightly bent in the middle. They had about 270 μm of mean length, about 4.6 μm of shaft width and about 4.8 μm of tyle width. Microscleres included palmate anisochelae (three size classes: Anisochela 1 of about 36 μm in average, anisochela 2 of about 27 μm in average, and anisochela 3 of
10 about 11 μm in average), sigmas (one class: Robust sigma of about 57 μm in average), and raphides (very scarce). Skeletal arrangement: Tracts of subtylostyles ascended outwards from the basal plate and terminated at the surface in slight tufts or brushes. Ectosome had a well developed reticulation of bundles of mycalostyles and microscleres were strewn at
15 random in both choanosome and ectosome. The anisochelae did not form rosettes. *Mycale crassissima* is common in the collected area of Mafia Island and has also been found in Mombassa, Zanzibar, Madagascar, Ceylon, and Arafura Sea, on rocks and coral reefs, from 1 to 60 m depth.

20

Additionally, compounds of the invention can be obtained by synthesis following usual procedures in synthetic organic chemistry and already known by a person skilled in the art. For example, compounds of this invention can be obtained adapting the procedures described in
25 the literature such as in Steyn et al. Nat. Prod. Rep. 1998, 15, 397-413; Huimin Gao et al in Nat. Prod. Rep., 2011, 28, 953; WO 01/79256; WO 2006/120472; and CA 2.418.458. The synthetic routes can use combinations of steps taken from more than one of these references.

30 Likewise, natural, synthetic or already modified compounds of the invention can be further modified by a variety of chemical reaction to obtain additional compounds of the invention. Thus, hydroxyl groups

can be acylated by standard coupling or acylation procedures, for instance by using acetic acid or acetic anhydride in pyridine or the like. Formate groups can be obtained by heating hydroxyl precursors in formic acid. Hydroxy groups can also be oxidized to oxo (=O), for instance, by using manganese dioxide or chromium, or converted into amino-lower alkoxy, for instance, by using a protected 2-bromoethylamine. Carboxy groups can be alkylated, for instance, methylated by treatment with diazomethane. Glycosidic moieties can be introduced by standard sugar coupling reactions.

10

An important feature of the above described compounds of formula **I** and **II** is their bioactivity and in particular their cytotoxic activity.

15

With this invention we provide novel pharmaceutical compositions of compounds of general formula **I** and **II** that possess cytotoxic activity and their use as anticancer agents. Thus the present invention further provides pharmaceutical compositions comprising a compound of this invention, or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof with a pharmaceutically acceptable carrier.

20

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules etc.) or liquid (solutions, suspensions or emulsions) composition for oral, topical or parenteral administration.

25

Administration of the compounds or compositions of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, and intraperitoneal and intravenous administration. We prefer that infusion times of up to 24 hours are used, more preferably 1-12 hours, with 1-6 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be 12 to 24

30

hours or even longer if required. Infusion may be carried out at suitable intervals of say 1 to 4 weeks. Pharmaceutical compositions containing compounds of the invention may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by
5 other standard delivery means.

The correct dosage of the compounds will vary according to the particular formulation, the mode of application, and the particular situs, host and tumour being treated. Other factors like age, body
10 weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

15 As used herein, the terms "treat", "treating" and "treatment" include the eradication, removal, modification, or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer.

20 The compounds of the invention have activity against cancers including, but not limited, lung cancer, colon cancer, and breast cancer.

EXAMPLES

25

EXAMPLE 1: DESCRIPTION OF THE MARINE ORGANISM AND COLLECTION SITE

Mycale (Aegogropila) crassissima (Dendy, 1905) was collected by hand
30 using SCUBA diving in Mafia Island (07° 39.558' S / 39° 55.043' E) at depths ranging between 5 and 31.4 m. The animal material was identified by Dr. José Luis Carballo (Universidad Nacional Autónoma of

Mexico). A sample of the specimen was deposited at the Institute of Marine Sciences and Limnology of the Universidad Nacional Autónoma de Mexico, with the reference code MFIA-399.

5

EXAMPLE 2: ISOLATION OF AEGOMYCINS A AND B

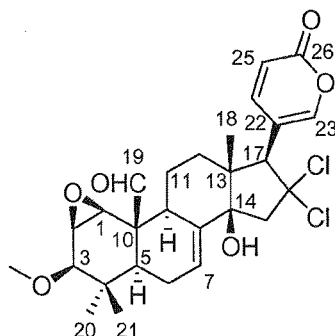
The frozen specimen of Example 1 (67 g) was triturated and extracted with H₂O and a mixture of MeOH:CH₂Cl₂ (50:50) at 23 °C. The
10 organic extract was evaporated under reduced pressure to yield a crude of 500 mg. This material was chromatographed (VLC) on Lichroprep RP-18 with a stepped gradient from H₂O to MeOH and CH₂Cl₂. Two fractions obtained from this chromatography were further purified as described below. The fraction eluted with H₂O:MeOH 1:3 (23 mg) was
15 subjected to semipreparative reversed phase HPLC (Symmetry Prep C18, 7.8 x 150 mm, gradient H₂O:MeCN from 60 to 75% of MeCN in 10 min then 75 to 100% of MeCN in 10 min, UV detection, flow 2.3 mL/min) to yield Aegomycin A (0.6 mg). The fraction eluted with MeOH (83 mg) was subjected to semipreparative reversed phase HPLC
20 (Symmetry Prep C18, 7.8 x 150 mm, gradient H₂O:MeCN from 50 to 75% of MeCN in 30 min, UV detection, flow 2.3 mL/min) to yield Aegomycin A (1.8 mg) and Aegomycin B (0.8 mg).

Aegomycin A: amorphous white solid. (+)HRMALDIMS m/z
25 523.1622 [M+H]⁺ (Calcd. for C₂₇H₃₃³⁵Cl₂O₆ 523.1649); ¹H (500 MHz) and ¹³C NMR (75 MHz) in CDCl₃ see Table 1

Aegomycin B: amorphous white solid. (+)HRMALDIMS m/z
525.1788 [M+H]⁺ (Calcd. for C₂₇H₃₅³⁵Cl₂O₆ 525.1805); ¹H (500 MHz) and
30 ¹³C NMR (75 MHz) in CD₃OD see Table 2.

Table 1. ^1H and ^{13}C NMR data of Aegomycin A (CDCl_3).

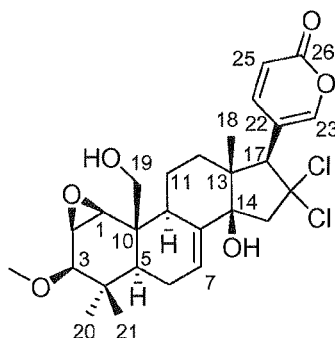
N°	^1H , m, J (Hz)	^{13}C , m	HMBC	ROESY
1	3.74, d (3.8)	54.3, d	C5,C9,C10,C19	H2,H11a
2	3.25, d (3.8)	55.7, d	C3,C4	OMe,H1,H3
3	2.88, s	84.4, d	C1,C2,C4, C20,C21,OMe	OMe,H2,H5,H20
4	-	36.7, s	-	-
5	1.51, dd (10.6, 7.8)	41.0, d	C4,C9,C10, C6,C19,C21	H3,H6,H9,H20
6	2.40, m	22.7, t	C7	H5,H7,H19,H20,H21
7	6.19, m	122.8, d	-	H6,14-OH
8	-	137.5, s	-	-
9	2.62, m	41.1, d	-	H5,H11a,H12a,H15a
10	-	49.8, s	-	-
11a	1.90, m	22.7, t	C8	H1,H9,H11b
11b	1.25, m		C9	H11a,H12b,H18,H19
12a	1.89, m	39.3, t	C13,C14,C15,C18	H9,H12b,H15a,H17
12b	1.72, m		C13	H11b,H12a,H17,H18
13	-	51.0, s	-	-
14	-	83.8, s	-	-
14-OH	1.87, m	-	C14	H7,H18
15a	3.47, d (15.8)	62.0, t	C13,C14,C16	H9,H12a,H15b
15b	2.81, d (15.8)		C13,C14,C16,C17	H15a
16	-	92.5, s	-	-
17	3.46, s	71.2, d	C12,C13,C16, C22,C23,C24	H12a,H12b,H23
18	0.74, s	16.5, q	C12,C13,C14,C17	H11b,H12b,H24,14-OH
19	9.87, s	205.6, d	C1,C10	H6,H11b,H21
20	0.94, s	25.0, q	C3,C4,C5,C21	OMe,H3,H5,H6,H21
21	0.66, s	16.2, q	C3,C4,C5,C20	H6,H19,H20
22	-	116.7, s	-	-
23	7.33, d (2.7)	151.0, d	C17,C22,C24	H17
24	8.00, dd (9.9, 2.7)	147.9, d	C26	H18,H25
25	6.28, d (9.9)	113.9, d	C22,C26	H24
26	-	161.4, s	-	-
OMe	3.51, s	58.3, q	C3	H2,H3,H20



Aegomycin A

Table 2. ^1H and ^{13}C NMR data of Aegomycin B (CD_3OD).

N°	^1H , m, J (Hz)	^{13}C , m	HMBC	ROESY
1	3.74, d (3.7)	56.6, d	C5,C10	H2,H11
2	3.18, d (3.7)	57.5, d	C3,C4	OMe,H1,H3
3	2.85, s	87.0, d	OMe,C1,C2,C4,C5, C20,C21	OMe,H2,H5,H20
4	-	37.6, s	-	-
5	1.05, dd (12.4, 5.0)	43.2, d	C3,C4,C6,C9,C10, C19,C21	H3,H9,H20
6	1.99, m	22.7, t	C7, C8	H7,H20
7	6.05, m	124.6, d	-	H6
8	-	139.6, s	-	-
9	2.42, m	46.1, d	-	H5,H15a
10	-	40.0, s	-	-
11	1.90, m	23.5, t	C12	H1,H18
12	1.79, m	40.7, t	C11	H17,H18
13	-	52.6, s	-	-
14	-	84.7, s	-	-
15a	3.43, d (15.8)	64.1, t	C8,C13,C14,C16	H9,H15b
15b	2.76, d (15.8)		C14,C16,C17	H15a
16	-	94.9, s	-	-
17	3.61, s	72.8, d	C12,C13,C14,C16, C22,C24,C25	H12,H23
18	0.79, s	17.3, q	C12,C13,C14,C17	H11,H12,H24
19a	3.98, d (12.1)	60.7, t	C1,C5,C9,C10	H19b,H21
19b	3.75, d (12.1)		C1,C5,C9,C10	H19a
20	0.89, s	26.4, q	C3,C4,C5,C21	H3,H5,H6
21	0.92, s	17.3, q	C3,C4,C5,C20	H19a
22	-	119.8, s	-	-
23	7.57, d (2.2)	152.9, d	C17,C22,C24,C26	H17
24	8.30, dd (9.8, 2.2)	151.5, d	C23,C26	H18,H25
25	6.28, d (9.8)	113.7, d	C22,C26	H24
26	-	164.1, s	-	-
OMe	3.49, s	58.4, q	C3	H2,H3



Aegomycin B

5 EXAMPLE 3: ISOLATION OF AEGOMYCINS C, D, E, F AND G

A second group of samples of the specimen of Example 1 (160 g) was triturated and extracted with H₂O and a mixture of MeOH:CH₂Cl₂ (50:50) at 23 °C. The organic extract was evaporated under reduced pressure to yield a crude of 3.12 g. This material was chromatographed (VLC) on Lichroprep RP-18 with a stepped gradient from H₂O to MeOH and CH₂Cl₂. Two fractions obtained from this chromatography were further purified as described below. The fraction eluted with H₂O:MeOH 1:3 (122 mg) was subjected to semipreparative reversed phase HPLC (Symmetry Prep C18, 7.8 x 150 mm, gradient H₂O:MeCN from 45 to 65% of MeCN in 30 min, UV detection, flow 2.3 mL/min) to yield Aegomycin F (2.6 mg) and a mixture of other Aegomycin compounds (5.1 mg). This mixture was further purified by semipreparative HPLC (X Terra Phenyl, 10 x 150 mm, gradient H₂O:MeCN from 45 to 60% of MeCN in 30 min, UV detection, flow 2.3 mL/min) to yield Aegomycin C (0.5 mg) and D (2.8 mg). The fraction eluted with MeOH (230 mg) was subjected to flash Silica gel CC eluting with a gradient of hexane:EtOAc to yield 11 fractions (S1 to S11). Fractions S6 (hexane:EtOAc 70:30) and S7 (hexane:EtOAc 60:40) were subjected to semipreparative reversed phase HPLC (X Terra Phenyl, 10 x 150 mm, gradient H₂O:MeCN from 50 to 55% of MeCN in 30 min, UV detection, flow 3.0 mL/min) to yield

Aegomycin E (1.3 mg) from S6 and Aegomycin G (0.3 mg) from S7.

Aegomycin C: amorphous white solid. (+)HRMALDIMS m/z 477.1581 $[M+H]^+$ (Calcd. for $C_{26}H_{31}^{35}Cl_2O_4$ 477.1594); 1H (500 MHz) and ^{13}C NMR (75 MHz) in CD_3OD see Table 3.

Aegomycin D: amorphous white solid. (+)HRMALDIMS m/z 509.1834 $[M+H]^+$ (Calcd. for $C_{27}H_{35}^{35}Cl_2O_5$ 509.1856); 1H (500 MHz) and ^{13}C NMR (125 MHz) in CD_3OD see Table 4.

Aegomycin E: amorphous white solid. (+)HRMALDIMS m/z 493.1898 $[M+H]^+$ (Calcd. for $C_{27}H_{35}^{35}Cl_2O_4$ 493.1907); 1H (500 MHz) and ^{13}C NMR (75 MHz) in CD_3OD see Table 5.

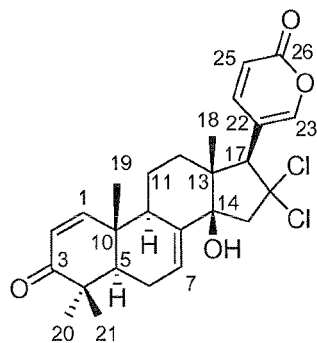
Aegomycin F: amorphous white solid. (+)HRMALDIMS m/z 443.1997 $[M+H]^+$ (Calcd. for $C_{26}H_{32}^{35}ClO_4$ 443.1984); 1H (500 MHz) and ^{13}C NMR (75 MHz) in CD_3OD see Table 6.

Aegomycin G: amorphous white solid. (+)HRMALDIMS m/z 459.2306 $[M+H]^+$ (Calcd. for $C_{27}H_{36}^{35}ClO_4$ 459.2297); 1H (500 MHz) and ^{13}C NMR (75 MHz) in CD_3OD see Table 7.

Table 3. 1H and ^{13}C NMR data of Aegomycin C (CD_3OD).

N°	1H , δ , J (Hz)	^{13}C , δ	HMBC	ROESY
1	7.12, d (10.3)	157.2, d	C3,C5,C10	H2,H11a
2	5.91, d (10.3)	124.4, d	C4,C10	H1
3	-	206.7, s	-	-
4	-	44.9, s	-	-
5	1.85, m	48.9, d	C4,C6,C10,C19	H6,H9,H20
6	2.17, m	24.0, t	-	H5,H7,H9,H20
7	6.15, m	124.4, d	C5,C14	H6
8	-	138.4, s	-	-
9	2.21, m	46.9, d	-	H5,H6,H15a
10	-	38.9, s	-	-
11a	1.87, m	21.9, t	C19	H1,H11b

N°	¹ H, m, J (Hz)	¹³ C, m	HMBC	ROESY
11b	1.54, dddd (13.7, 13.7, 13.7, 3.4)		-	H11a,H12b,H18,H19
12a	1.96, ddd (13.7, 13.7, 3.5)	40.3, t	-	H12b,H15a,H17
12b	1.79, ddd (13.7, 3.4, 3.4)		C18	H11b,H12a,H17,H18
13	-	52.4, s	-	-
14	-	84.7, s	-	-
15a	3.44, d (16.1)	63.6, t	C8,C13,C14,C16	H9,H12a,H15b
15b	2.78, d (16.1)		C14,C16,C17	H15a
16	-	94.9, s	-	-
17	3.62, s	72.5, d	C12,C13,C14,C16, C22,C23	H12a,H12b,H23
18	0.77, s	17.2, q	C12,C13,C14,C17	H11b,H12b
19	1.07, s	14.9, q	C1,C5,C9,C10	H11b,H21
20	1.15, s	24.0, q	C3,C4,C5,C21	H5,H6
21	1.13, s	22.5, q	C3,C4,C5,C20	H19
22	-	119.7, s	-	-
23	7.58, d (2.2)	152.9, d	C22,C24,C26	H17
24	8.32, dd (10.3, 2.2)	151.4, d	C23,C26	H25
25	6.29, d (10.3)	113.7, d	C22,C26	H24
26	-	164.1, s	-	-

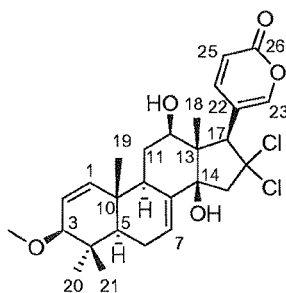


Aegomycin C

Table 4. ¹H and ¹³C NMR data of Aegomycin D (CD₃OD).

N°	¹ H, m, J (Hz)	¹³ C, m	HMBC	ROESY
1	5.82, dd (10.7, 2.4)	135.3, d	C3,C5	H2,H11a,H19
2	5.67, dd (10.7, 1.0)	126.5, d	-	H1,OMe
3	3.40, m	87.3, d	OMe,C1,C2, C4,C20,C21	H5,H20
4	-	37.7, s	-	-
5	1.45, dd (11.9, 4.2)	49.2, d	C3,C4,C6,C9, C10,C19,C21	H3,H9,H20
6a	2.14, m	23.4, t	C7,C8	H6b,H7,H20
6b	2.04, m		-	H6a,H19,H21

N°	^1H , m, J (Hz)	^{13}C , m	HMBC	ROESY
7	6.12, m	125.9, d	C5,C9,C14	H6a
8	-	137.9, s	-	-
9	2.08, m	46.8, d	C8,C10	H5,H11a,H12,H15a
10	-	38.4, s	-	-
11a	1.83, ddd (12.7, 4.4, 4.2)	30.3, t	C8,C9,C12,C13	H1,H9,H12,H11b
11b	1.53, ddd (12.7, 12.7, 11.9)		C9,C10,C12,C13	H11a,H18,H19
12	3.84, dd (11.9, 4.2)	74.9, d	C17,C18	H9,H11a,H15a,H17
13	-	58.3, s	-	-
14	-	85.0, s	-	-
15a	3.28, d (16.1)	64.0, t	C8,C14,C16	H9,H12,H15b
15b	2.80, d (16.1)		C13,C14,C16,C17	H15a
16	-	95.1, s	-	-
17	4.15, s	68.2, d	C12,C13,C14,C16, C22,C23,C24	H12,H18,H23
18	0.65, s	10.5, q	C12,C13,C14,C17	H11b,H17,H19,H24
19	0.92, s	15.3, q	C1,C5,C9,C10	H1,H6b,H11b,H18,H21
20	0.99, s	26.6, q	C3,C4,C5,C21	H3,H5,H6a,H21
21	0.85, s	17.2, q	C3,C4,C5,C20	H6b,H19,H20
22	-	120.0, s	-	-
23	7.54, d (2.9)	156.0, d	C22,C24,C26	H17
24	8.27, dd (9.8, 2.9)	151.6, d	C23,C26	H18,H25
25	6.28, d (9.8)	113.7, d	C22,C26	H24
26	-	164.1, s	-	-
OMe	3.41, s	58.3, q	C3	H2

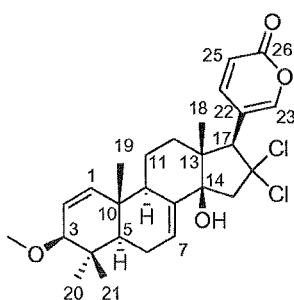


Aegomycin D

Table 5. ^1H and ^{13}C NMR data of Aegomycin E (CD_3OD).

N°	^1H , m, J (Hz)	^{13}C , m	HMBC	ROESY
1	5.83, dd (10.5, 2.3)	135.7, d	C2,C5,C9	H2,H11a,H19
2	5.65, dd (10.5, 1.5)	126.2, d	C4	H1,H3
3	3.40, m	87.3, d	C1	H2,H5,H20
4	-	37.7, s	-	-
5	1.42, dd (12.0, 4.5)	48.9, d	C19	H3,H9,H20
6a	2.12, m	23.4, t	-	H6b,H7,H20
6b	2.01, m			H6a,H19,H21

Nº	¹ H, m, J (Hz)	¹³ C, m	HMBC	ROESY
7	6.11, br d (5.6)	125.2, d	C5,C14	H6a
8	-	139.0, s	-	-
9	2.02, m	49.1, d	-	H5,H15a
10	-	38.6, s	-	-
11a	1.71, m	21.9, t	-	H1,H11b
11b	1.51, dddd (13.8, 13.7, 13.7, 3.4)			H11a,H18,H19
12a	1.90, ddd (13.7, 13.7, 3.4)	40.5, t	-	H12b,H15a,H17
12b	1.74, m			H12a,H17
13	-	52.5, s	-	-
14	-	84.8, s	-	-
15a	3.43, d (15.6)	63.9, t	C16	H9,H12a,H15b
15b	2.76, d (15.6)		C14,C16,C17	H15a
16	-	95.0, s	-	-
17	3.59, s	72.6, d	C14,C16,C22, C23,C24	H12a,H12b,H23
18	0.74, s	17.2, q	C12,C13, C14,C17	H11b,H24
19	0.91, s	15.3, q	C1,C5,C9,C10	H1,H6b,H11b,H21
20	0.99, s	26.7, q	C3,C4,C5,C21	H3,H5,H6a,H21
21	0.85, s	17.2, q	C3,C4,C5,C20	H6b,H19,H20
22	-	119.7, s	-	-
23	7.57, d (2.4)	152.8, d	C22	H17
24	8.31, dd (9.8, 2.4)	151.5, d	-	H18,H25
25	6.28, d (9.8)	113.7, d	C22,C26	H24
26	-	164.1, s	-	-
OMe	3.41, s	58.3, q	C3	-

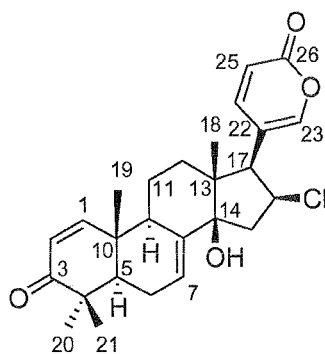


Aegomycin E

5 Table 6. ¹H and ¹³C NMR data of Aegomycin F (CD₃OD).

Nº	¹ H, m, J (Hz)	¹³ C, m	HMBC	ROESY
1	7.10, d (10.3)	157.5, d	C3,C5,C6, C9,C10,C19	H2,H11a,H19
2	5.88, d (10.3)	126.1, d	C4,C10,C19	H1
3	-	206.8, s	-	-

Nº	¹ H, m, J (Hz)	¹³ C, m	HMBC	ROESY
4	-	45.0, s	-	-
5	1.83, dd (12.1, 4.2)	48.5, d	C4,C6,C9, C19,C20,C21	H6,H9,H20
6	2.18, m	23.9, t	C7,C8	H5,H7,H19,H20,H21
7	6.13, br d (5.0)	123.0, d	C5,C6,C14	H6
8	-	140.0, s	-	-
9	2.14, m	47.3, d	C7,C8,C10	H5,H11a,H12b,H15a
10	-	38.5, s	-	-
11a	1.79, m	21.8, t	C8,C9,C12,C13	H1,H9,H11b
11b	1.48, dddd (12.6, 12.6, 12.6, 3.9)		C9,C12	H11a,H18,H19
12a	1.65, ddd (13.7, 3.9, 3.9)	39.5, t	C9,C11,C13,C14,C18	H12b,H17,H18
12b	1.59, ddd (13.7, 12.6, 3.0)		C11,C13	H9,H12a,H17
13	-	52.0, s	-	-
14	-	84.7, s	-	-
15a	3.00, dd (16.0, 9.5)	52.2, t	C8,C16	H9,H15b,H16
15b	2.01, dd (16.0, 2.9)		C13,C14,C16,C17	H15a
16	4.90, ddd (9.5, 9.5, 2.9)	60.3, d	C14,C22	H15a,H17
17	3.12, d (9.5)	58.9, d	C12,C13,C14,C15, C16,C23,C24	H12a,H12b,H16, H18,H23
18	0.76, s	17.6, q	C12,C13,C14,C17	H11b,H12a,H17, H23,H24
19	1.05, s	14.9, q	C1,C5,C9,C10	H1,H6,H11b,H21
20	1.13, s	25.5, q	C3,C4,C5,C21	H5,H6
21	1.11, s	22.5, q	C3,C4,C5,C20	H6,H19
22	-	121.2, s	-	-
23	7.46, d (2.3)	152.4, d	C17,C22,C24,C26	H17,H18
24	8.36, dd (9.8, 2.3)	153.3, d	C23,C26	H18,H25
25	6.22, d (9.8)	112.8, d	C22,C26	H24
26	-	164.6, s	-	-

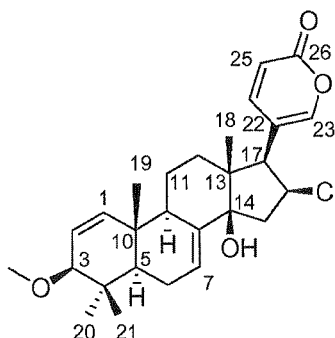


Aegomycin F

Table 7. ^1H and ^{13}C NMR data of Aegomycin G (CD_3OD).

N°	^1H , m, J (Hz)	^{13}C , m	HMBC	ROESY
1	5.81, br d (10.4)	136.0, d	C3	H2,H11a,H19
2	5.62, d (10.4)	120.0, d	C4,C10	H1,H3,OMe
3	3.67, br s	87.4, d	OMe,C1,C2, C4,C20,C21	H2,H5,H20
4	-	37.7, s	-	-
5	1.40, dd (12.0, 4.3)	49.4, d	-	H3,H6a,H9,H20
6a	2.07, m	23.7, t	-	H5,H7,H20
6b	1.99, m			H7,H21
7	6.08, br d (5.4)	123.8, d	C14	H6a,H6b
8	-	140.6, s	-	-
9	1.99, m	49.0, d	-	H5,H15a
10	-	38.6, s	-	-
11a	1.62, m	21.8, t	-	H1,H11b
11b	1.45, dddd (12.6, 12.6,12.6, 4.1)			H11a,H18,H19
12a	1.58, m	39.7, t	-	H17
12b	1.54, m			H15a,H17
13	-	52.0, s	-	-
14	-	85.0, s	-	-
15a	2.97, dd (15.7, 9.6)	52.3, t	C17	H9,H12b,H15b,H16
15b	2.00, dd (15.7, 3.0)		-	H15a
16	4.89, ddd (9.6, 9.5, 3.0)	60.3, d	-	H15a,H17
17	3.09, d, (9.5)	59.0, d	C12,C13,C14, C22,C24	H12a,H12b,H16, H23
18	0.73, s	17.6, q	C12,C13,C14, C17	H11b,H24
19	0.90, s	15.4, q	C1,C5,C9,C10	H1,H11b
20	0.97, s	26.7, q	C4,C5,C3,C21	H3,H5,H6a
21	0.83, s	17.2, q	C4,C5,C3,C20	H6b
22	-	121.3, s	-	-
23	7.45, d (2.5)	152.3, d*	C22,C24,C26	H17
24	8.36, dd (9.9, 2.5)	152.3, d*	-	H18,H25
25	6.21, d (9.9)	112.7, d	C22,C26	H24
26	-	164.7, s	-	-
OMe	3.39, s	58.3, q	C3	H2

*Assignments may be interchanged



Aegomycin G

EXAMPLE 4: ISOLATION OF AEGOMYCIN D, F AND H

5 A third group of samples of the specimen of Example 1 (700 g) was triturated and extracted with H₂O and a mixture of MeOH:CH₂Cl₂ (50:50) at 23 °C. The organic extract was evaporated under reduced pressure to yield a crude of 33 g. The crude was dissolved in MeOH:H₂O (1:9, 500 mL) and extracted with Hexane (3 x 500 mL), EtOAc (3 x 500 mL) and nBuOH (2 x 500 mL).

The Hexane fraction (4 g) was chromatographed (VLC) on Lichroprep RP-18 with a stepped gradient from H₂O:MeOH (3:1) to MeOH and then to CH₂Cl₂. The fraction eluted with H₂O:MeOH 1:3 (430 mg) was subjected to preparative reversed phase HPLC (Symmetry Prep C18, 19 x 150 mm, gradient H₂O:MeCN from 45 to 65% of MeCN in 30 min, UV detection, flow 14.6 mL/min) to yield 7 fractions (H1 to H7). Fraction H4 was subjected to semipreparative reversed phase HPLC (X Terra Phenyl, 10 x 150 mm, gradient H₂O:MeCN from 30 to 50% of MeCN in 30 min, UV detection, flow 3.8 mL/min) to yield Aegomycin F (8.3 mg). Fraction H5 was subjected to semipreparative reversed phase HPLC (X Terra Phenyl, 10 x 150 mm, gradient H₂O:MeCN from 45 to 60% of MeCN in 30 min, UV detection, flow 3.8 mL/min) to yield Aegomycin D (20.4 mg).

25

The EtOAc fraction (1.2 g) was chromatographed (VLC) on

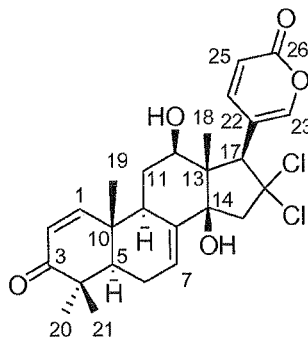
Lichroprep RP-18 with a stepped gradient from H₂O:MeOH (3:1) to MeOH and then to CH₂Cl₂. The fraction eluted with H₂O:MeOH 1:3 (162 mg) was subjected to preparative reversed phase HPLC (Symmetry Prep C18, 19 x 150 mm, gradient H₂O:MeCN from 45 to 65% of MeCN in 30 min, UV detection, flow 14.6 mL/min) to yield 7 fractions (H1 to H7). Fraction H2 was subjected to semipreparative reversed phase HPLC (X Terra Phenyl, 10 x 150 mm, gradient H₂O:MeCN from 30 to 55% of MeCN in 30 min, UV detection, flow 3.8 mL/min) to yield Aegomycin H (1.4 mg). Fraction H4 was subjected to semipreparative reversed phase HPLC (X Terra Phenyl, 10 x 150 mm, gradient H₂O:MeCN from 30 to 50% of MeCN in 20 min, UV detection, flow 3.8 mL/min) to yield Aegomycin F (12.2 mg). Fraction H5 was subjected to semipreparative reversed phase HPLC (X Terra Phenyl, 10 x 150 mm, gradient H₂O:MeCN from 45 to 60% of MeCN in 30 min, UV detection, flow 3.8 mL/min) to yield Aegomycin D (21.7 mg).

Aegomycin H: amorphous white solid. (+)ESIMS m/z 493 [M+H]⁺, ¹H (500 MHz) and ¹³C NMR (75 MHz) in CD₃OD see Table 8.

Table 8. ¹H and ¹³C NMR data of Aegomycin H (CD₃OD).

N°	¹ H, δ , J (Hz)	¹³ C, δ	HMBC	ROESY
1	7.10, d (10.3)	156.7, d	C3,C4,C5, C9,C10,C19	H2,H9, H11a,H19
2	5.91, d (10.3)	126.4, d	C4,C10	H1
3	-	206.5, s	-	-
4	-	45.0, s	-	-
5	1.89, dd (11.7, 4.5)	48.5, d	C4,C6,C7, C9,C10,C19	H9,H20
6	2.19, m	24.0, t	C8	H7,H19, H20,H21
7	6.15, m	125.1, d	C5,C14	H6
8	-	137.3, s	-	-
9	2.27, m	44.6, d		H1,H5,H11a, H12,H15a
10	-	38.6, s	-	-
11a	1.95, ddd (12.6, 4.2, 4.2)	30.2, t	C8,C9,C12,C13	H1,H9,H11b,H12

N°	¹ H, m, J (Hz)	¹³ C, m	HMBC	ROESY
11b	1.55, ddd (12.6, 12.6, 12.6)		C8,C9,C10,C12,C13	H11a,H18,H19
12	3.89, dd (12.6, 4.2)	74.7, d	C17,C18	H9,H11a, H15a,H17
13	-	58.2, s	-	-
14	-	84.9, s	-	-
15a	3.33, d (15.9)	63.7, t	C8,C14,C16	H9,H12,H15b
15b	2.80, d (15.9)		C13,C14,C16,C17	H15a
16	-	95.0, s	-	-
17	4.15, s	68.2, d	C12,C13,C14,C16, C22,C23,C24	H12,H18,H23
18	0.67, s	10.4, q	C12,C13,C14,C17	H11b,H17, H23,H24
19	1.07, s	14.9, q	C1,C5,C9,C10	H1,H6,H11b
20	1.14, s	25.4, q	C4,C5,C21	H5,H6
21	1.12, s	22.5, q	C4,C5,C20	H6
22	-	119.9, s	-	-
23	7.55, d (2.6)	153.0, d	C17,C22,C24,C26	H17,H18
24	8.27, dd (9.8, 2.6)	151.5, d	C23,C26	H18,H25
25	6.28, d (9.8)	113.7, d	C22,C26	H24
26	-	164.1, s	-	-



Aegomycin H

5 EXAMPLE 5: BIOASSAYS FOR THE DETECTION OF ANTITUMOR ACTIVITY

The aim of this assay is to evaluate the *in vitro* cytostatic (ability to delay or arrest tumor cell growth) or cytotoxic (ability to kill tumor cells) activity of the samples being tested.

CELL LINES

Name	N° ATCC	Species	Tissue	Characteristics
A549	CCL-185	human	lung	lung carcinoma (NSCLC)
HT29	HTB-38	human	colon	colorectal adenocarcinoma
MDA-MB-231	HTB-26	human	breast	breast adenocarcinoma

EVALUATION OF CYTOTOXIC ACTIVITY USING THE SBR COLORIMETRIC ASSAY

5

A colorimetric assay, using sulforhodamine B (SRB) reaction has been adapted to provide a quantitative measurement of cell growth and viability (following the technique described by Skehan et al. J. Natl. Cancer Inst. 1990, 82, 1107-1112).

10

This form of assay employs SBS-standard 96-well cell culture microplates (Faircloth et al. Methods in Cell Science, 1988, 11(4), 201-205; Mosmann et al, Journal of Immunological Methods, 1983, 65(1-2), 55-63). All the cell lines used in this study were obtained from the American Type Culture Collection (ATCC) and derive from different types of human cancer.

15

Cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% Fetal Bovine Serum (FBS), 2mM L-glutamine, 100 U/mL penicillin and 100 U/mL streptomycin at 37 °C, 5% CO₂ and 98% humidity. For the experiments, cells were harvested from subconfluent cultures using trypsinization and resuspended in fresh medium before counting and plating.

20

25

Cells were seeded in 96 well microtiter plates, at 5×10^3 cells per well in aliquots of 150 μ L, and allowed to attach to the plate surface for

18 hours (overnight) in drug free medium. After that, one control (untreated) plate of each cell line was fixed (as described below) and used for time zero reference value. Culture plates were then treated with test compounds (50 μ L aliquots of 4X stock solutions in complete
5 culture medium plus 4% DMSO) using ten serial dilutions (concentrations ranging from 10 to 0.00262 μ g/mL) and triplicate cultures (1% final concentration of DMSO). After 72 hours treatment, the antitumor effect was measured by using the SRB methodology: Briefly, cells were washed twice with PBS, fixed for 15 min in 1%
10 glutaraldehyde solution at room temperature, rinsed twice in PBS, and stained in 0.4% SRB solution for 30 min at room temperature. Cells were then rinsed several times with 1% acetic acid solution and air-dried at room temperature. SRB was then extracted in 10 mM trizma base solution and the absorbance measured in an automated
15 spectrophotometric plate reader at 490 nm. Effects on cell growth and survival were estimated by applying the NCI algorithm (Boyd MR and Paull KD. Drug Dev. Res. 1995, 34, 91-104).

Using the mean $\pm$ SD of triplicate cultures, a dose-response curve
20 was automatically generated using nonlinear regression analysis. Three reference parameters were calculated (NCI algorithm) by automatic interpolation: GI₅₀ = compound concentration that produces 50% cell growth inhibition, as compared to control cultures; TGI = total cell growth inhibition (cytostatic effect), as compared to control cultures, and LC₅₀ =
25 compound concentration that produces 50% net cell killing (cytotoxic effect).

Tables 9 and 10 illustrate data on the biological activity of compounds of the present invention.

30

Table 9. Cytotoxicity assay-Activity Data (Molar) of Aegomycin A, B, C and D.

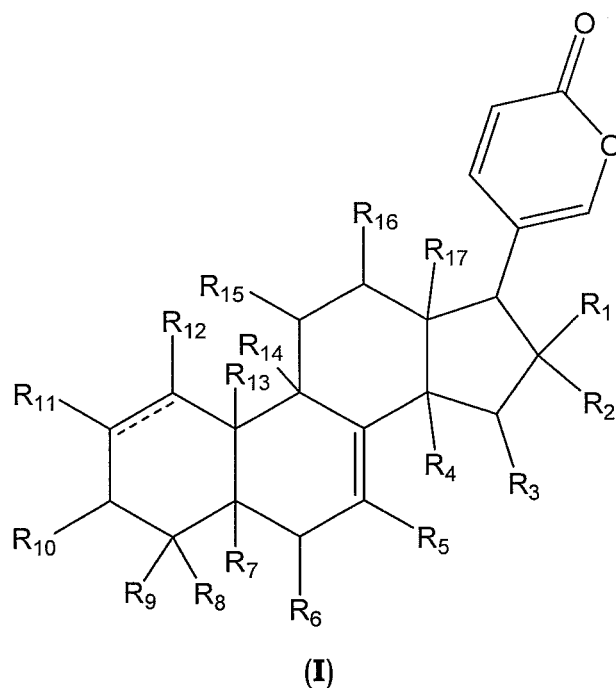
		Aegomycin A	Aegomycin B	Aegomycin C	Aegomycin D
MDA-MB- 231	GI ₅₀	1.91E-8	7.61E-8	6.28E-8	6.48E-8
	TGI	3.63E-8	1.67E-7	1.97E-7	9.81E-8
	LC ₅₀	6.11E-8	3.81E-7	6.91E-7	1.73E-7
HT29	GI ₅₀	1.05E-8	3.04E-8	9.84E-9	3.14E-8
	TGI	3.25E-8	2.28E-7	1.05E-7	1.35E-7
	LC ₅₀	1.15E-7	3.04E-6	>2.09E-5	1.45E-6
A549	GI ₅₀	3.82E-9	5.90E-9	7.54E-9	8.64E-9
	TGI	4.39E-9	7.61E-9	1.72E-8	1.28E-8
	LC ₅₀	5.35E-9	1.14E-8	4.19E-8	1.83E-8

Table 10. Cytotoxicity assay-Activity Data (Molar) of Aegomycin E, F, G and H

		Aegomycin E	Aegomycin F	Aegomycin G	Aegomycin H
MDA-MB- 231	GI ₅₀	1.97E-7	8.80E-8	1.70E-7	8.11E-8
	TGI	3.65E-7	2.71E-7	4.36E-7	2.03E-7
	LC ₅₀	7.50E-7	9.48E-7	1.29E-6	6.08E-7
HT29	GI ₅₀	1.18E-7	6.55E-8	1.46E-7	3.65E-8
	TGI	4.86E-7	4.06E-7	6.75E-7	2.03E-7
	LC ₅₀	5.27E-6	3.16E-6	3.92E-6	4.86E-6
A549	GI ₅₀	4.26E-8	2.48E-8	3.92E-8	8.31E-9
	TGI	5.67E-8	3.84E-8	6.32E-8	1.46E-8
	LC ₅₀	7.50E-8	6.10E-8	1.11E-7	2.84E-8

CLAIMS

1. A compound of general formula **I**



- 5 wherein

R_1 is selected from hydrogen and halogen;

R_2 is halogen;

- 10 each R_3 , R_{15} , and R_{16} is independently selected from hydrogen, OR_a , $OCOR_a$, $OCOOR_a$, and $=O$, with the proviso that when a $=O$ group exists the hydrogen of the C atom to which the $=O$ is attached is absent;

- each R_4 , R_5 , R_6 , R_7 , R_{11} , R_{12} , and R_{14} is independently selected from
 15 hydrogen, OR_a , $OCOR_a$, and $OCOOR_a$;

- each R_8 , R_9 , and R_{17} is independently selected from hydrogen, OR_a , $OCOR_a$, $OCOOR_a$, substituted or unsubstituted C_1 - C_{12} alkyl, substituted or unsubstituted C_2 - C_{12} alkenyl, and substituted or
 20 unsubstituted C_2 - C_{12} alkynyl;

R₁₀ is selected from hydrogen, OR_b, OCOR_a, OCOOR_a, and =O, with the proviso that when a =O group exists the hydrogen of the C atom to which the =O is attached is absent;

- 5 R₁₃ is selected from hydrogen, COR_a, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, and substituted or unsubstituted C₂-C₁₂ alkynyl;

each R_a is independently selected from hydrogen, substituted or
10 unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocyclic group;

15 each R_b is independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, substituted or unsubstituted C₂-C₁₂ alkenyl, substituted or unsubstituted C₂-C₁₂ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic group, and substituted or unsubstituted sugar; and

20

the ----- line represents an additional bond, an epoxy group, or is absent;

or a pharmaceutically acceptable salt or stereoisomer thereof.

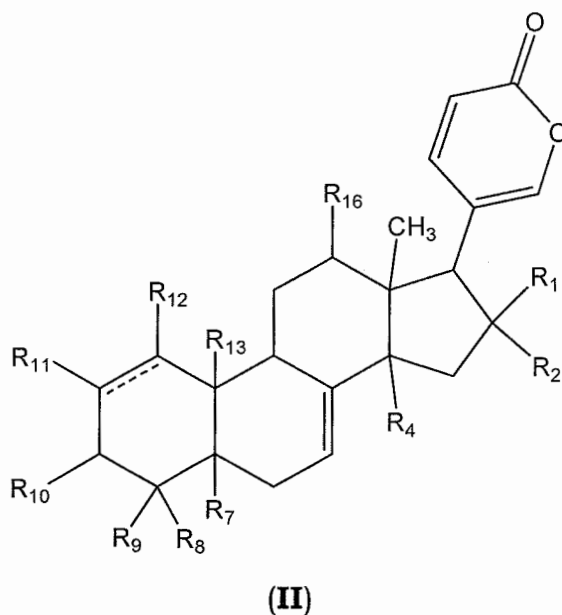
25

2. A compound according to claim 1, wherein R₃, R₅, R₆, R₁₄, and R₁₅ are each independently selected from hydrogen, OR_a, and OCOR_a, and wherein R_a is selected from hydrogen and substituted or unsubstituted C₁-C₆ alkyl.

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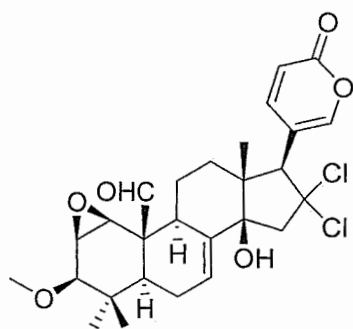
3. A compound according to any preceding claim, wherein R₁₇ is a substituted or unsubstituted C₁-C₆ alkyl.

4. A compound according to claim 1, having the following formula **II**

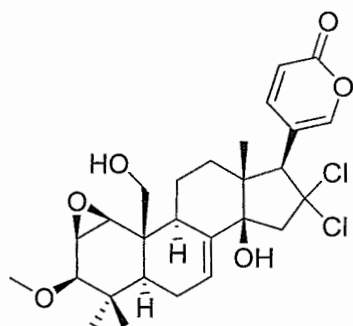


- 5 wherein R₁, R₂, R₄, R₇, R₈-R₁₃, R₁₆, and the ----- line are as defined in claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof.
5. A compound according to any preceding claim, wherein R₁ is selected from hydrogen and Cl; and wherein R₂ is Cl.
- 10
6. A compound according to any preceding claim, wherein R₄ is selected from hydrogen and OR_a, and wherein R_a is selected from hydrogen and substituted or unsubstituted C₁-C₆ alkyl.
- 15
7. A compound according to any preceding claim, wherein R₇ is selected from hydrogen, OR_a, and OCOR_a, and wherein R_a is selected from hydrogen and substituted or unsubstituted C₁-C₆ alkyl.
8. A compound according to any preceding claim, wherein R₈ and R₉
- 20 are each independently selected from hydrogen, substituted or unsubstituted C₁-C₁₂ alkyl, OR_a, and OCOR_a, and wherein R_a is selected from hydrogen and substituted or unsubstituted C₁-C₆ alkyl.

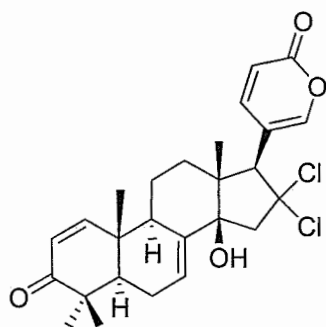
9. A compound according to any preceding claim, wherein R_{10} is selected from OR_b , $OCOR_a$, and $=O$, and wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl and R_b is selected from hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, monosaccharide, disaccharide, and trisaccharide, with the proviso that when R_{10} is $=O$ the hydrogen of the C atom to which R_{10} is attached is absent.
10. A compound according to any preceding claim, wherein R_{13} is selected from hydrogen, substituted or unsubstituted C_1 - C_{12} alkyl, and COR_a , and wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl.
11. A compound according to any preceding claim, wherein R_{16} is selected from hydrogen, OR_a , and $OCOR_a$, and wherein R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl.
12. A compound according to any preceding claim, wherein the ----- line is absent, R_{11} and R_{12} are each independently selected from hydrogen, OR_a , and $OCOR_a$, and R_a is selected from hydrogen and substituted or unsubstituted C_1 - C_6 alkyl.
13. A compound according to any of claims 1 to 11, wherein the ----- line represents an additional bond or an epoxy group, and R_{11} and R_{12} are hydrogen.
14. A compound according to claim 1, having the following structure:



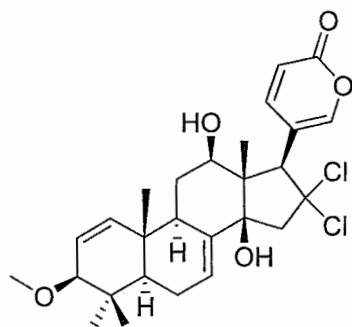
Aegomycin A,



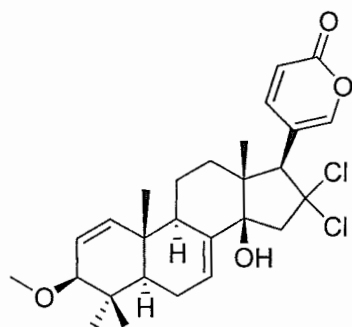
Aegomycin B,



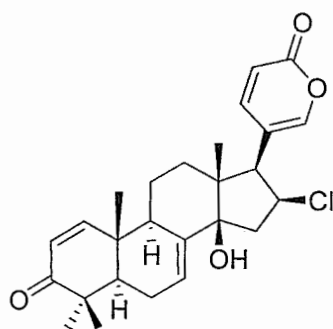
Aegomycin C,



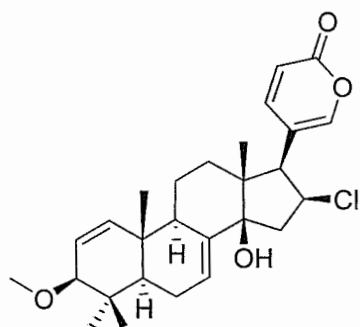
Aegomycin D,



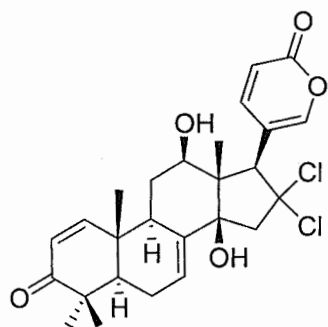
Aegomycin E,



Aegomycin F,



Aegomycin G, or



Aegomycin H;

or a pharmaceutically acceptable salt thereof.

5

15. A pharmaceutical composition comprising a compound according to any preceding claim, or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier or diluent.

10

16. A compound according to any of claims 1 to 14, or a pharmaceutically acceptable salt or stereoisomer thereof, for use as a medicament.

15 17. Use of a compound according to any of claims 1 to 14, or a pharmaceutically acceptable salt or stereoisomer thereof, in the preparation of a medicament for the treatment of cancer.