"Medicinal use of serrulatane diterpenes"

Technical Field

This invention relates to terpenes and uses thereof. In particular, the invention relates to serrulatane diterpenes and to the use of such compounds in the treatment of diseases and disorders such as cancer.

Throughout this application, various publications are referred to by first author and year of publication. Full citations for these publications, in the order they appear in the application, are presented in a References section immediately before the claims.

Background of the Invention

Plant secondary metabolites have been a major source of medicinal substances providing lead compounds for drug discovery and development.

Plants produce resins and exudates containing secondary metabolites to protect young flower and leaf buds against bacteria and fungi, and damage from sunlight. Accordingly, compounds from plant resins and exudates frequently possess antimicrobial and antioxidant/free radical scavenging activities. Worker honey bees (*Apis mellifera*) collect plant resins/exudates of young shoots and buds from certain trees and shrubs. The resulting mixture is called propolis, or so called bee glue. Propolis is a complex resinous substance and a rich source of bioactive substances. It is used by the bees to mix with wax to seal cracks and holes in their hives and as a disinfectant to protect against microbial infections. The medicinal properties of propolis have been exploited by man since Ancient civilizations.

Currently, propolis is extensively available as a natural health product, and is widely used in cosmetics. However, its modern use in medicine is limited, largely due to the wide variations in chemical compositions arising from honey bees collecting from different or a mixture of plant sources. The composition of propolis is dependent upon the surrounding flora to which the bees have access, and as such, differences in flora may result in differences in propolis compositions. For example, it is known that flavonoids are the major pharmacologically active compounds in European propolis, polyprenylated benzophenones are the main substances in Cuban and Venuzuelan

propolis, and prenylated cinnamic acid derivatives are predominant in Brazilian propolis.

Recognition of the botanical origin of the propolis produced by honey bees enables beehives to be placed in favourable locations such that propolis from a single botanical source may be produced to enable manufacture of medicines of high quality and efficacy.

The medicinal uniqueness of propolis is determined by the selective collecting ability of honey bees, as they can recognise natural materials that are relatively non-polar and have antibiotic properties. As reported, the common source of propolis is leaf and flower bud exudates, which are of high antibiotic character in order to protect the delicate growing of plant tissue from attack by microorganisms. It has also been reported that honey bees collect exudates from wounded or diseased plant tissues. Such sources are potentially rich in antibiotic substances produced by plants in response to wounding or attack from insects, microorganisms and viruses.

Medicinal properties of a propolis are associated with the biological activities of the individual plant resins/exudates. It is not clear from previous studies whether the bees simply collect a plant material that is known as propolis, or if there is metabolic modification or addition from the bees. However, there does not appear to be evidence of significant amounts of material added from honey bees, or strong evidence for metabolic transformation. Thus, a better understanding is required regarding the composition of propolis in specific geographical locations to be able to utilize it to its full benefit in the development of new agents in the treatment of diseases and disorders such as cancer.

Summary of the Invention

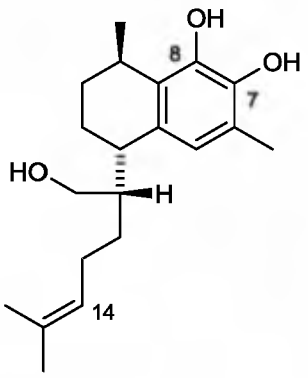
In work leading up to the present invention a survey of propolis samples isolated from Kangaroo Island (South Australia) was conducted. Surprisingly, the Inventors found that unlike other propolis which commonly contains flavonoids as active constituents, Kangaroo Island propolis from the *Myoporum* genus of plants, in particular *Myoporum insulare*, contains serrulatane diterpenes. Thus, the present invention relates to

compounds isolated from the resins/exudates of leaves and leaf buds of *Myoporum insulare*, propolis sourced from the same plant and uses thereof.

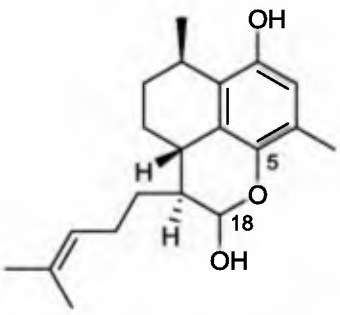
Myoporum insulare species is a shrub occurring on ridges and coastal cliffs in Australia. Common names include boobialla, native juniper and, in Western Australia, blueberry tree. *Myoporum* is a genus of approximately 30 species, of which sixteen are found in Australia. *Myoporum insulare* species has a variable growth habitat and may be a dense or an open shrub or a small tree up to 6 metres. The leaves are lance-shaped to elliptical, 30-100 mm long by 10-20 mm wide with glossy green colour. The flowers occur in groups of up to 8 in the leaf axils in late spring and summer and are usually white or occasionally pale pink.

The Inventors have isolated five major compounds, namely compounds **1** to **5**, from propolis obtained from *Myoporum insulare*. Compounds **1** to **5** are shown in Table **1**. The conventional numbering for serrulatane compounds is shown with respect to compound **1**. In general, serrulatane diterpenes have the (1*R*,4*S*)-configuration (Ghisalberti, 1994).

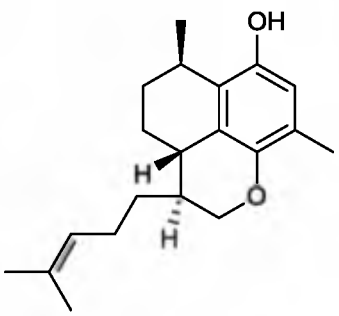
Compound **1** gives a derivative, compound **6**, on oxidation. Further in regard to derivatization, the compounds can also be acylated, alkylated, alkenylated or benzoylated through the free hydroxyl groups. For example, compounds **1** and **2** can be acetylated to give derivatives **7** and **8** while benzoylation can give derivatives **9** and **10**.



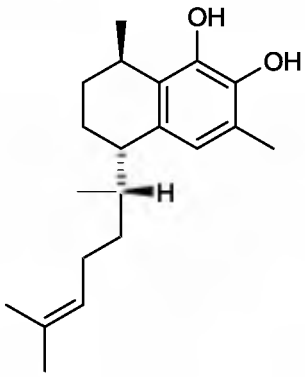
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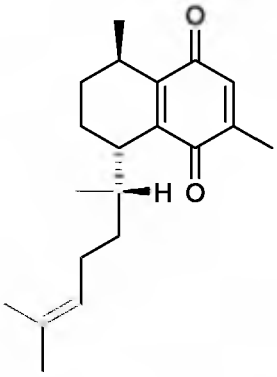
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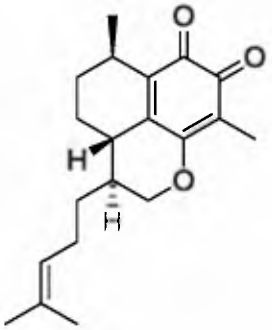


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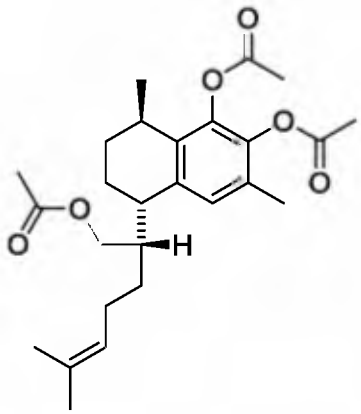


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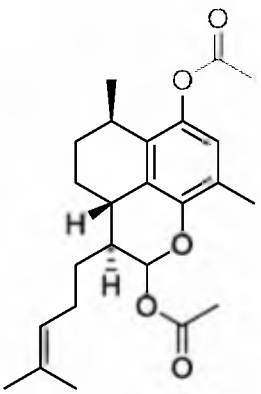
Table 1. Representative serrulatane diterpenoid compounds.



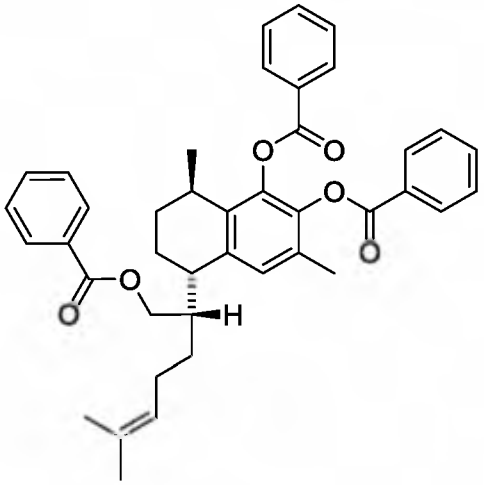
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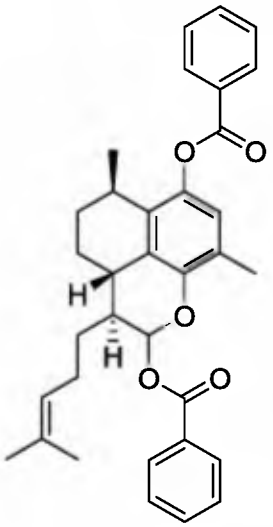
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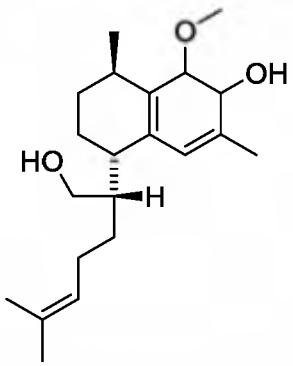
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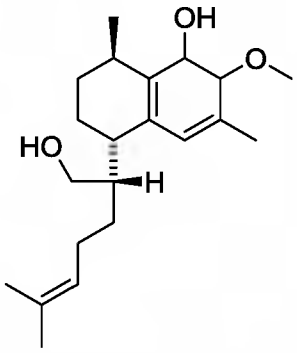
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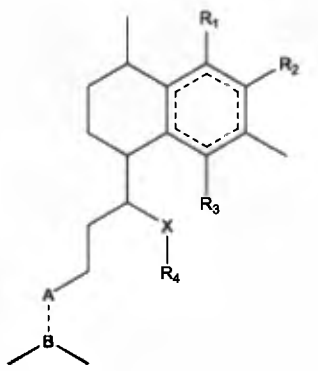


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Table 2. Serrulatane diterpenoid derivatives.

Representative compounds were evaluated for pharmacological activity and were found to be useful in modulating a number of diseases or disorders. For example, the compounds were found to inhibit cancer cell proliferation and showed moderate to strong inhibition of various targets associated with cancer pathology. This indicates that the serrulatane diterpene compounds of the present disclosure may be useful as therapeutic agents e.g. for the treatment of cancer. Therefore, the serrulatane diterpenes described herein provide a potentially attractive lead for pharmaceutical research and development and as biological tools for further understanding the pathophysiology of diseases and disorders such as cancer.

Accordingly, in a first aspect, there is provided a method of treating a cancer, the method comprising administering a therapeutically effective amount of a compound of Formula (**I**),



(**I**)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof, or pharmaceutical composition including said compounds, to a subject in need thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC_{4\text{-}5}$alkadienyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl, $OC(O)C_{4\text{-}5}$alkadienyl or =O;

R_2 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC_{4\text{-}5}$alkadienyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl, $OC(O)C_{4\text{-}5}$alkadienyl or =O;

R_3 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;

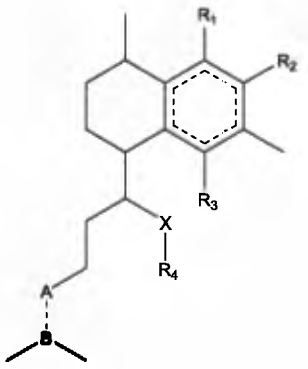
and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH.

According to a second aspect, there is provided use of a compound of Formula (**I**),



(**I**)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

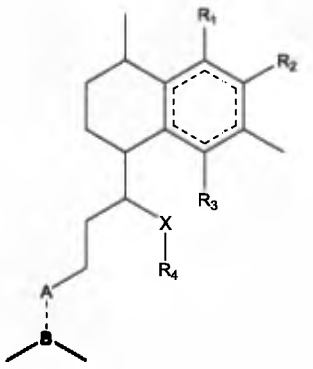
where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH,

in the preparation of a medicament for treating a cancer.

According to a third aspect, there is provided use of a compound of Formula (**I**),



(**I**)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

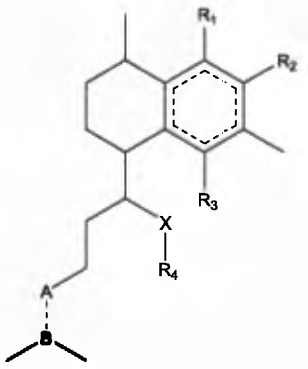
where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH,

in treating a cancer.

According to a fourth aspect, there is provided a compound of Formula (**I**),



(**I**)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

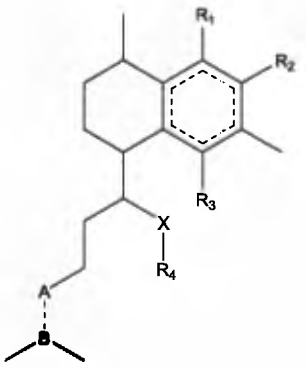
where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH,

for use in treating a cancer.

According to a fifth aspect, there is provided a compound of Formula (**I**),



(**I**)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH.

According to a sixth aspect, there is provided a pharmaceutical composition comprising a compound, geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof, according to the fifth aspect and a pharmaceutically acceptable excipient.

According to a seventh aspect, there is provided a pharmaceutical composition comprising a compound, geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof, according to the fifth aspect, or a mixture thereof, and a pharmaceutically acceptable excipient.

According to an eighth aspect, there is provided a compound as defined in the fifth aspect isolated from propolis, wherein the propolis originates from plants of the *Myoporum* genus.

According to a ninth aspect, there is provided a compound as defined in the fifth aspect isolated from the resin, gum or exudate of *Myoporum* genus.

According to a tenth aspect, there is provided a method of treating a disease or disorder, the method comprising administering a therapeutically effective amount of a compound according to the fifth aspect or a composition according to the sixth or seventh aspect.

According to an eleventh aspect, there is provided use of a compound according to the fifth aspect in the preparation of a medicament for treating a disease or disorder.

According to a twelfth aspect, there is provided use of a compound according to the fifth aspect or a composition according to the sixth aspect or seventh aspect in treating a disease or disorder.

According to a thirteenth aspect of the present invention, there is provided a compound according to the fifth aspect or a composition according to the sixth aspect or seventh aspect for use in treating a disease or disorder.

Brief Description of Drawings

Figure 1. Representative ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the 4:1 mixture of mono-methylated products (compounds **11** and **12**).

Figure 2. Representative ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of the 4:1 mixture of mono-methylated products (compounds **11** and **12**).

Figures 3 to **Figure 6** show example binding curves for compound **1** against epigenetic targets.

Figure 3 ASH1L (h) bromodomain binding curve.

Figure 4 CECR2(h) bromodomain binding curve.

Figure 5 SP140 *(h)* bromodomain binding curve.

Figure 6 UHRF1(108-286) (h) binding curve.

Figure 7 shows binding against 5-lipoxygenase for compound **1** (blue circles, IC_{50} = 2.31 μM) and a reference compound NGA (red squares, IC_{50} = 0.64 μM).

Figure 8 shows binding against lipid peroxidase for compound **1** (blue circles, IC_{50} = 1.47 μM) and a reference compound N-propyl gallate (red squares, IC_{50} = 165 μM).

Figure 9 shows binding against monoamine oxidase (MAO-A) for compound **1** (blue circles, IC_{50} = 6.74 μM) and a reference compound clorgyline (red squares, IC_{50} = 1.43 nM).

Figure 10 shows transcription response and binding against NF-κB for compound 1 (blue circles, IC_{50} = 1.36 μM) and a reference compound cyclosporin A (red squares, IC_{50} = 0.029 μM).

Figure 11 shows proliferation response when cell line MDA-MB-415 is treated with compound **1**.

Figure 12 shows proliferation response when cell line RKO-AS45-1 is treated with compound **1**.

Figure 13 shows proliferation response when cell line SW480 is treated with compound **1**.

Figure 14 shows proliferation response when cell line 639-V is treated with compound **1**.

Figure 15 shows proliferation response when cell line Hs 729 is treated with compound **1**.

Figure 16 shows proliferation response when cell line Hs 852.T is treated with compound **1**.

Figure 17 shows proliferation response when cell line HCT-8 is treated with compound **1**.

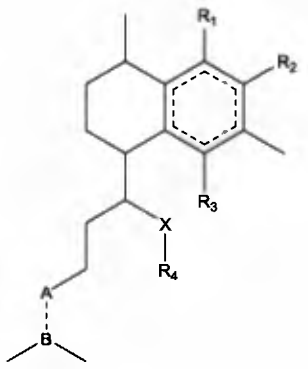
Figure 18 shows proliferation response when cell line IM-9 is treated with compound **1**.

Figure 19 shows the response when the cell line HREC is treated with compound **1** in an OncoPanel Normal Cell Proliferation Assay.

Specific embodiments of the disclosure are described below. It will be appreciated that these embodiments are illustrative and not restrictive.

Detailed Description of the Invention

Disclosed herein is a method of treating a cancer, the method comprising administering a therapeutically effective amount of a compound of Formula (**I**),



(I)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof, or pharmaceutical composition including said compounds, to a subject in need thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CHOH;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

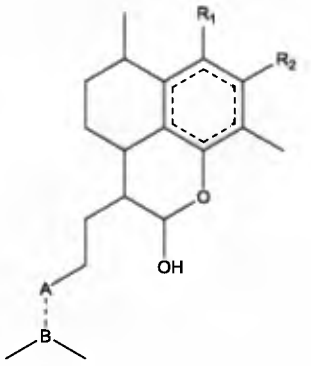
and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

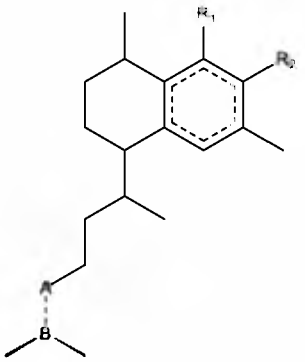
A---B is CH=C or CH_2-CH.

Preferably, the compound is a compound of Formula (**Ia**):



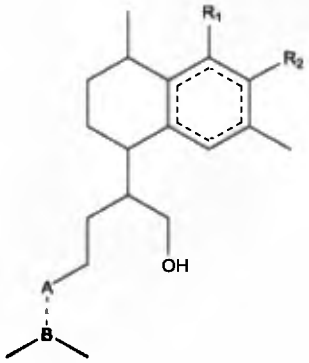
(**Ia**).

Preferably, the compound is a compound of Formula (**Ib**):



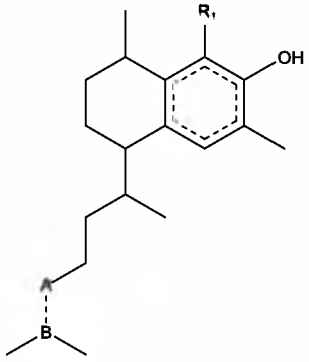
(**Ib**).

Preferably, the compound is a compound of Formula (**Ic**):



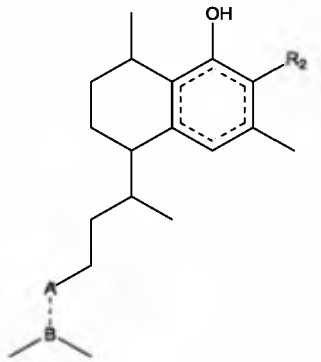
(**Ic**).

Preferably, the compound is a compound of Formula (**Id**):



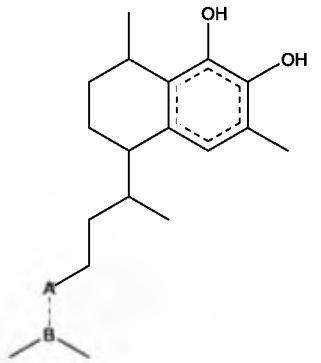
(**Id**).

Preferably, the compound is a compound of Formula (**Ie**):



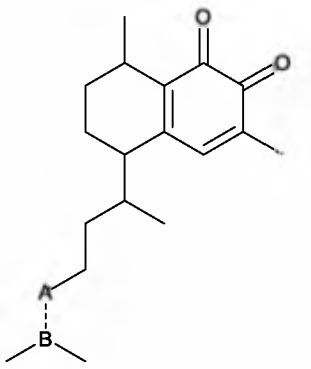
(**Ie**).

Preferably, the compound is a compound of Formula (**If**):



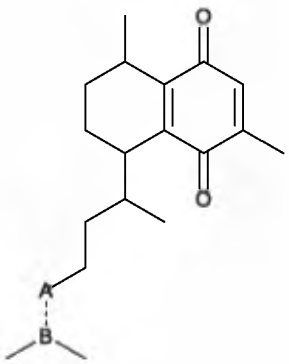
(**If**).

Preferably, the compound is a compound of Formula (**Ig**):



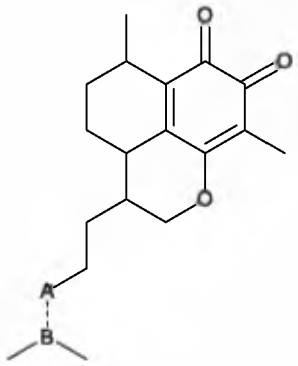
(**Ig**).

Preferably, the compound is a compound of Formula (**Ih**):



(**Ih**).

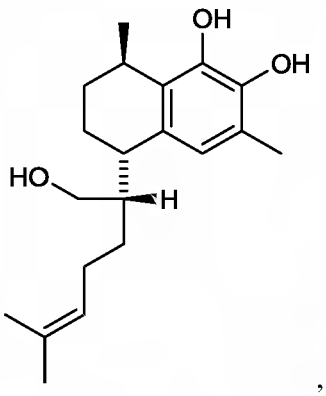
Preferably, the compound is a compound of Formula (**Ii**):



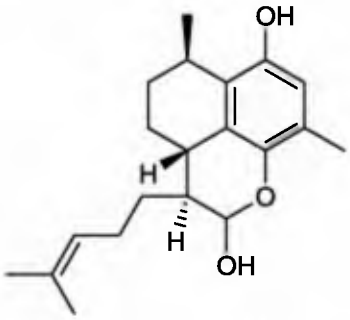
(**Ii**).

Preferably, A---B is CH=C.

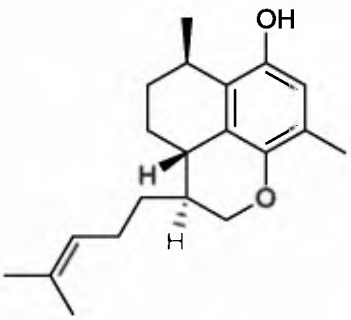
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OH
OH
HO
H

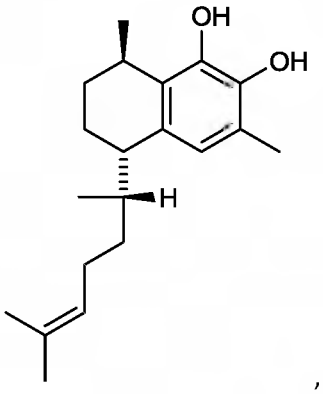
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OH
H
O
H
OH

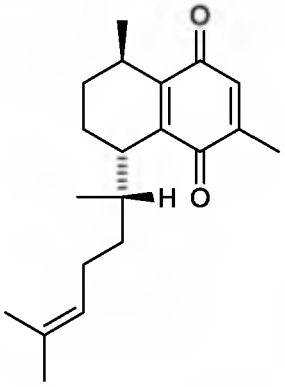
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OH
H
O
H

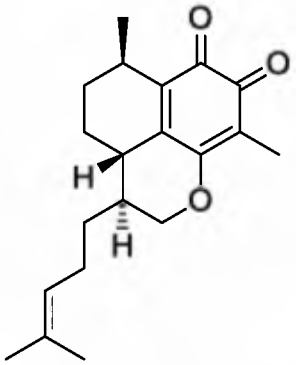
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OH
OH
H

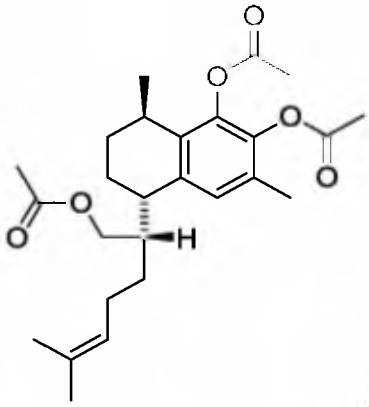
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O
H
O
O

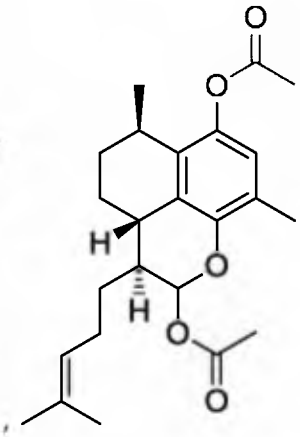
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O
O
H
O
H

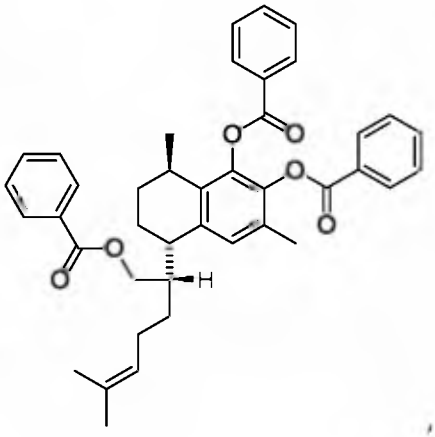
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O
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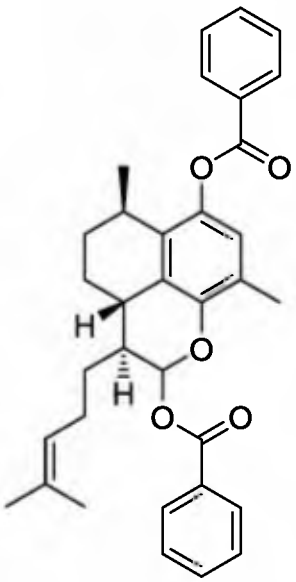
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O
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H
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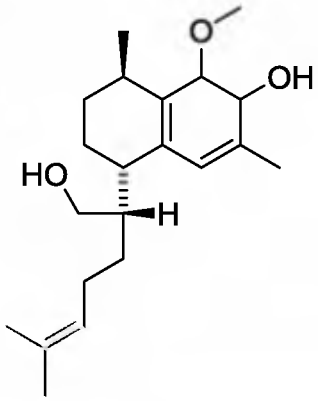
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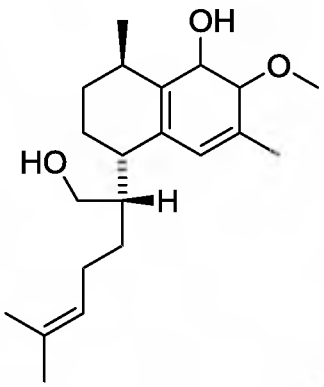

O
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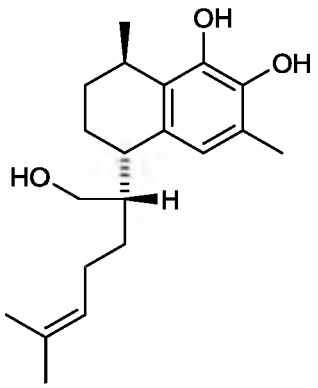
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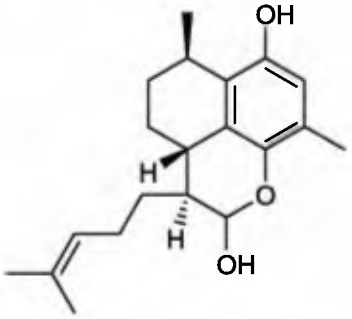


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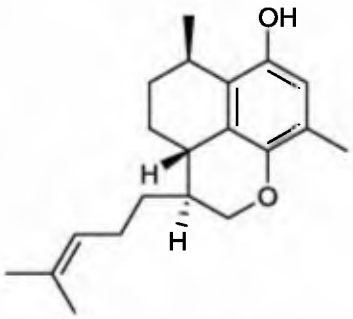
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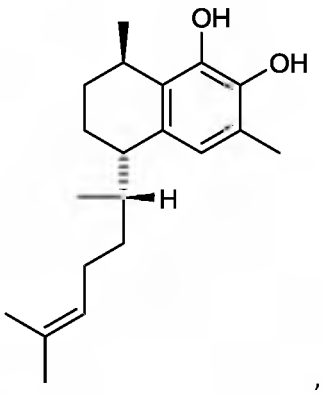


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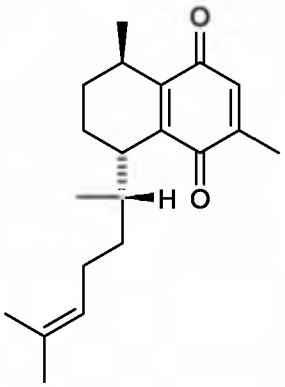


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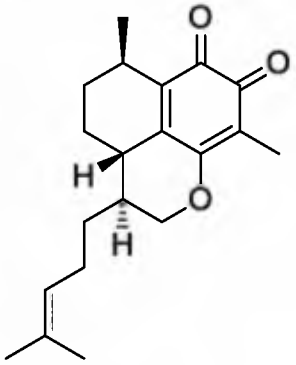




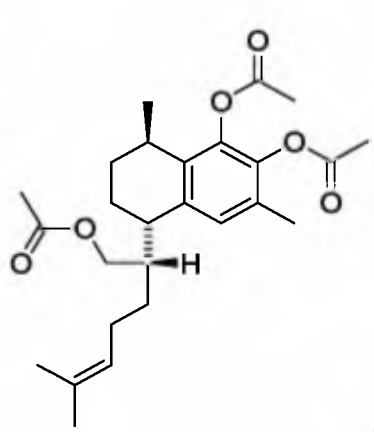
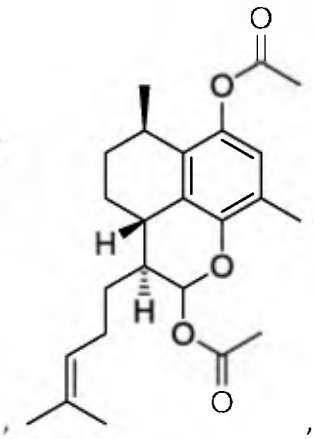
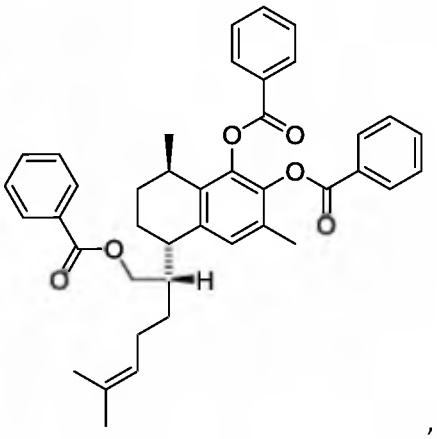
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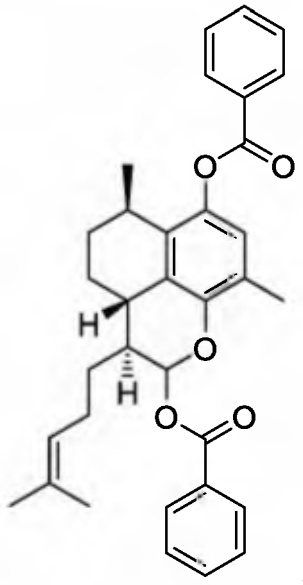
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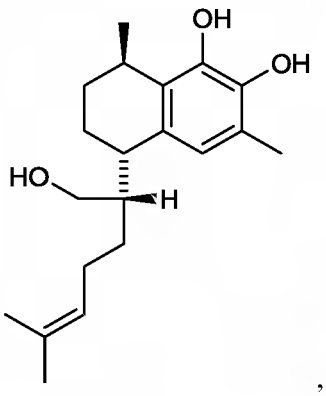




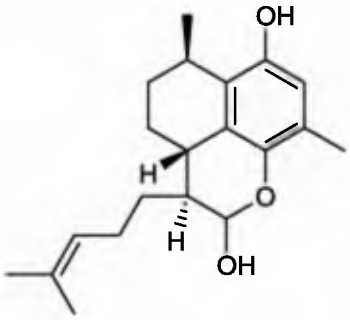
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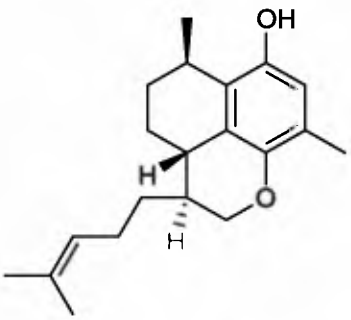


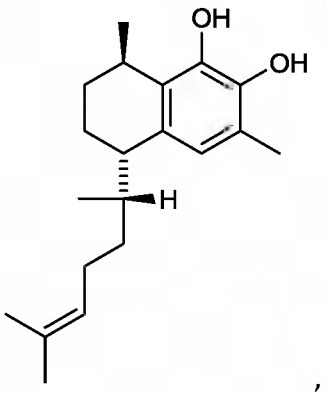
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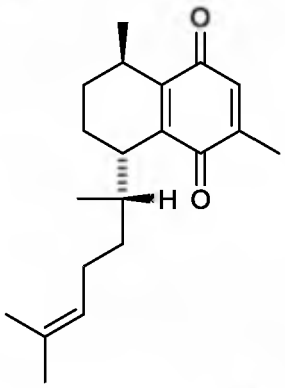
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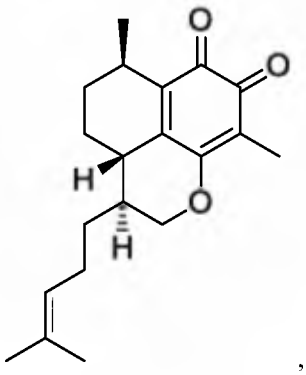


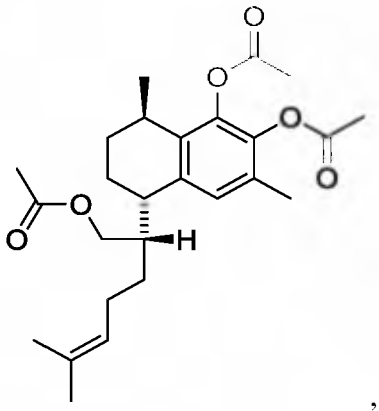
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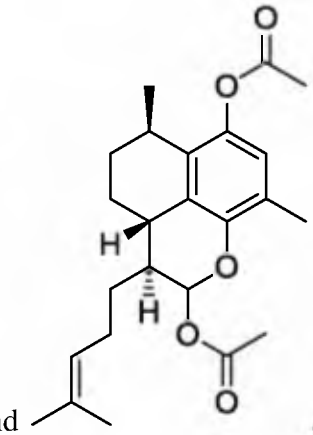
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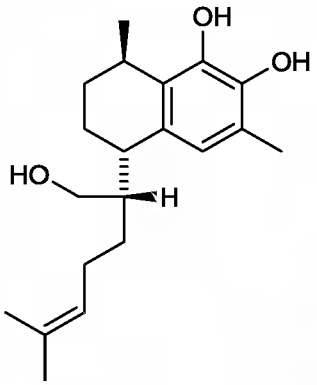
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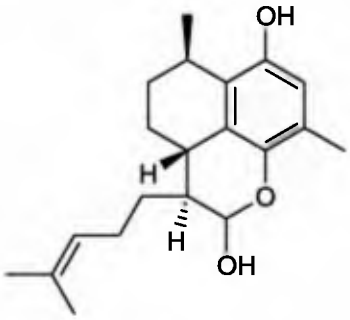
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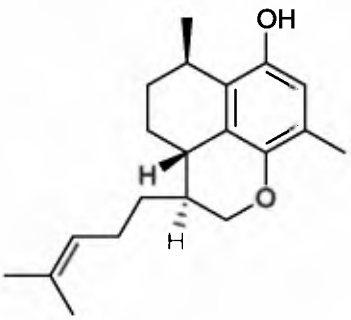


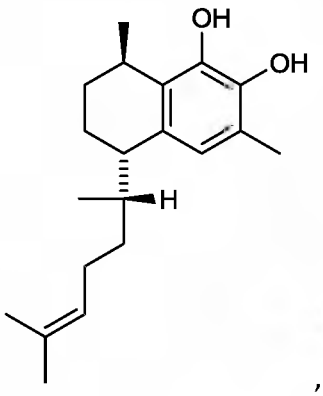
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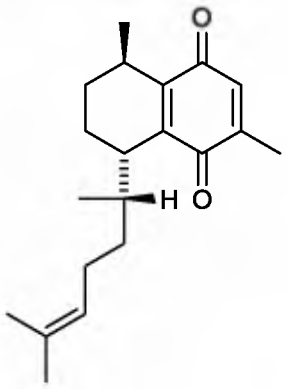
Preferably, the compound is selected from the group consisting of:

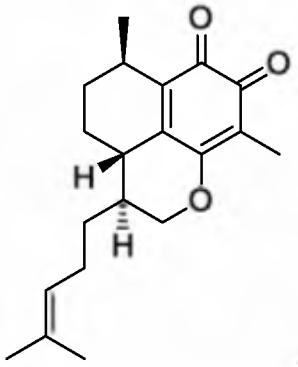


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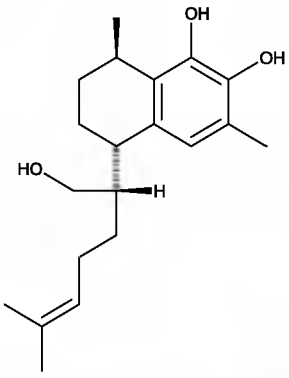


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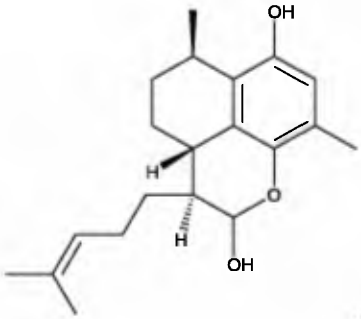


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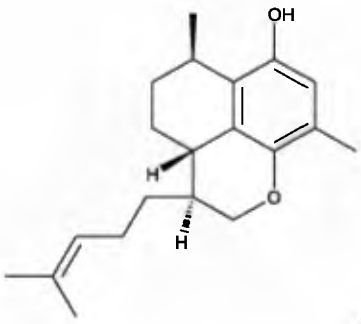
The compound is preferably:



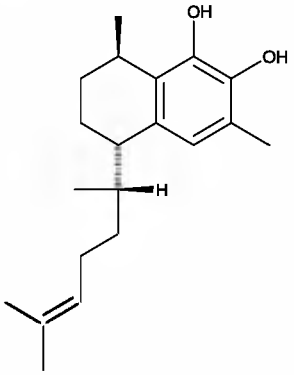
Preferably, the compound is:



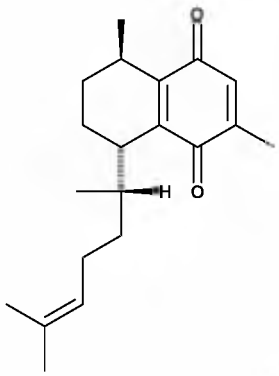
The compound is preferably:



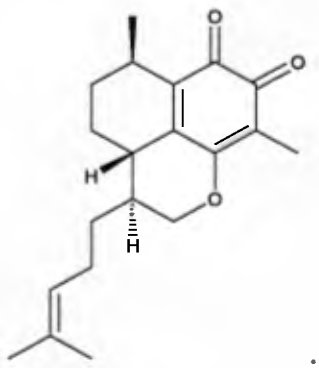
Preferably, the compound is:



The compound is preferably:



Preferably, the compound is:



Preferably, the cancer is bladder cancer, bone cancer, brain cancer, breast cancer, a cancer of the central nervous system, cancer of the adrenal glands, cancer of the placenta, cancer of the testis, cervical cancer, colon cancer, kidney cancer, head and neck cancer, myeloma, leukemia, liver cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, stomach cancer, thyroid cancer, uterine cancer, a carcinoma, a lymphoma, a sarcoma, eye cancer, esophageal cancer, bile duct cancer or vulva cancer.

The cancer of the central nervous system is preferably a glioma. Preferably, the cancer of the central nervous system is a medulloblastoma. The cancer of the central nervous system is preferably a neuroblastoma.

Preferably, the lung cancer is a non-small cell lung cancer. The lung cancer is preferably a small cell lung cancer.

Preferably, the carcinoma is adenosquamous cell carcinoma or squamous cell carcinoma.

The sarcoma is preferably a liposarcoma, rhabdomyosarcoma, or fibrosarcoma. Preferably, the sarcoma is a soft tissue sarcoma. The soft tissue sarcoma is preferably a soft tissue osteosarcoma.

Preferably, the lymphoma is Burkitt's lymphoma, Hodgkin's lymphoma, or non-Hodgkin's lymphoma.

While it is possible that, for use in therapy a therapeutically effective amount of the compounds as defined herein, or a pharmaceutically acceptable salt or solvate thereof, may be administered as the raw chemical; in the first aspect of the present invention the active ingredient is administered as a pharmaceutical composition. Thus, the present

invention also contemplates a pharmaceutical composition comprising a compound of formula **(I)** to **(Ii)**, or a pharmaceutically acceptable salt or a solvate thereof, and a pharmaceutically acceptable excipient. The excipient must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

When applicable, the compounds of the present invention, including the compounds of formula (**I**) to (**Ii**) may be in the form of and/or may be administered as a pharmaceutically acceptable salt.

As used herein the term "pharmaceutically acceptable salt" refers to salts which are toxicologically safe for systemic administration. The pharmaceutically acceptable salts may be selected from alkali or alkaline earth metal salts, including, sodium, lithium, potassium, calcium, magnesium and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, triethanolamine and the like.

As used herein the term "pharmaceutically acceptable excipient" refers to a solid or liquid filler, carrier, diluent or encapsulating substance that may be safely used in administration. Depending upon the particular route of administration, a variety of carriers, well known in the art may be used. These carriers or excipients may be selected from a group including sugars, starches, cellulose and its derivatives, malt, gelatine, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffered solutions, emulsifiers, isotonic saline, and pyrogen-free water.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this disclosure, a compound of formula (**I**) to (**Ii**) or a salt or physiologically functional derivative thereof) and a solvent. Such solvents for the purpose of the disclosure may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. In particular the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation,

water, ethanol, acetic acid, glycerol, liquid polyethylene glycols and mixtures thereof. A particular solvent is water.

Administration of compounds of the formula (**I**) to (**Ii**) may be in the form of a "prodrug". A prodrug is an inactive form of a compound which is transformed *in vivo* to the active form. Suitable prodrugs include esters, phosphonate esters *etc*, of the active form of the compound.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question.

The compounds of the present disclosure may be suitable for the treatment of diseases in a human or animal subject. In one example, the subject is a mammal including a human, horse, dog, cat, sheep, cow, or primate. In another example, the subject is a human. In a further example, the subject is not a human. The terms "subject" and "patient" are used interchangeably herein.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician.

Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function. The term also includes within its scope amounts effective to prevent a disease, disorder, or side effect.

As used herein the term "treatment" refers to defending against or inhibiting a symptom, treating a symptom, delaying the appearance of a symptom, reducing the severity of the development of a symptom, and/or reducing the number or type of symptoms suffered by an individual, as compared to not administering a pharmaceutical composition comprising a compound of the invention. The term also

includes within its scope prevention of a disease, disorder, or side effect. The term "treatment" encompasses use in a palliative setting

The antitumor effect of the compounds of the present disclosure may be applied as a sole therapy or as a combination therapy i.e. where two or more serrulatane diterpenoids may be administered in combination. Therapy may also involve administration of a mixture of two or more serrulatane diterpenoids. Therapy may involve, in addition, administration of one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer such as a combination of surgery, radiotherapy and/or chemotherapy. In particular, it is known that irradiation or treatment with antiangiogenic and/or vascular permeability reducing agents can enhance the amount of hypoxic tissue within a tumour. Therefore the effectiveness of the compounds of the present invention may be improved by conjoint treatment with radiotherapy and/or with an antiangiogenic agent.

The individual components of such combinations can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present disclosure is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other anti-neoplastic agents includes in principle any combination with any pharmaceutical composition useful for treating cancer.

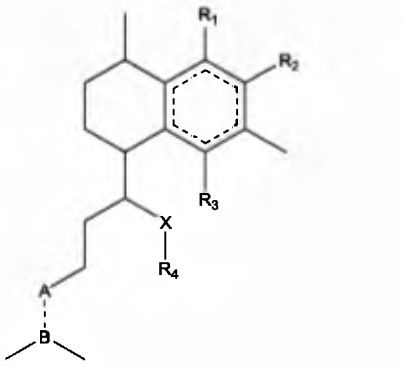
When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation and may be formulated for administration. When formulated separately they may be provided in any convenient formulation, conveniently in such a manner as are known for such compounds in the art.

Pharmaceutical compositions of the present disclosure may be formulated for administration by any appropriate route, for example by the oral (including buccal or

sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Therefore, the pharmaceutical compositions of the invention may be formulated, for example, as tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions. Such pharmaceutical formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Such pharmaceutical formulations may be prepared as enterically coated granules, tablets or capsules suitable for oral administration and delayed release formulations.

When a compound is used in combination with a second therapeutic agent active against the same disease, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Also disclosed herein is use of a compound of Formula (**I**),



(**I**)

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC_{4\text{-}5}$alkadienyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl, $OC(O)C_{4\text{-}5}$alkadienyl or =O;

R_2 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC_{4\text{-}5}$alkadienyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl, $OC(O)C_{4\text{-}5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH,

in the preparation of a medicament for treating a cancer.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CHOH;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

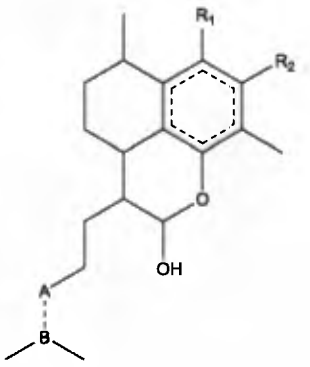
and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

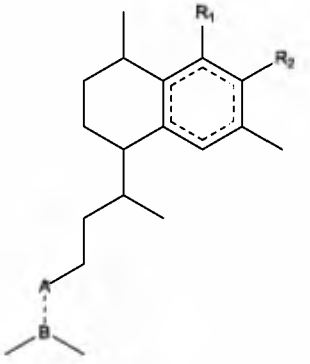
A---B is CH=C or CH_2-CH.

Preferably, the compound is a compound of Formula (**Ia**):



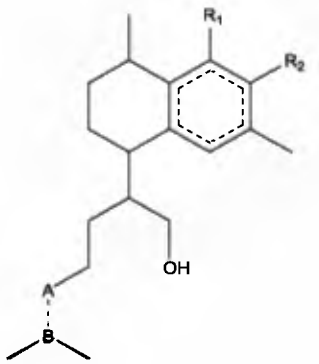
(**Ia**).

Preferably, the compound is a compound of Formula (**Ib**):



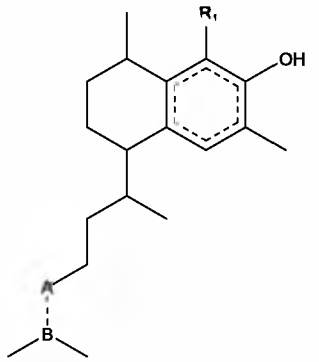
(**Ib**).

Preferably, the compound is a compound of Formula (**Ic**):



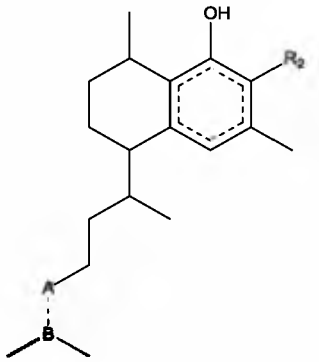
(**Ic**).

Preferably, the compound is a compound of Formula (**Id**):



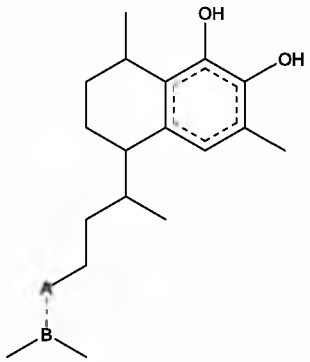
(**Id**).

Preferably, the compound is a compound of Formula (**Ie**):



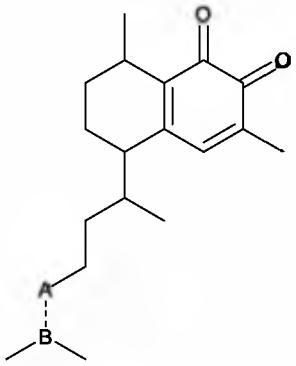
(**Ie**).

Preferably, the compound is a compound of Formula (**If**):



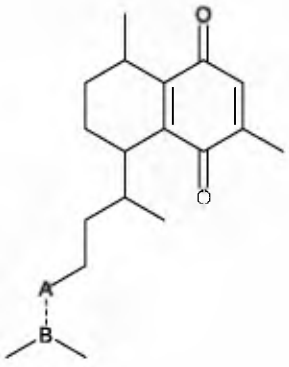
(**If**).

Preferably, the compound is a compound of Formula (**Ig**):



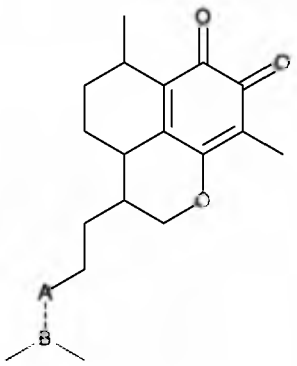
(**Ig**).

Preferably, the compound is a compound of Formula (**Ih**):



(**Ih**).

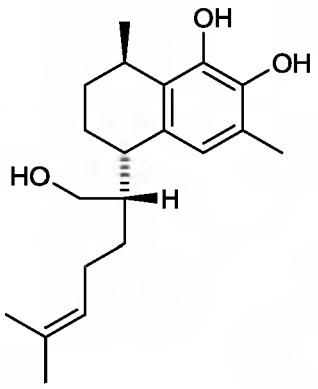
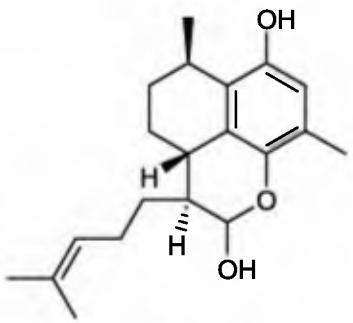
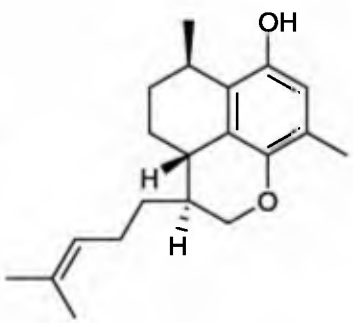
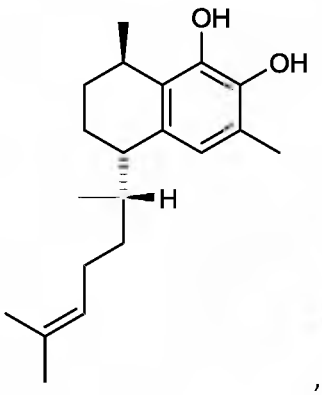
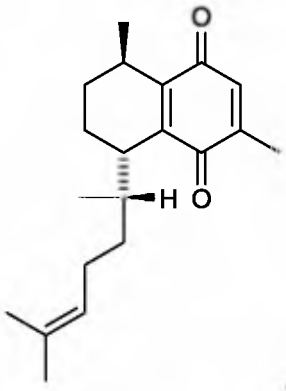
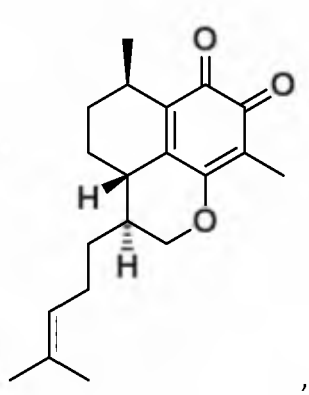
Preferably, the compound is a compound of Formula (**Ii**):

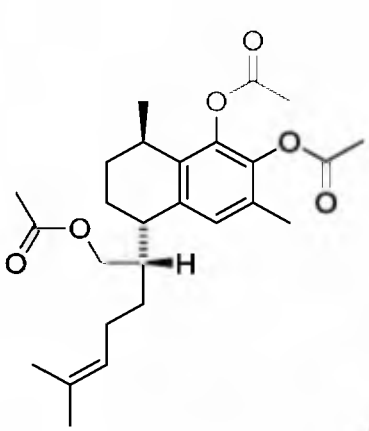
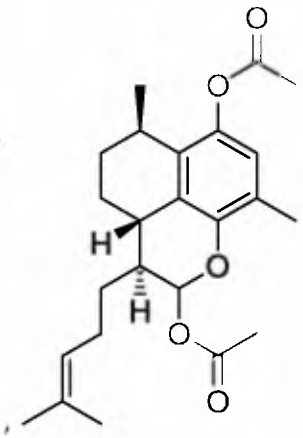
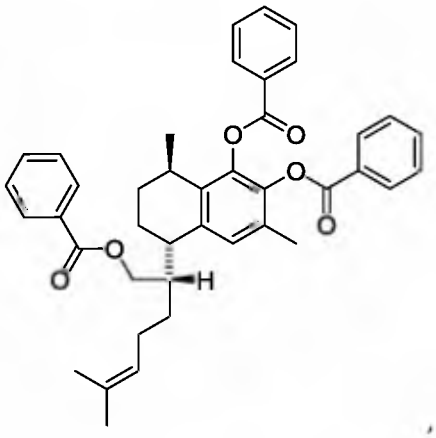
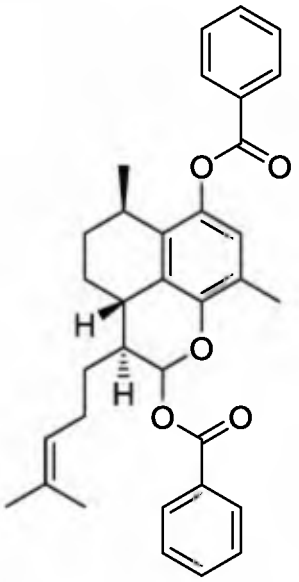
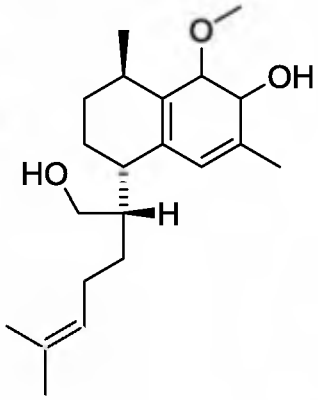
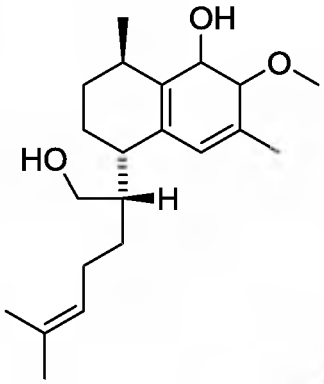


(**Ii**).

Preferably, A---B is CH=C.

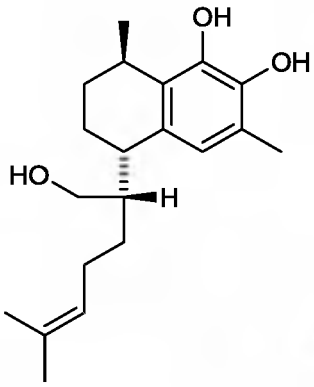
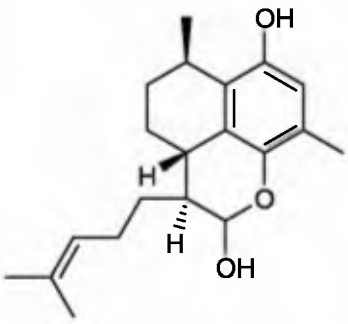
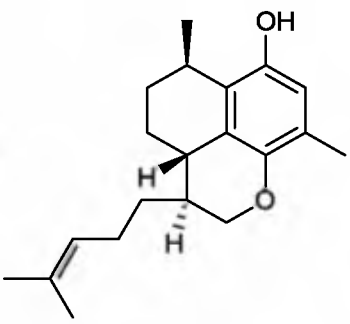
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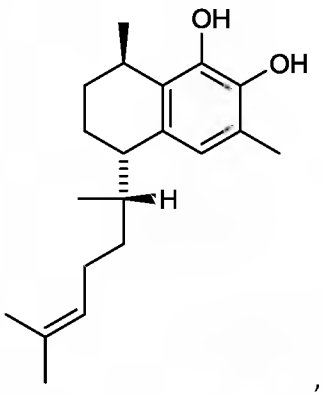
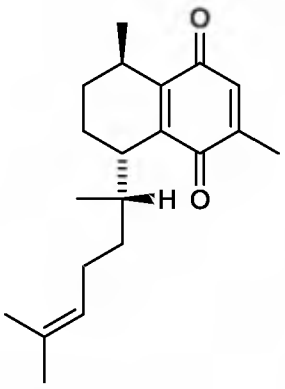
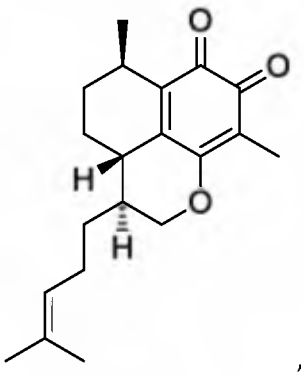
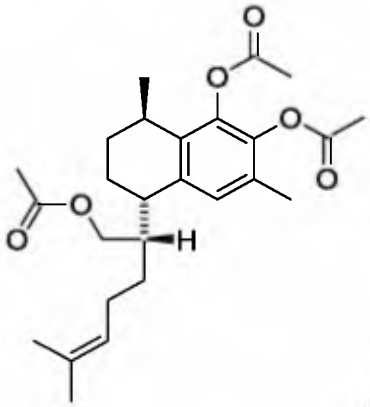
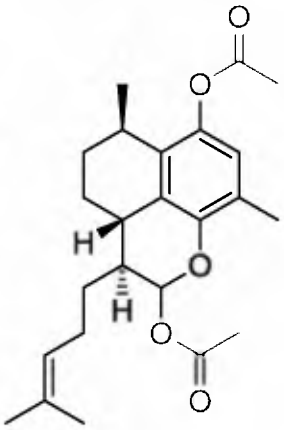
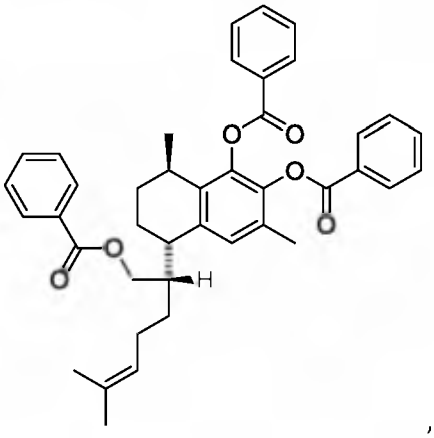

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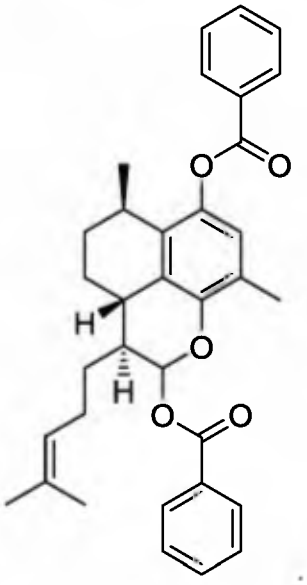
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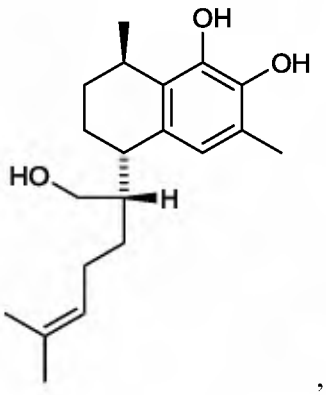







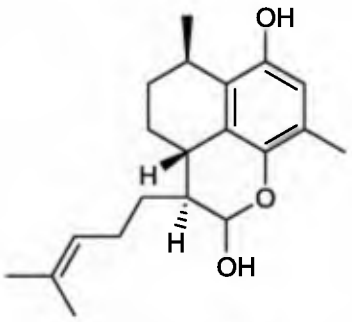
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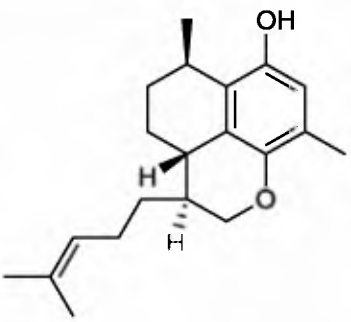


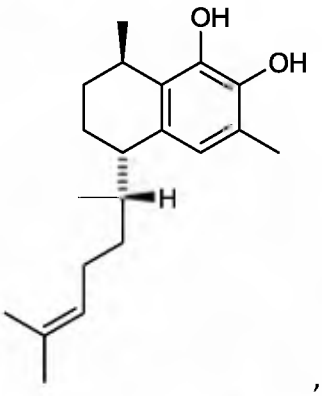
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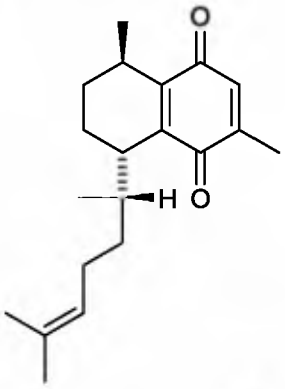
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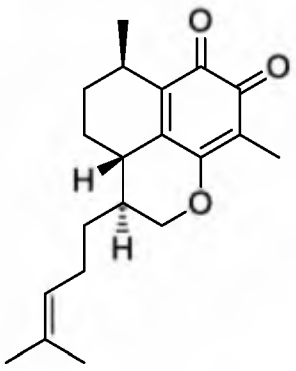


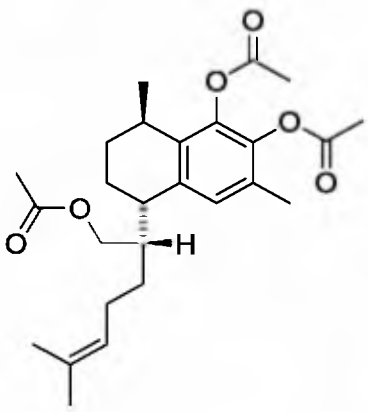
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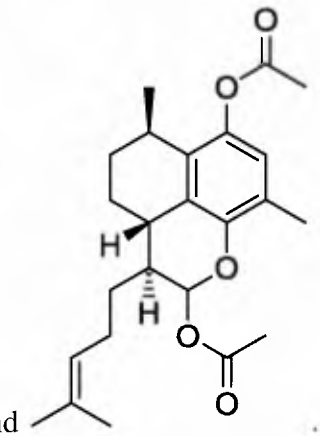
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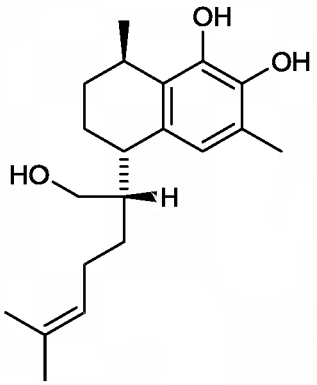
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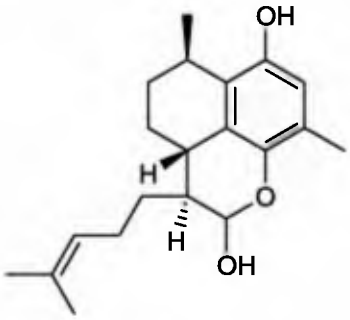


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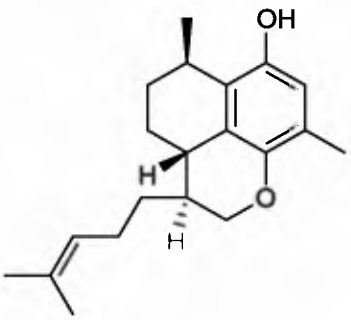
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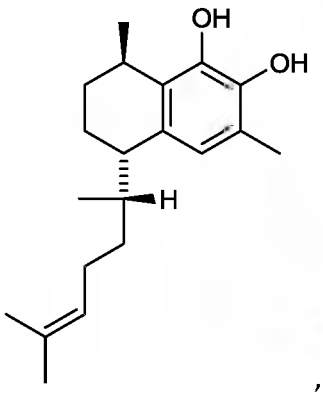


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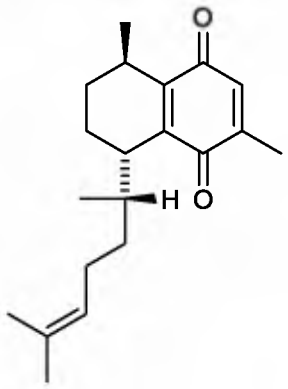


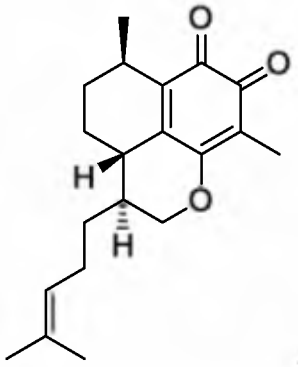
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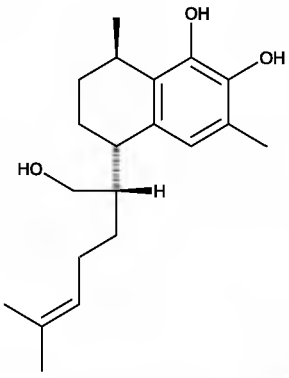
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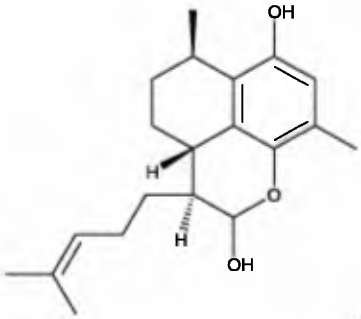


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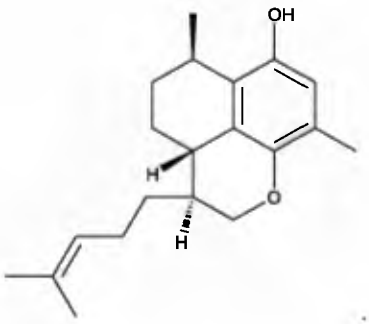
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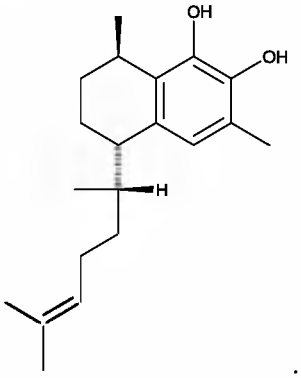
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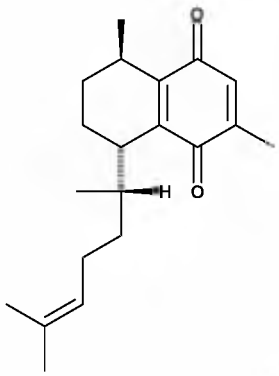
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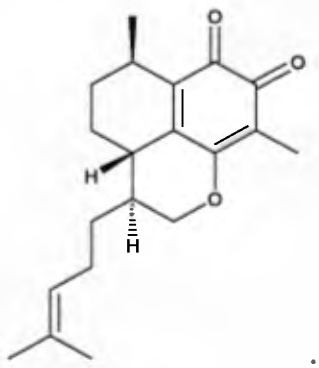
Preferably, the compound is:



The compound is preferably:



Preferably, the compound is:



Preferably, the cancer is bladder cancer, bone cancer, brain cancer, breast cancer, a cancer of the central nervous system, cancer of the adrenal glands, cancer of the placenta, cancer of the testis, cervical cancer, colon cancer, kidney cancer, head and neck cancer, myeloma, leukemia, liver cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, stomach cancer, thyroid cancer, uterine cancer, a carcinoma, a lymphoma, a sarcoma, eye cancer, esophageal cancer, bile duct cancer or vulva cancer.

The cancer of the central nervous system is preferably a glioma. Preferably, the cancer of the central nervous system is a medulloblastoma. The cancer of the central nervous system is preferably a neuroblastoma.

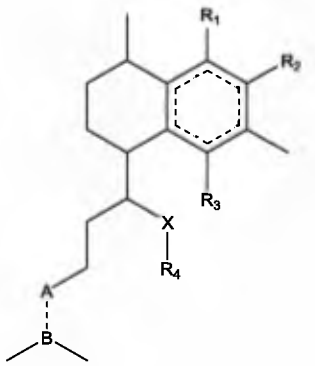
Preferably, the lung cancer is a non-small cell lung cancer. The lung cancer is preferably a small cell lung cancer.

Preferably, the carcinoma is adenosquamous cell carcinoma or squamous cell carcinoma.

The sarcoma is preferably a liposarcoma, rhabdomyosarcoma, or fibrosarcoma. Preferably, the sarcoma is a soft tissue sarcoma. The soft tissue sarcoma is preferably a soft tissue osteosarcoma.

Preferably, the lymphoma is Burkitt's lymphoma, Hodgkin's lymphoma, or non-Hodgkin's lymphoma.

Also disclosed herein is use of a compound of Formula (**I**),



(I)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt, or solvate thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH,

in treating a cancer.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CHOH;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

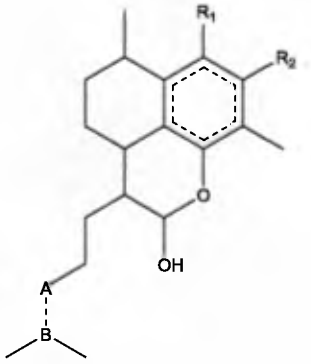
and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

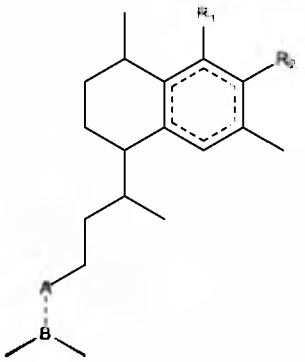
A---B is CH=C or CH_2-CH.

Preferably, the compound is a compound of Formula (**Ia**):



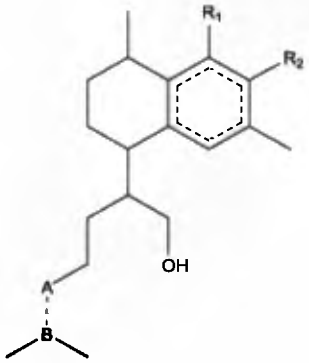
(**Ia**).

Preferably, the compound is a compound of Formula (**Ib**):



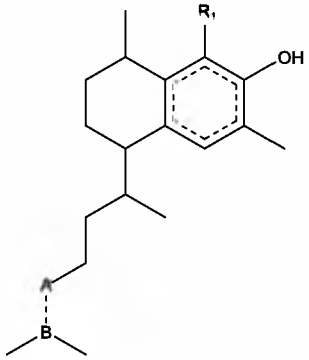
(**Ib**).

Preferably, the compound is a compound of Formula (**Ic**):



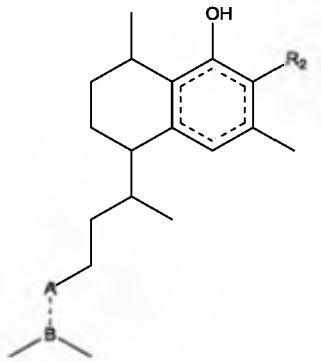
(**Ic**).

Preferably, the compound is a compound of Formula (**Id**):



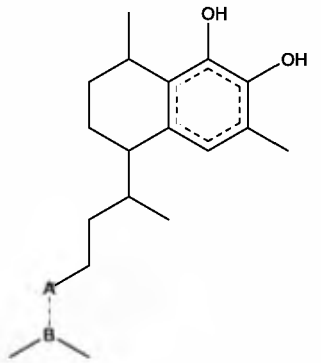
(**Id**).

Preferably, the compound is a compound of Formula (**Ie**):



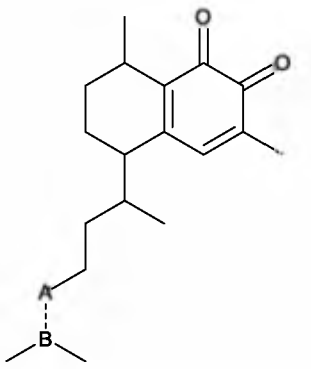
(**Ie**).

Preferably, the compound is a compound of Formula (**If**):



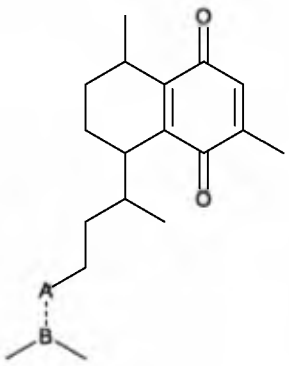
(**If**).

Preferably, the compound is a compound of Formula (**Ig**):



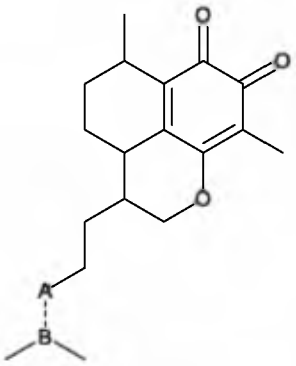
(**Ig**).

Preferably, the compound is a compound of Formula (**Ih**):



(**Ih**).

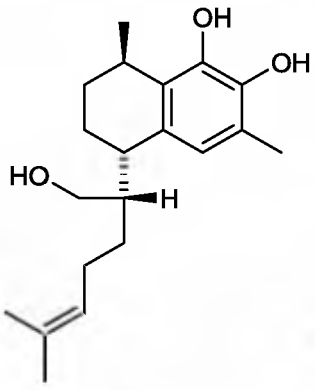
Preferably, the compound is a compound of Formula (**Ii**):



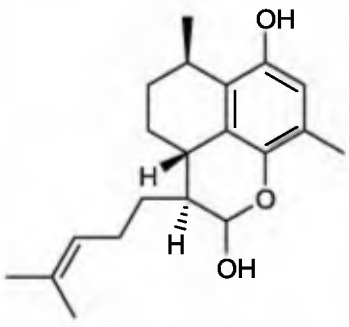
(**Ii**).

Preferably, A---B is CH=C.

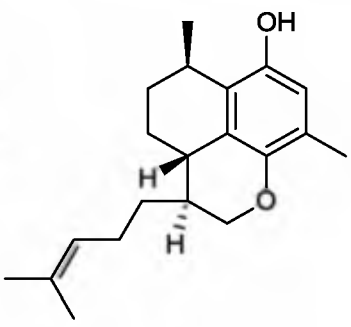
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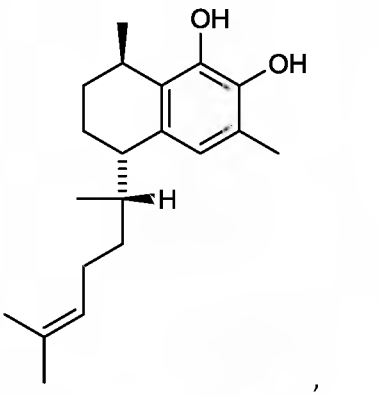
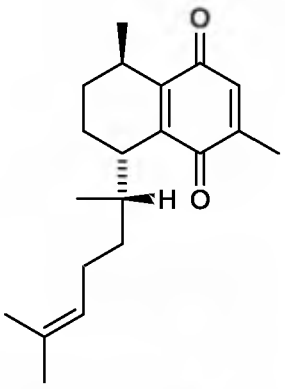
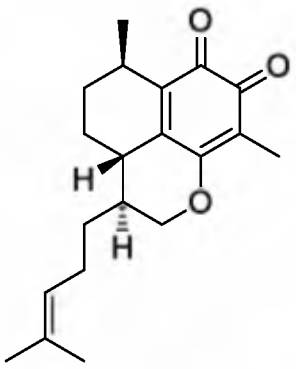
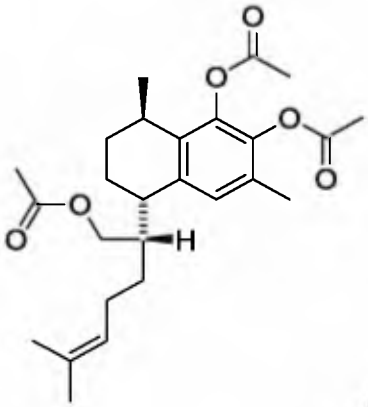
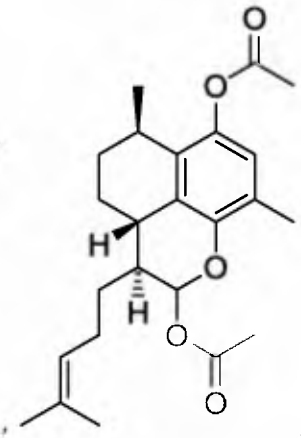
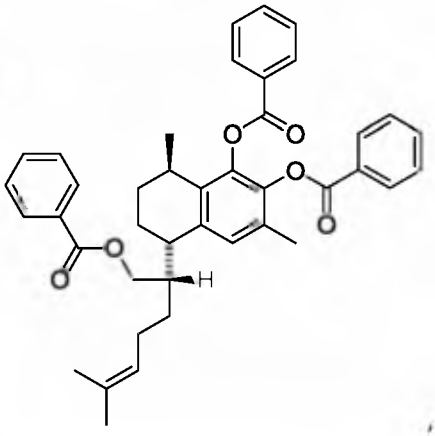
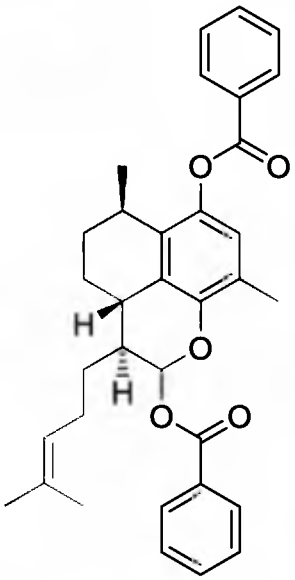
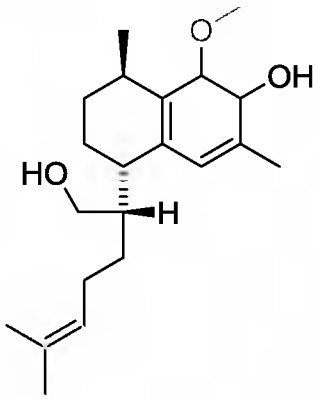
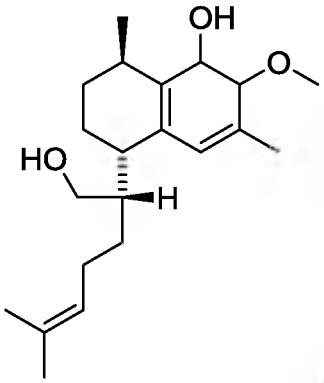
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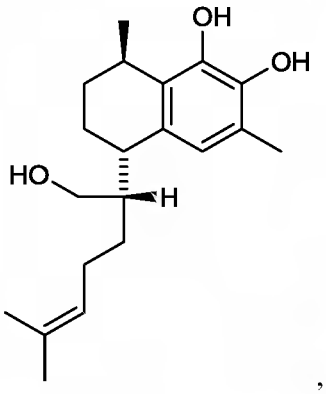
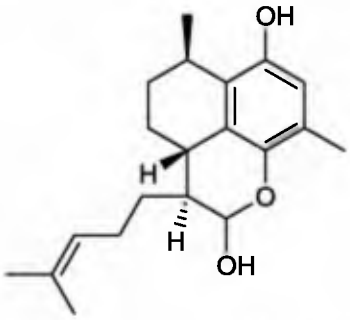
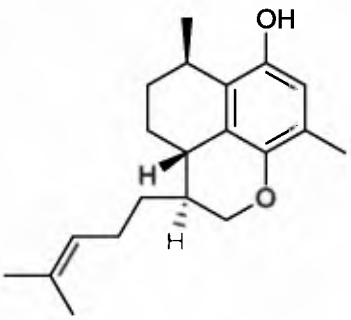
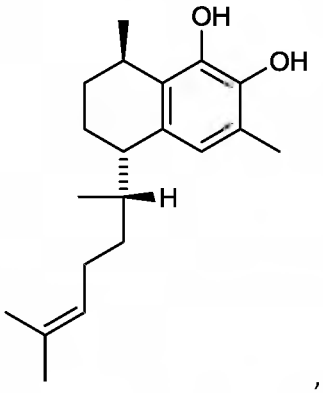
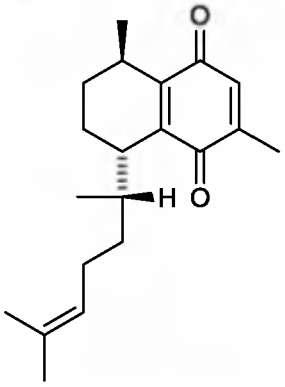
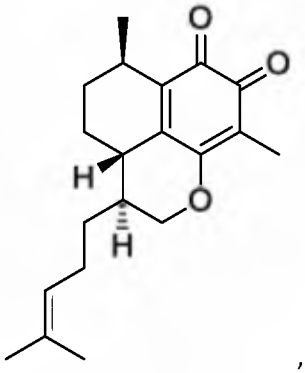
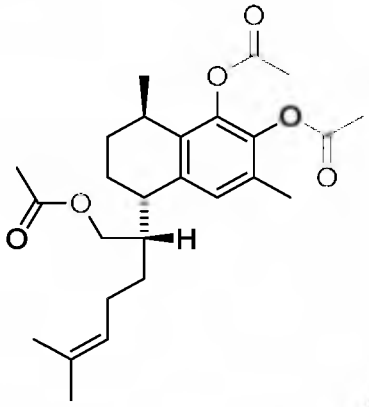
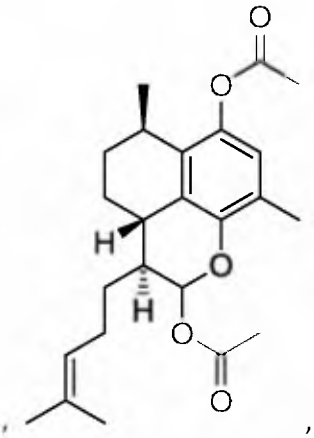
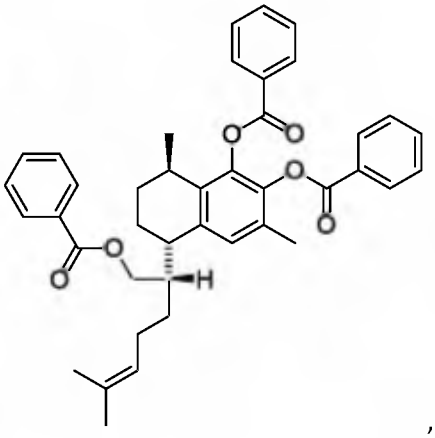


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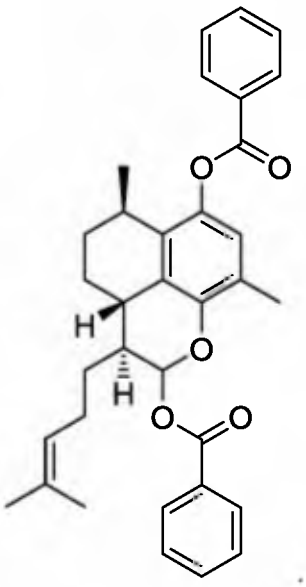










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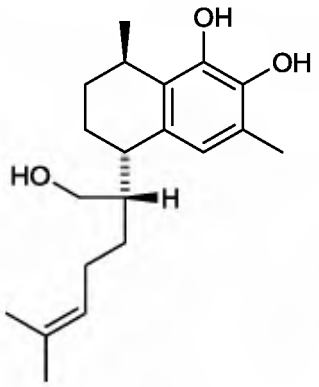
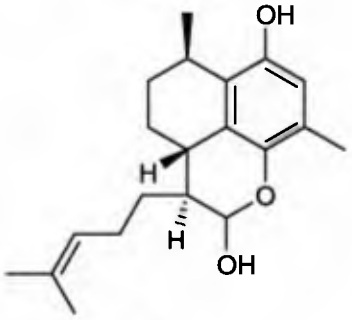
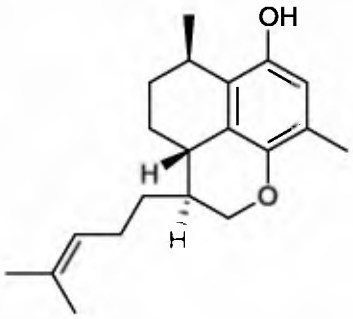
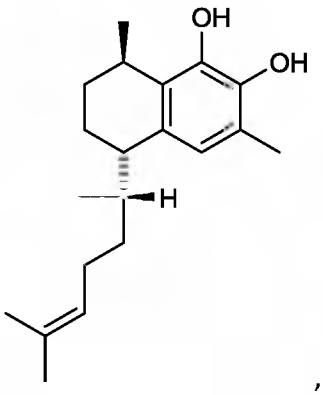
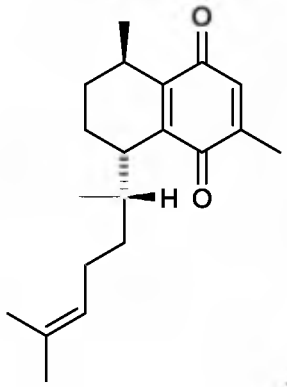
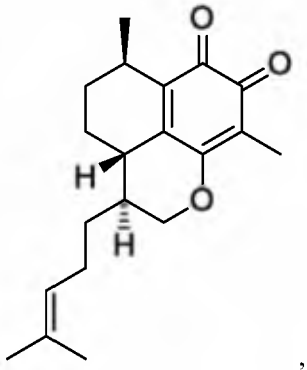
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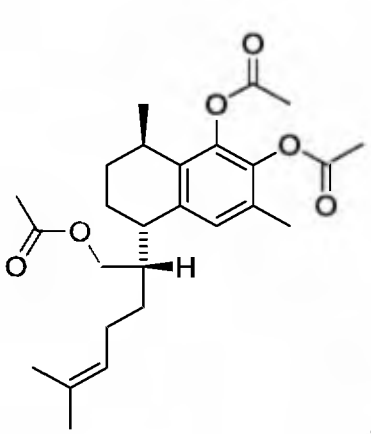
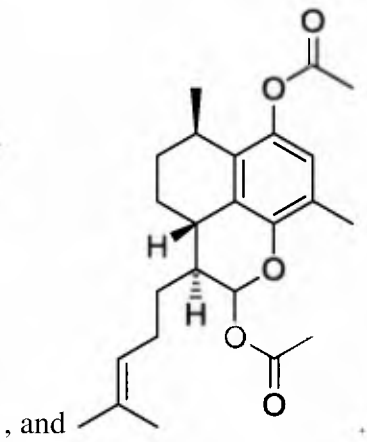

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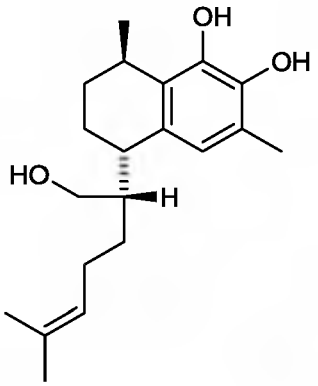
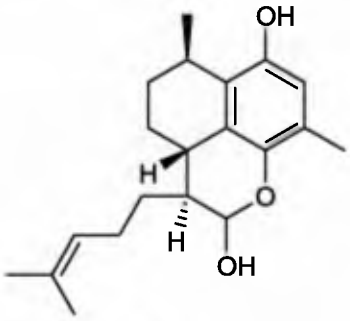
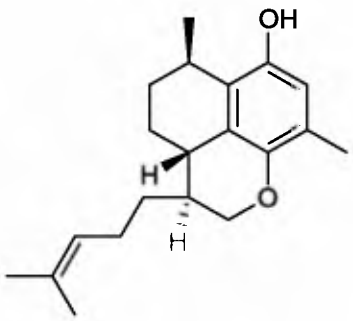
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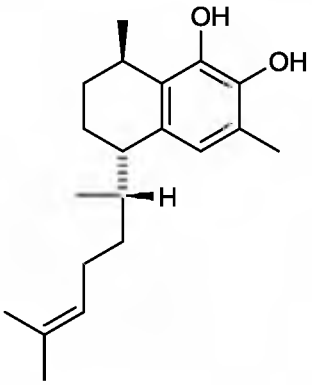
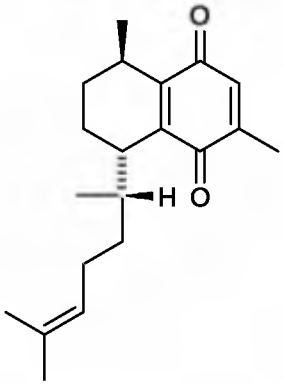
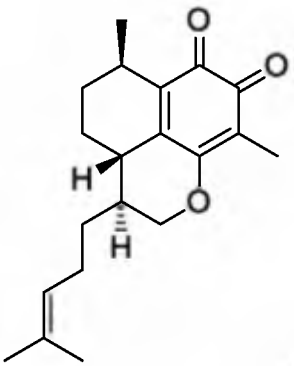



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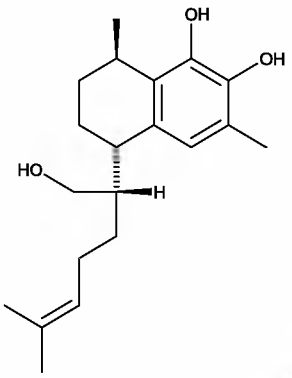




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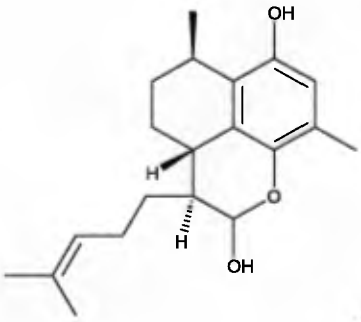




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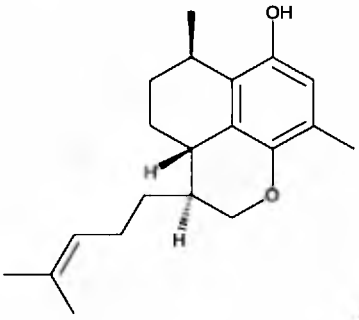
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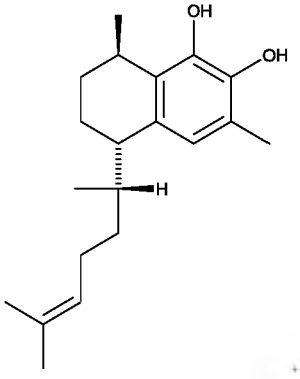
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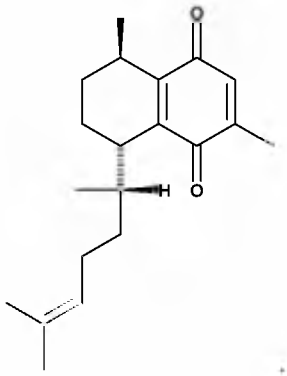
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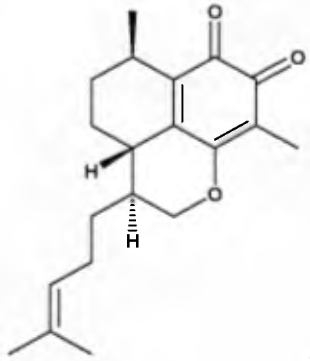
Preferably, the compound is:



The compound is preferably:



Preferably, the compound is:



Preferably, the cancer is bladder cancer, bone cancer, brain cancer, breast cancer, a cancer of the central nervous system, cancer of the adrenal glands, cancer of the placenta, cancer of the testis, cervical cancer, colon cancer, kidney cancer, head and neck cancer, myeloma, leukemia, liver cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, stomach cancer, thyroid cancer, uterine cancer, a carcinoma, a lymphoma, a sarcoma, eye cancer, esophageal cancer, bile duct cancer or vulva cancer.

The cancer of the central nervous system is preferably a glioma. Preferably, the cancer of the central nervous system is a medulloblastoma. The cancer of the central nervous system is preferably a neuroblastoma.

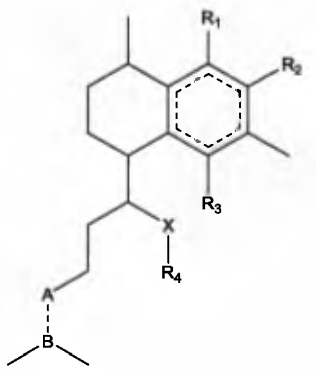
Preferably, the lung cancer is a non-small cell lung cancer. The lung cancer is preferably a small cell lung cancer.

Preferably, the carcinoma is adenosquamous cell carcinoma or squamous cell carcinoma.

The sarcoma is preferably a liposarcoma, rhabdomyosarcoma, or fibrosarcoma. Preferably, the sarcoma is a soft tissue sarcoma. The soft tissue sarcoma is preferably a soft tissue osteosarcoma.

Preferably, the lymphoma is Burkitt's lymphoma, Hodgkin's lymphoma, or non-Hodgkin's lymphoma.

Also disclosed herein is a compound of Formula (**I**),



(**I**)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC_{4\text{-}5}$alkadienyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl, $OC(O)C_{4\text{-}5}$alkadienyl or =O;

R_2 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC_{4\text{-}5}$alkadienyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl, $OC(O)C_{4\text{-}5}$alkadienyl or =O;

R_3 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC_{4\text{-}5}$alkadienyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl or $OC(O)C_{4\text{-}5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH,

for use in treating a cancer.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CHOH;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

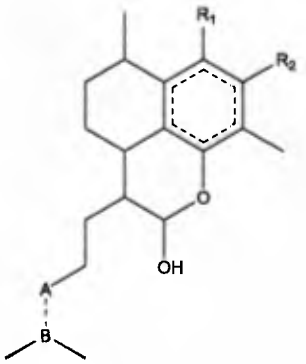
and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

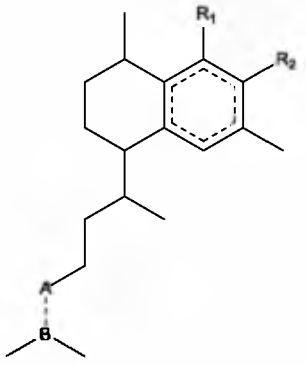
A---B is CH=C or CH_2-CH.

Preferably, the compound is a compound of Formula (**Ia**):



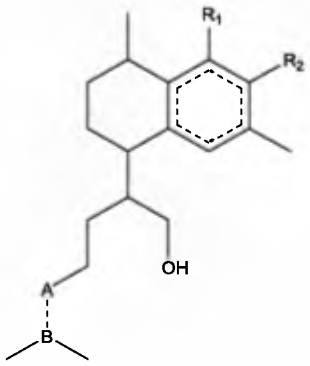
(**Ia**).

Preferably, the compound is a compound of Formula (**Ib**):



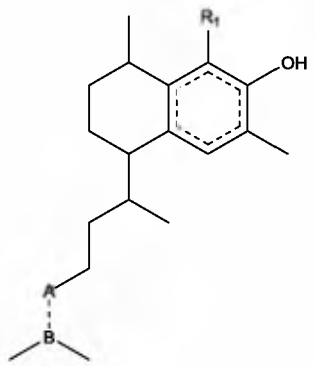
(**Ib**).

Preferably, the compound is a compound of Formula (**Ic**):



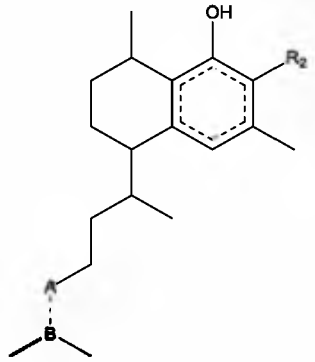
(**Ic**).

Preferably, the compound is a compound of Formula (**Id**):



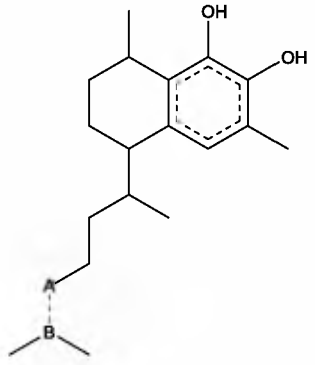
(**Id**).

Preferably, the compound is a compound of Formula (**Ie**):



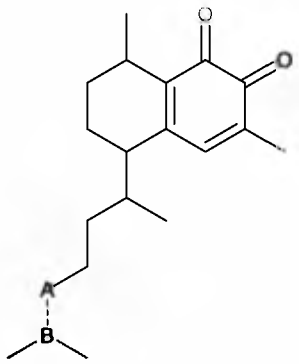
(**Ie**).

Preferably, the compound is a compound of Formula (**If**):



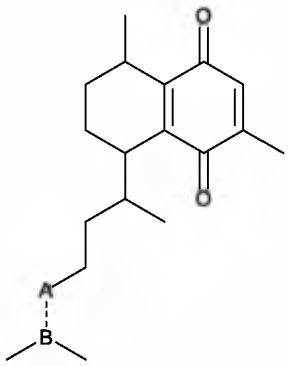
(**If**).

Preferably, the compound is a compound of Formula (**Ig**):



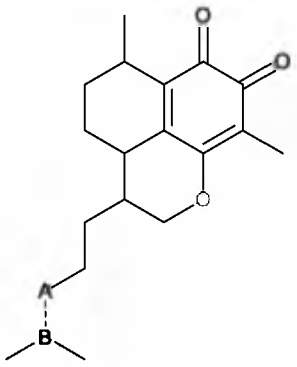
(**Ig**).

Preferably, the compound is a compound of Formula (**Ih**):



(**Ih**).

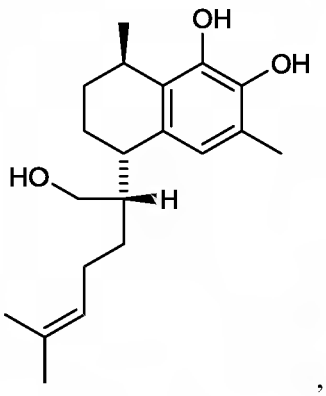
Preferably, the compound is a compound of Formula (**Ii**):



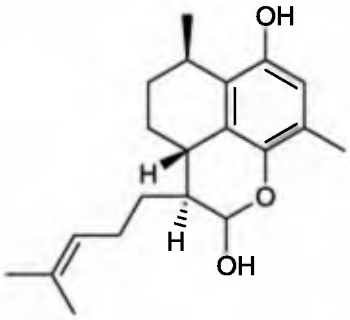
(**Ii**).

Preferably, A---B is CH=C.

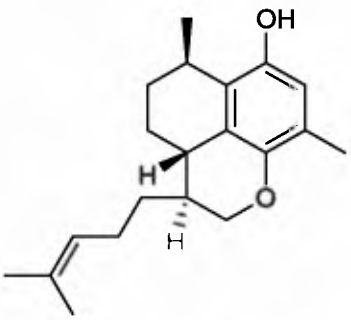
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OH
OH
HO
H

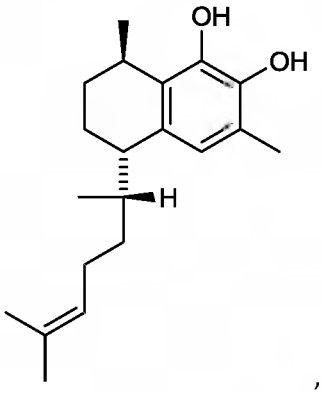
,


OH
H
O
H
OH

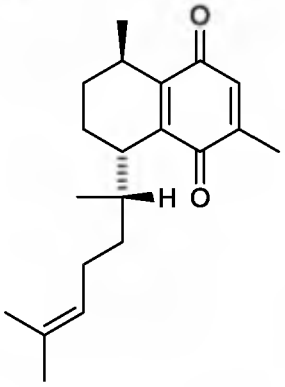
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OH
H
O
H

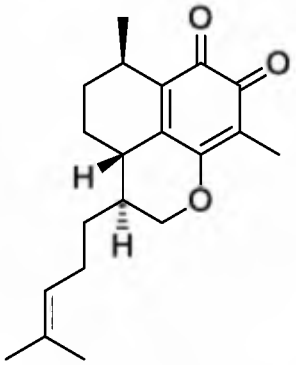
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OH
OH
H

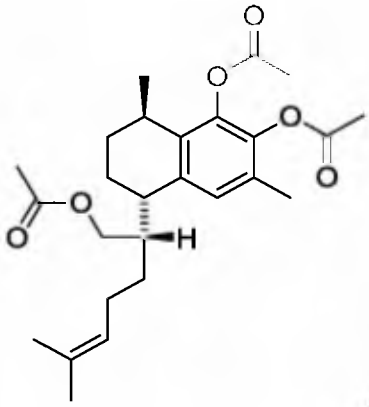
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O
H
O

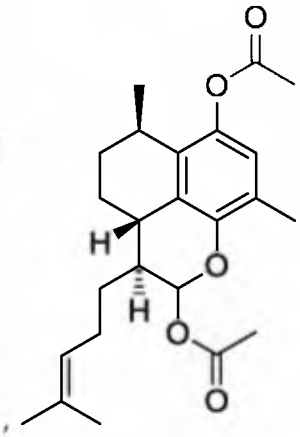
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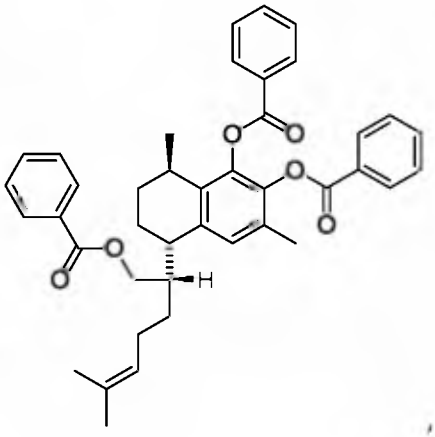
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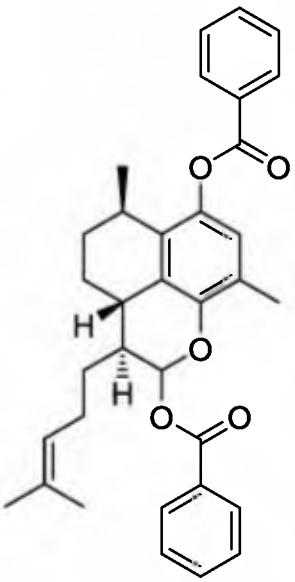
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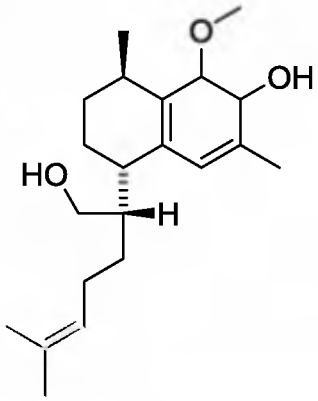
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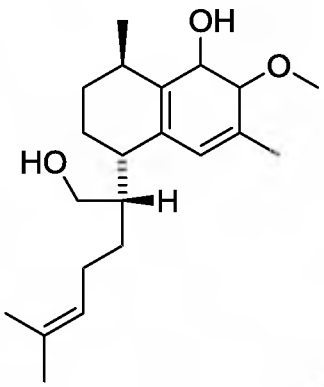

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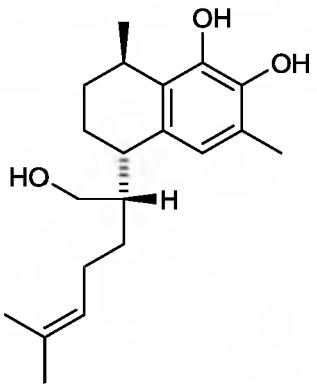
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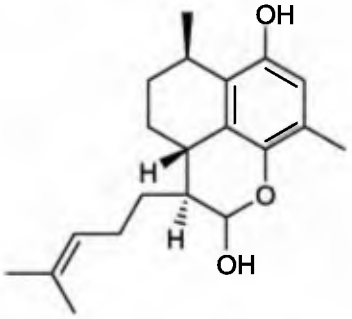


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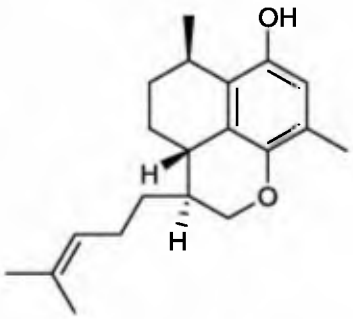
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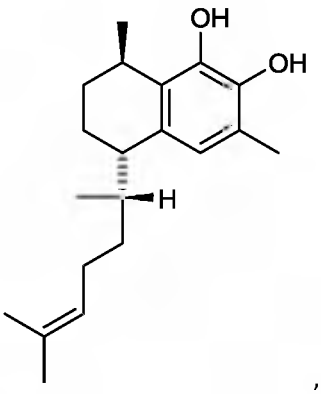


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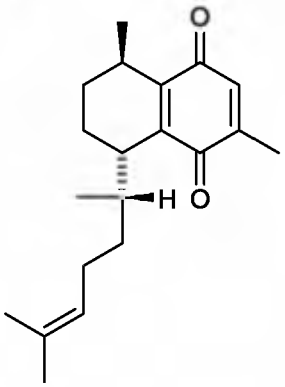


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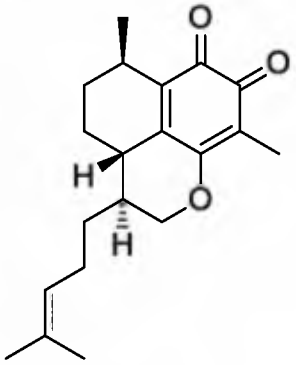




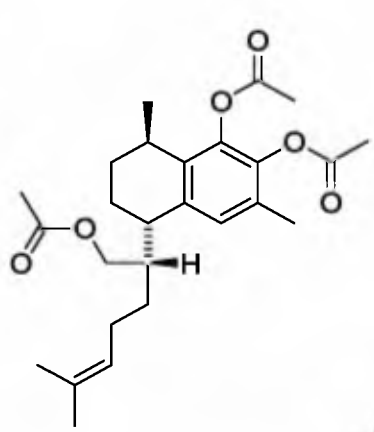
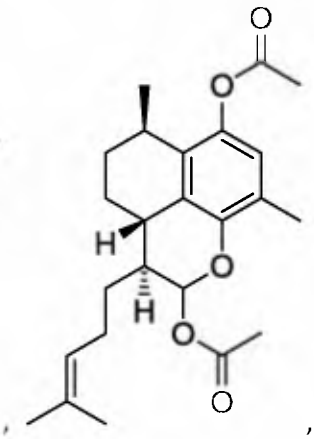
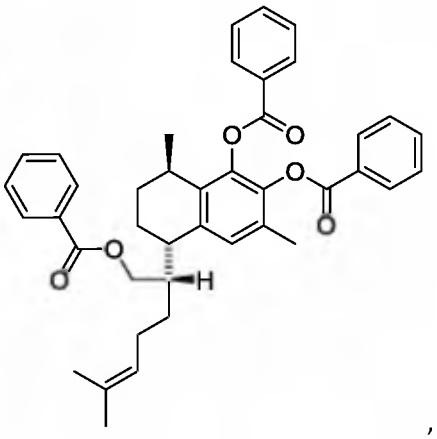
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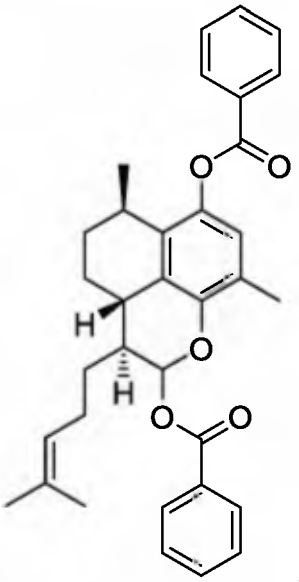
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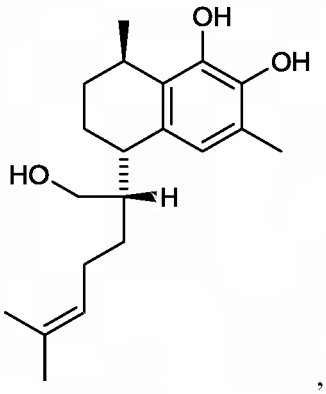
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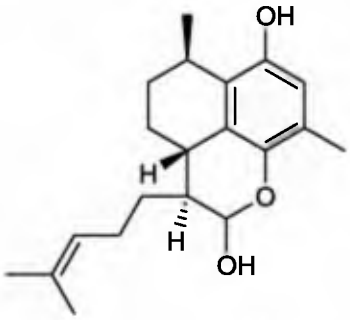

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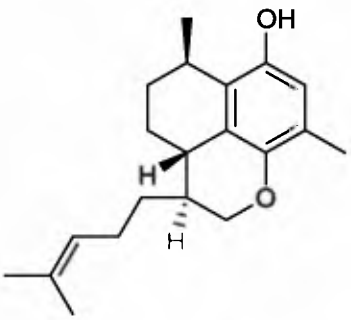
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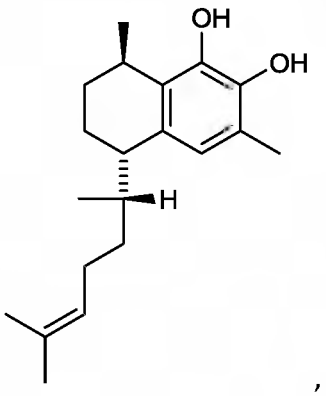

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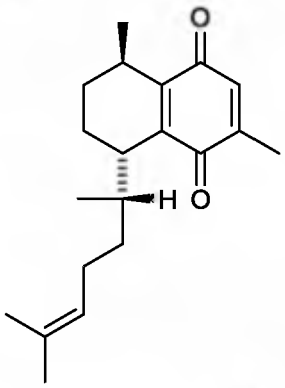
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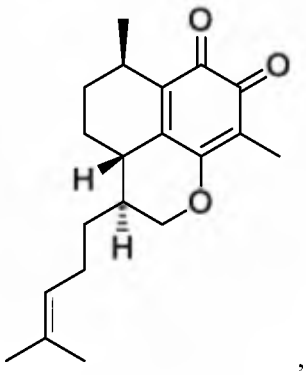


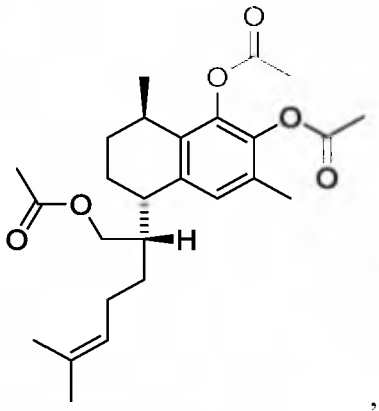
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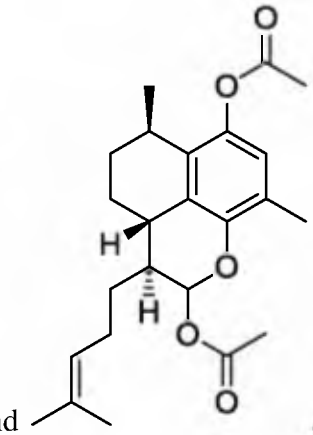
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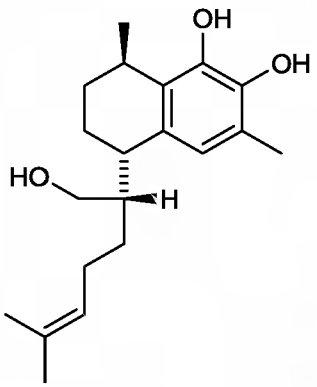
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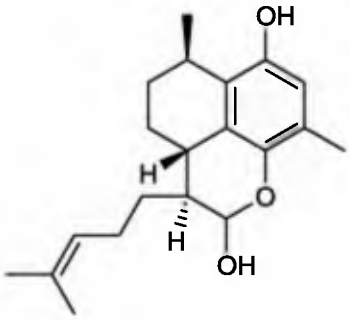
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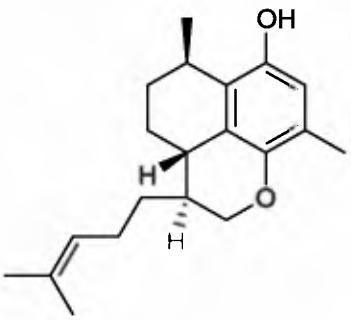


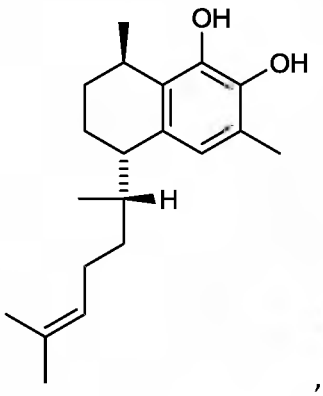
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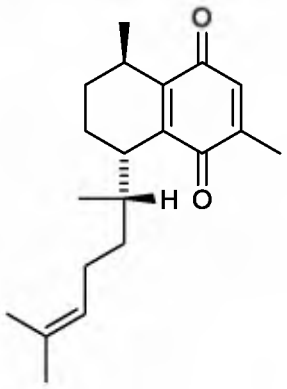
Preferably, the compound is selected from the group consisting of:

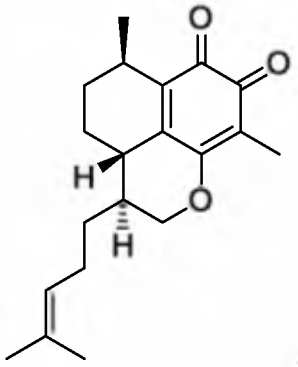


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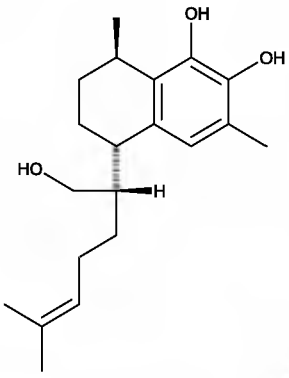


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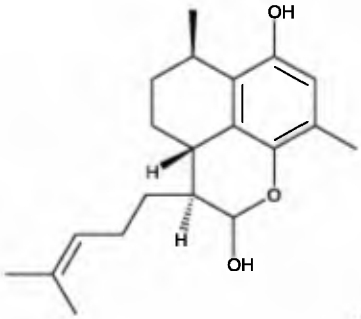


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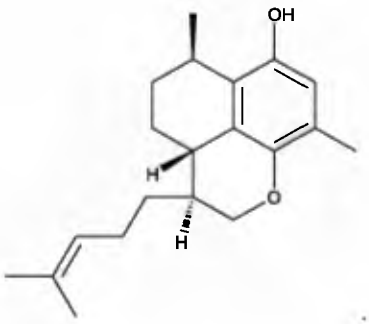
The compound is preferably:



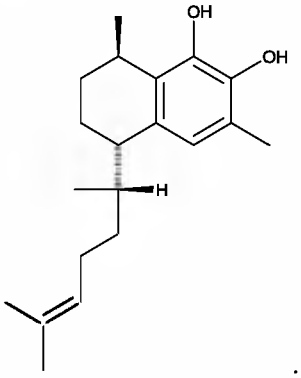
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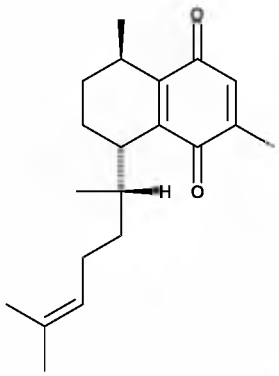
The compound is preferably:



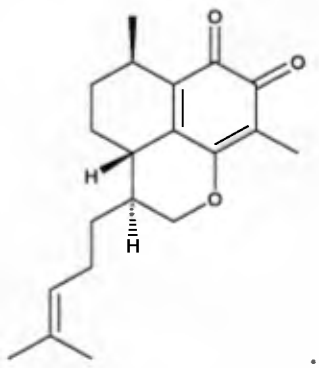
Preferably, the compound is:



The compound is preferably:



Preferably, the compound is:



Preferably, the cancer is bladder cancer, bone cancer, brain cancer, breast cancer, a cancer of the central nervous system, cancer of the adrenal glands, cancer of the placenta, cancer of the testis, cervical cancer, colon cancer, kidney cancer, head and neck cancer, myeloma, leukemia, liver cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, stomach cancer, thyroid cancer, uterine cancer, a carcinoma, a lymphoma, a sarcoma, eye cancer, esophageal cancer, bile duct cancer or vulva cancer.

The cancer of the central nervous system is preferably a glioma. Preferably, the cancer of the central nervous system is a medulloblastoma. The cancer of the central nervous system is preferably a neuroblastoma.

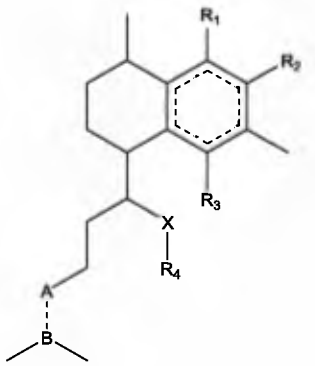
Preferably, the lung cancer is a non-small cell lung cancer. The lung cancer is preferably a small cell lung cancer.

Preferably, the carcinoma is adenosquamous cell carcinoma or squamous cell carcinoma.

The sarcoma is preferably a liposarcoma, rhabdomyosarcoma, or fibrosarcoma. Preferably, the sarcoma is a soft tissue sarcoma. The soft tissue sarcoma is preferably a soft tissue osteosarcoma.

Preferably, the lymphoma is Burkitt's lymphoma, Hodgkin's lymphoma, or non-Hodgkin's lymphoma.

Also disclosed herein is a compound of Formula (**I**),



(I)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CH_2;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is CHOH;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

Preferably:

X is C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

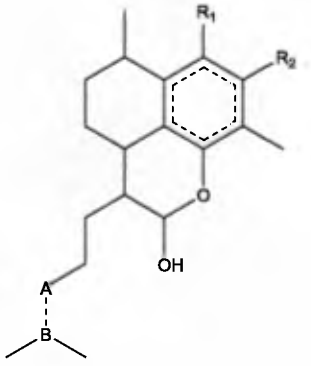
and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

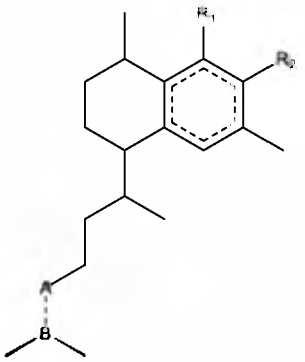
A---B is CH=C or CH_2-CH.

Preferably, the compound is a compound of Formula (**Ia**):



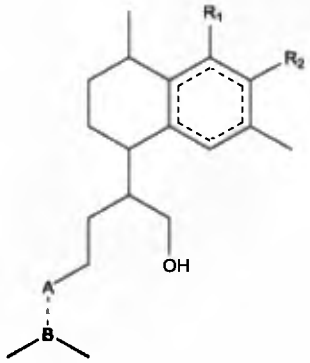
(**Ia**).

Preferably, the compound is a compound of Formula (**Ib**):



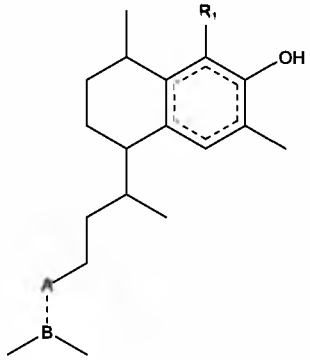
(**Ib**).

Preferably, the compound is a compound of Formula (**Ic**):



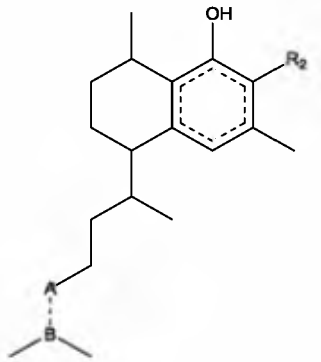
(**Ic**).

Preferably, the compound is a compound of Formula (**Id**):



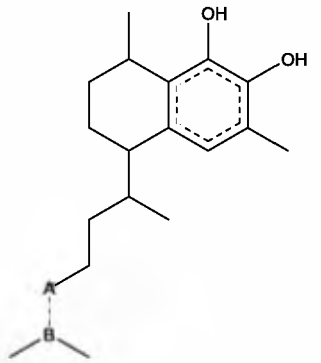
(**Id**).

Preferably, the compound is a compound of Formula (**Ie**):



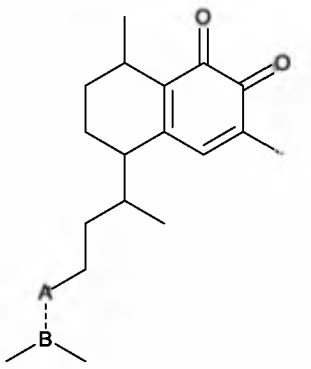
(**Ie**).

Preferably, the compound is a compound of Formula (**If**):



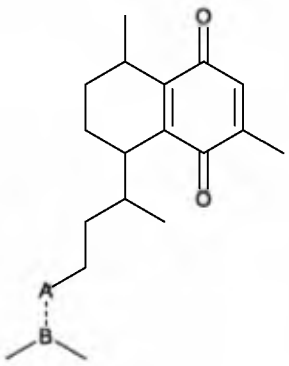
(**If**).

Preferably, the compound is a compound of Formula (**Ig**):



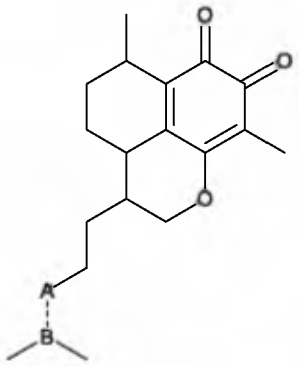
(**Ig**).

Preferably, the compound is a compound of Formula (**Ih**):



(**Ih**).

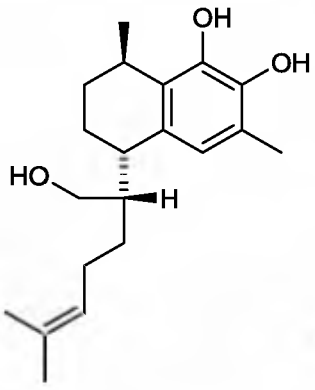
Preferably, the compound is a compound of Formula (**Ii**):



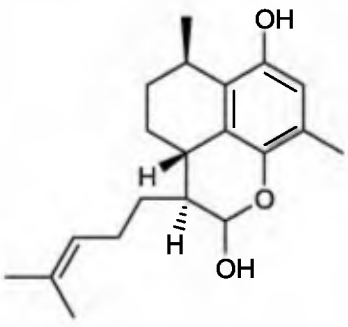
(**Ii**).

Preferably, A---B is CH=CH.

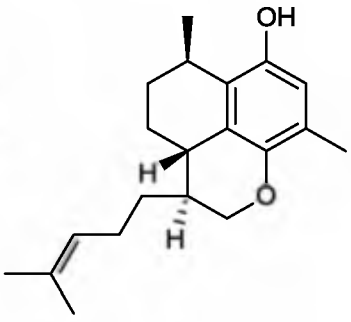
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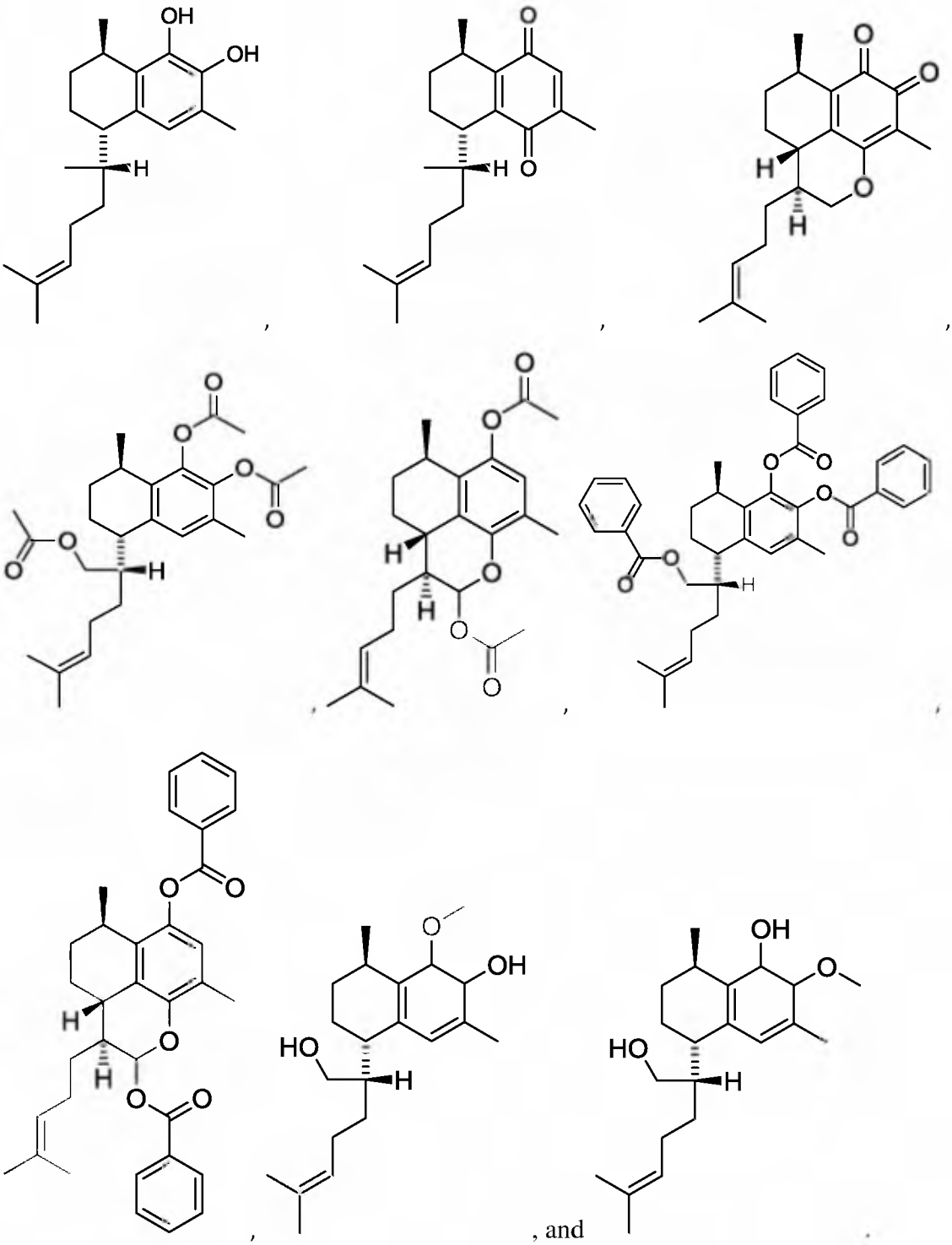


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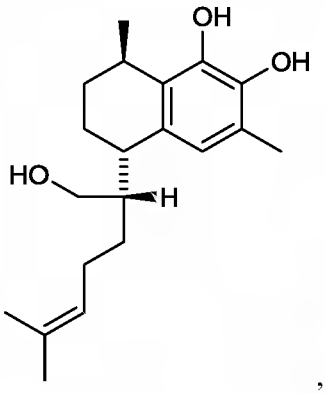
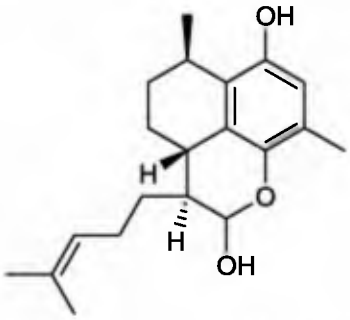
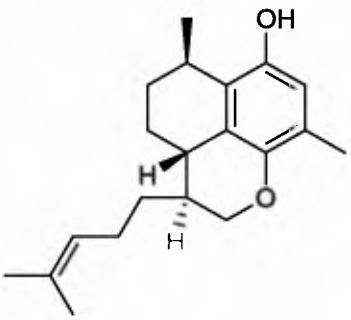
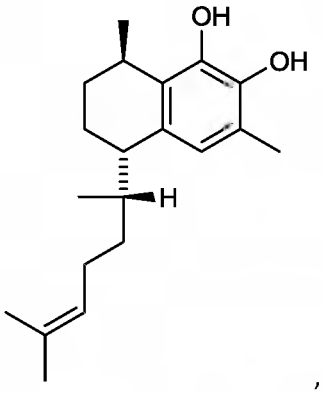
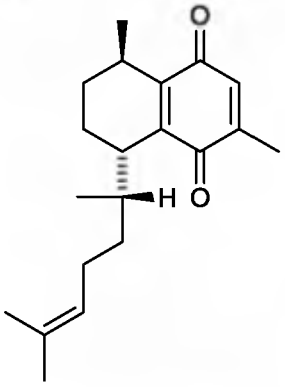
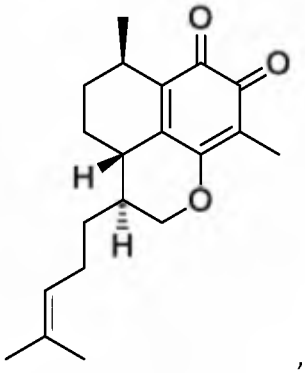
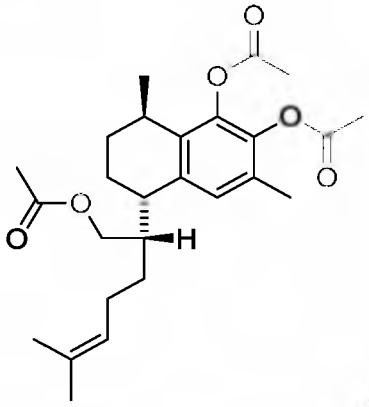
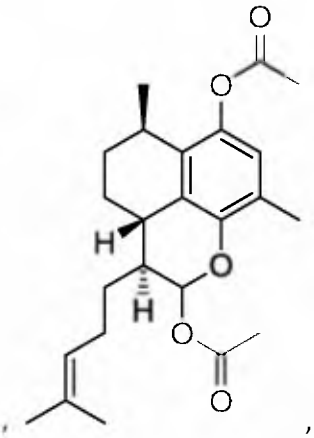
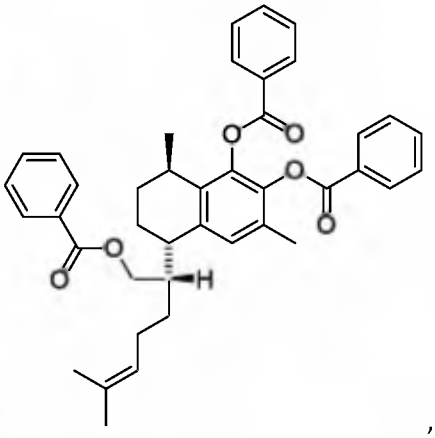


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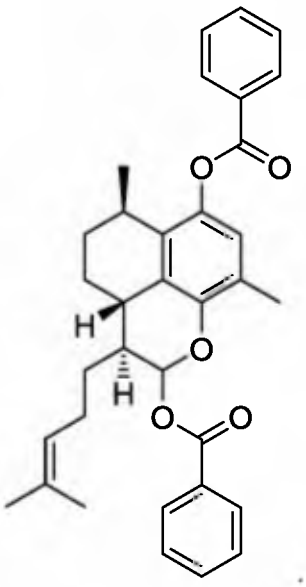




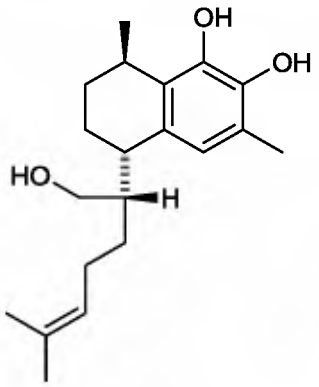
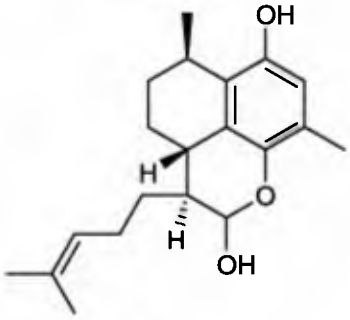
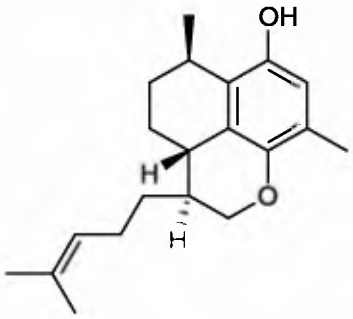
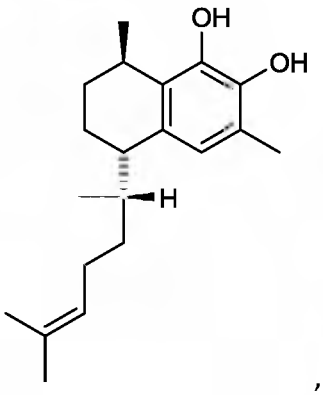
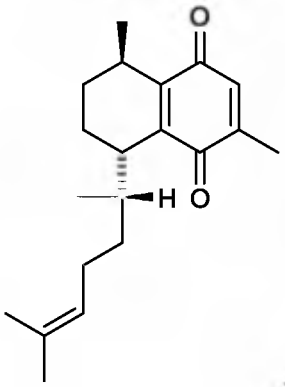
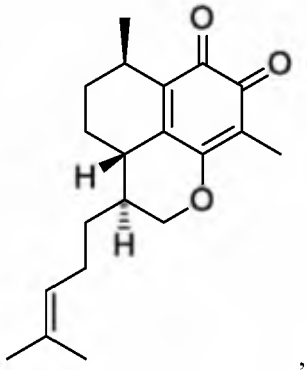
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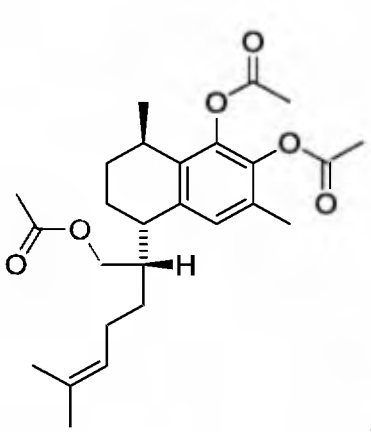
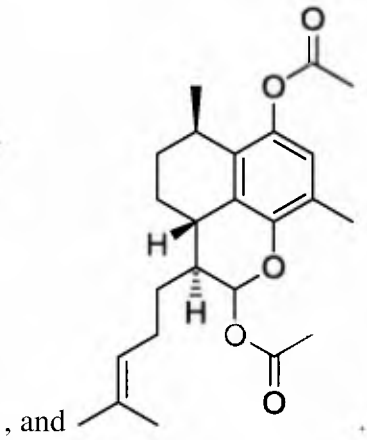

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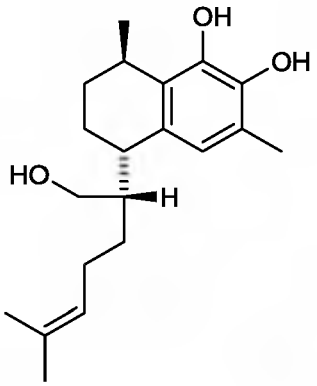
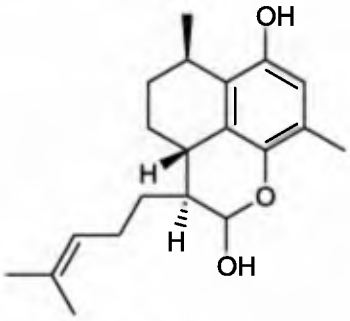
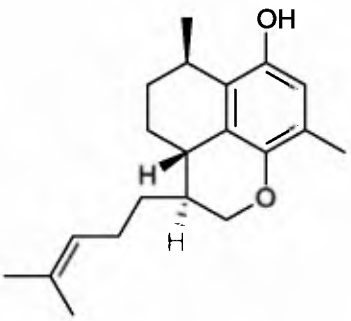
The compound is preferably selected from the group consisting of:


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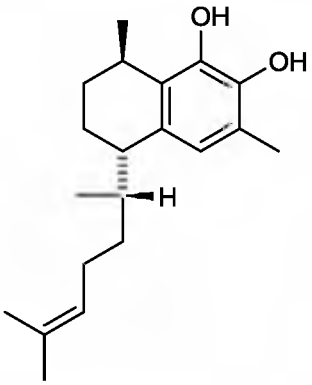
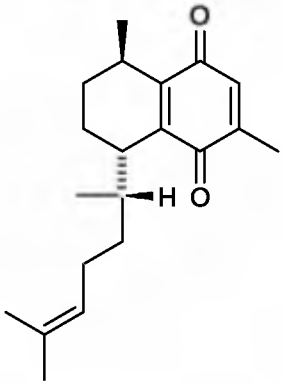
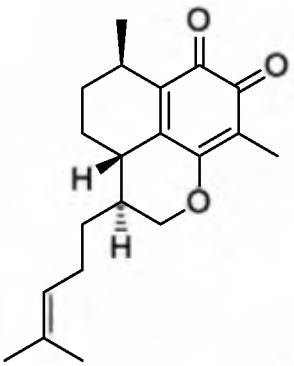



, and .

Preferably, the compound is selected from the group consisting of:

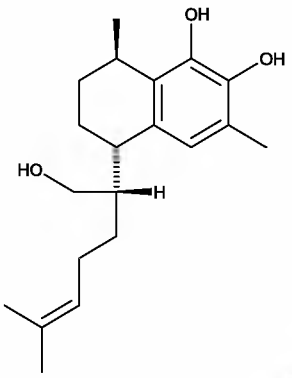




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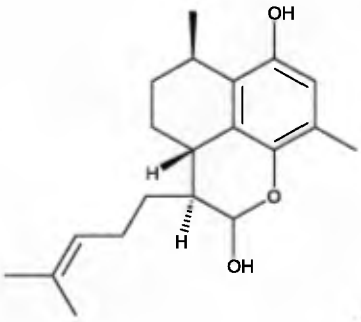




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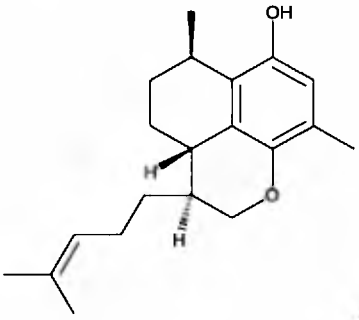
The compound is preferably:



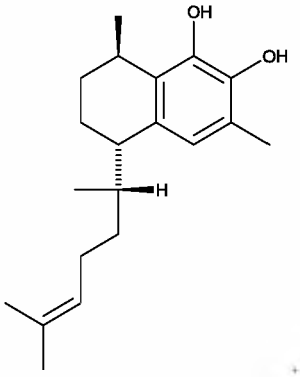
Preferably, the compound is:



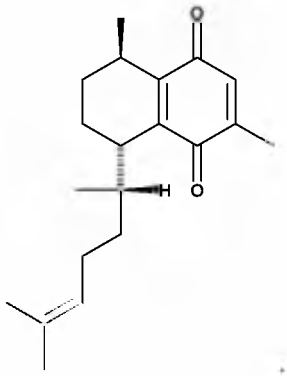
The compound is preferably:



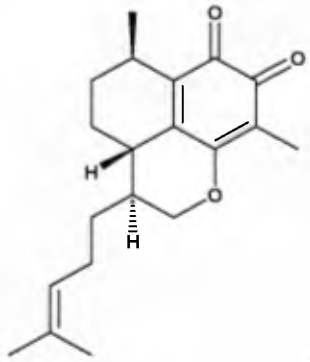
Preferably, the compound is:



The compound is preferably:



Preferably, the compound is:



Also disclosed herein is a pharmaceutical composition comprising a compound, geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof, as described herein, and a pharmaceutically acceptable excipient.

Also disclosed herein is a pharmaceutical composition comprising a compound, geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof, as described herein, or a mixture thereof, and a pharmaceutically acceptable excipient.

The compounds or pharmaceutical compositions disclosed above are preferably for use as a medicament.

The compounds or pharmaceutical compositions disclosed above are preferably for use in therapy.

Also disclosed is a compound described above isolated from propolis, wherein the propolis originates from plants of the *Myoporum* genus. Preferably, the propolis originates from *Myoporum insulare*.

Also disclosed is a compound described above isolated from the resin, gum or exudate of *Myoporum* genus. Preferably, the compound is isolated from the resin, gum or exudate of *Myoporum insulare*.

Also disclosed is a method of treating a disease or disorder, the method comprising administering a therapeutically effective amount of a compound or a composition described herein.

Also disclosed is use of a compound described herein in the preparation of a medicament for treating a disease or disorder.

Also disclosed herein is use of a compound or a composition described herein in treating a disease or disorder.

Also disclosed herein is a compound or a composition described herein for use in treating a disease or disorder.

Preferably, the disease or disorder is selected from the group consisting of: acute coronary syndrome, an aging-related disease or disorder; an allergic disease or a related condition; Alzheimer's disease, atherosclerosis, an autoimmune disease; a bacterial infection, cancer; dementia, depression or a related condition; diabetes; dyslipidemia, hyperlipidemia, hypertension, itchytosis, an immune disease; a metabolic disease or disorder; a neurological disease or disorder; obesity; Parkinson's disease; pain; rheumatoid arthritis and a skin disease or disorder.

The disease or disorder is preferably cancer.

Preferably, the cancer is bladder cancer, bone cancer, brain cancer, breast cancer, a cancer of the central nervous system, cancer of the adrenal glands, cancer of the placenta, cancer of the testis, cervical cancer, colon cancer, kidney cancer, head and neck cancer, myeloma, leukemia, liver cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, stomach cancer, thyroid cancer, uterine cancer, a carcinoma, a lymphoma, a sarcoma, eye cancer, esophageal cancer, bile duct cancer or vulva cancer.

The cancer of the central nervous system is preferably a glioma. Preferably, the cancer of the central nervous system is a medulloblastoma. The cancer of the central nervous system is preferably a neuroblastoma.

Preferably, the lung cancer is a non-small cell lung cancer. The lung cancer is preferably a small cell lung cancer.

Preferably, the carcinoma is adenosquamous cell carcinoma or squamous cell carcinoma.

The sarcoma is preferably a liposarcoma, rhabdomyosarcoma, or fibrosarcoma. Preferably, the sarcoma is a soft tissue sarcoma. The soft tissue sarcoma is preferably a soft tissue osteosarcoma.

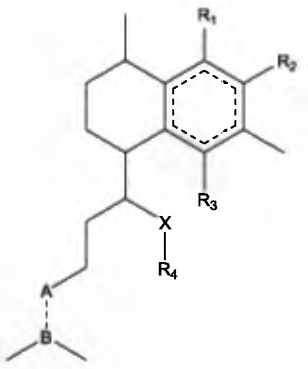
Preferably, the lymphoma is Burkitt's lymphoma, Hodgkin's lymphoma, or non-Hodgkin's lymphoma.

The skin disease or disorder is preferably selected from the group consisting of: eczema, psoriasis, acne, a scar, inflammation, a burn, sunburn, skin damage and skin irritation.

Representative compounds were evaluated for pharmacological activity and were found to be useful in modulating a number of diseases or disorders. For example, the compounds were found to inhibit cancer cell proliferation and showed moderate to strong inhibition of various targets associated with cancer pathology. Further discussion of compound activity is presented below in the Examples.

Example Embodiments

1. A method of treating a cancer, the method comprising administering a therapeutically effective amount of a compound of Formula (**I**),



(**I**)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof, or pharmaceutical composition including said compounds, to a subject in need thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

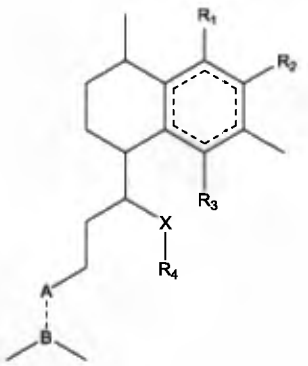
and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH.

2. Use of a compound of Formula (**I**),



(**I**)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

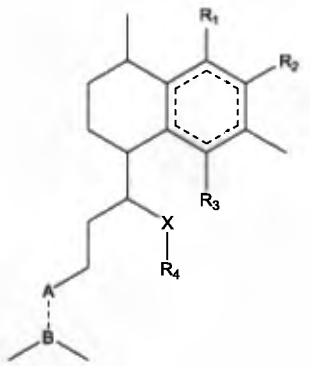
where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH,

in the preparation of a medicament for treating a cancer.

3. Use of a compound of Formula (**I**),



(I)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH,

in treating a cancer.

4. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl; and

A---B is CH=C or CH_2-CH.

5. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph; and

A---B is CH=C or CH_2-CH.

6. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

7. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein:

X is CH_2;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

8. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein:

X is CHOH;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

9. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein:

X is C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

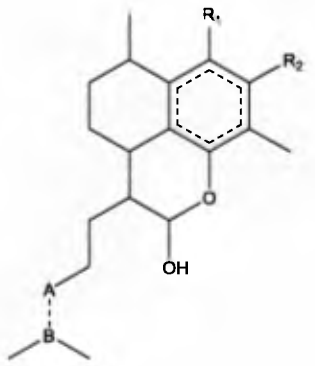
and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

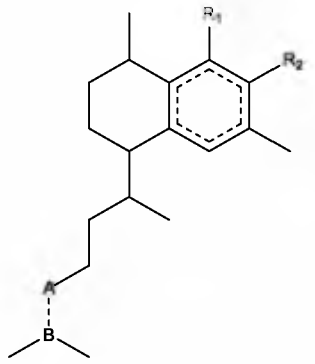
A---B is CH=C or CH_2-CH.

10. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein the compound is a compound of Formula (**Ia**):



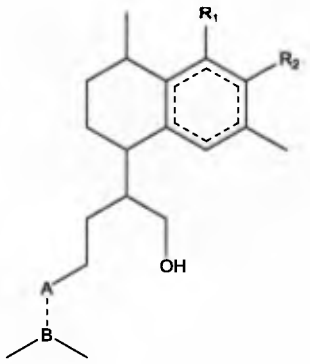
(**Ia**).

11. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein the compound is a compound of Formula (**Ib**):



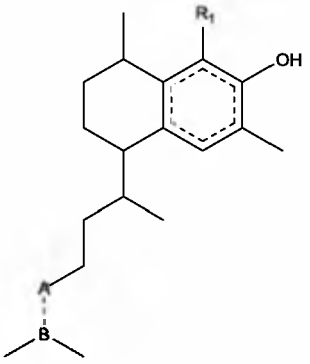
(**Ib**).

12. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein the compound is a compound of Formula (**Ic**):



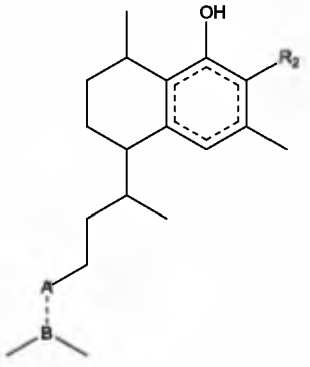
(**Ic**).

13. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein the compound is a compound of Formula (**Id**):



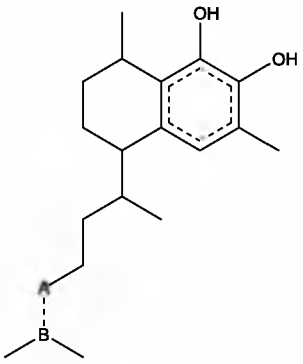
(**Id**).

14. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein the compound is a compound of Formula (**Ie**):



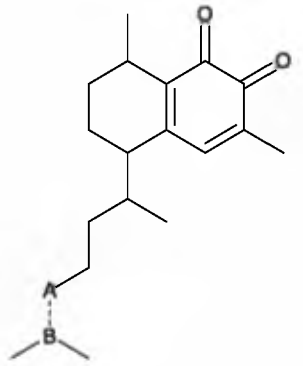
(**Ie**).

15. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein the compound is a compound of Formula (**If**):



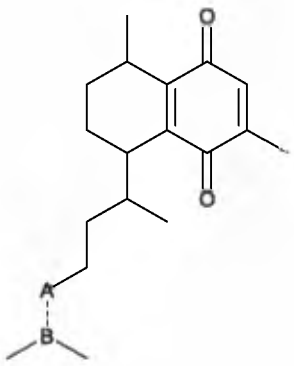
(**If**).

16. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein the compound is a compound of Formula (**Ig**):



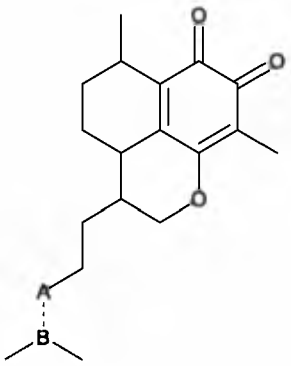
(**Ig**).

17. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein the compound is a compound of Formula (**Ih**):



(**Ih**).

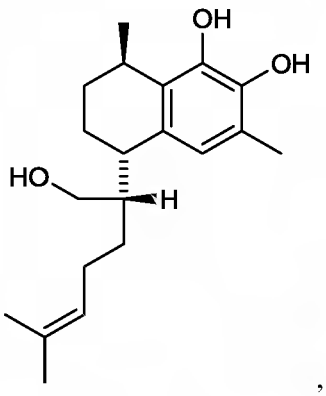
18. The method according to example embodiment 1 or the use according to example embodiment 2 or example embodiment 3, wherein the compound is a compound of Formula (**Ii**):



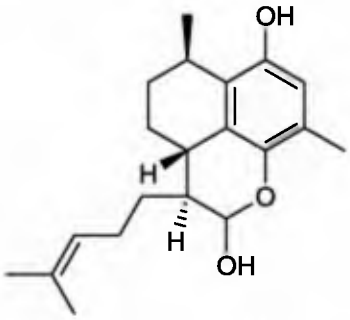
(**Ii**).

19. The method or use according to any one of example embodiments 1 to 16, wherein A---B is CH=C.

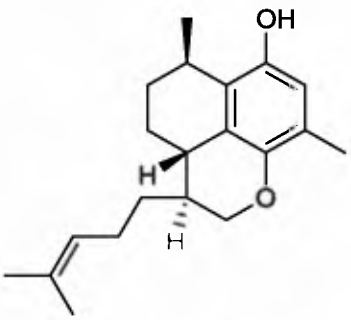
20. The method according to any one of example embodiments 1 to 19 or the use according to any one of example embodiments 2 to 19, wherein the compound is selected from the group consisting of:


OH
OH
HO
H

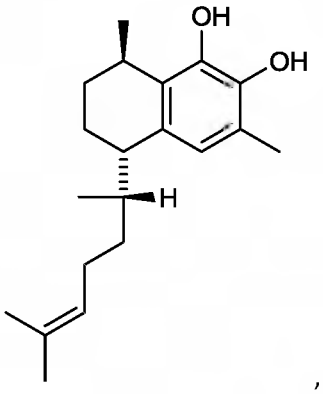
,


OH
H
O
H
OH

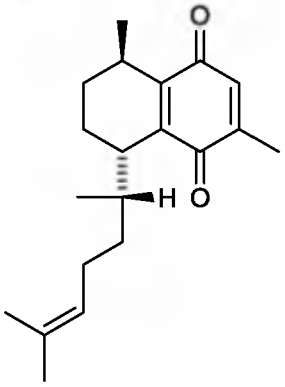
,


OH
H
O
H

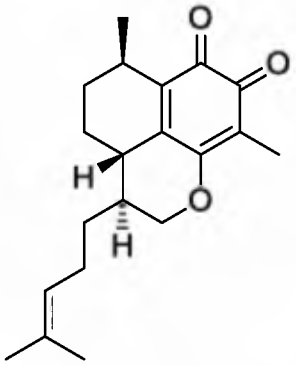
,


OH
OH
H

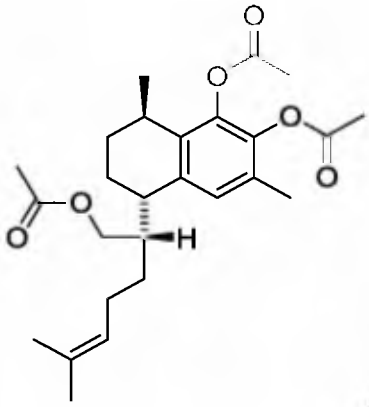
,


O
H
O

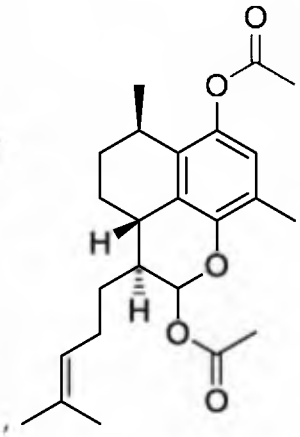
,


O
O
H
O
H

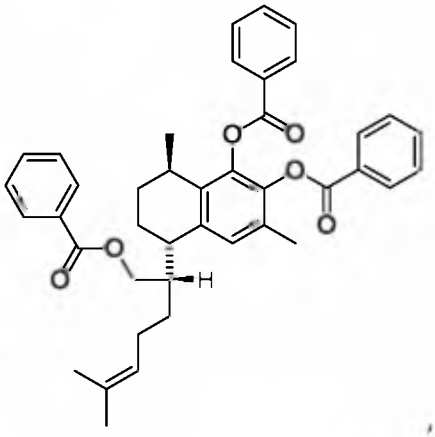
,


O
O
O
O
O
H

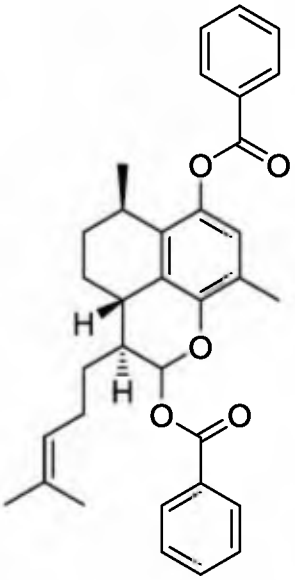
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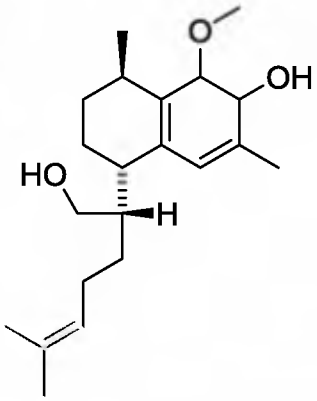

O
O
H
O
H
O
O

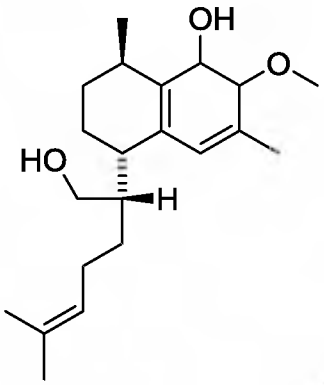
,


O
O
O
O
O
H

,

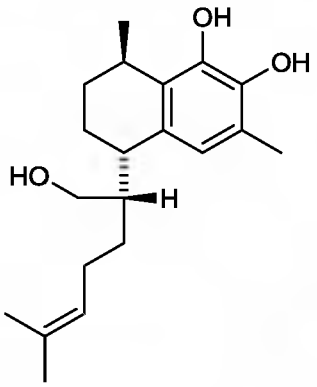


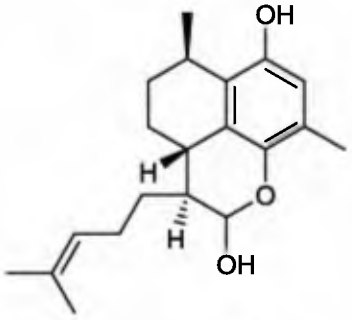
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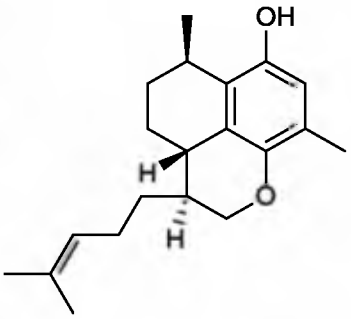
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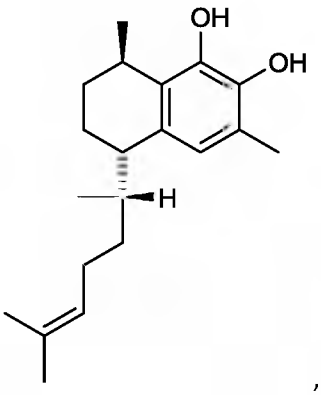
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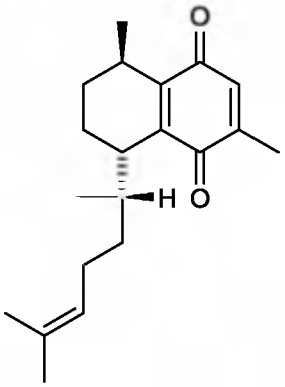
21. The method or use according to example embodiment 20, wherein the compound is selected from the group consisting of:

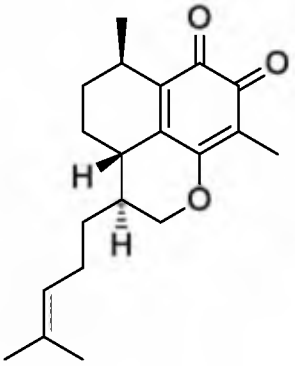


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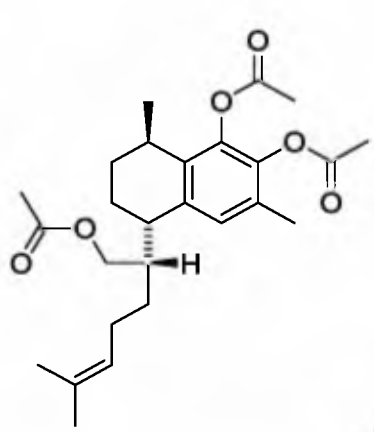
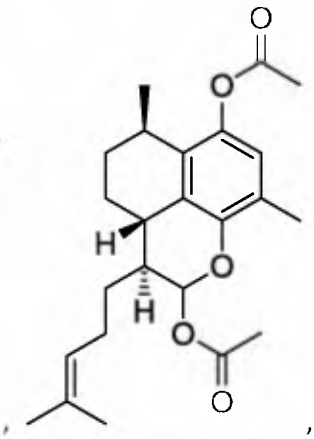
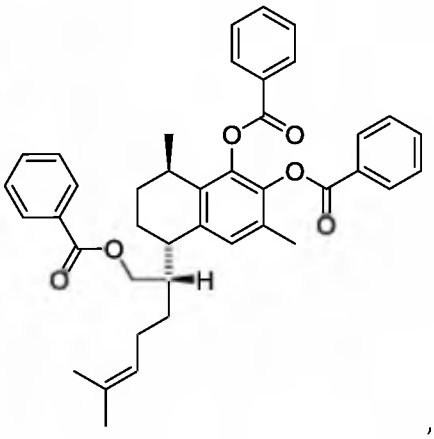
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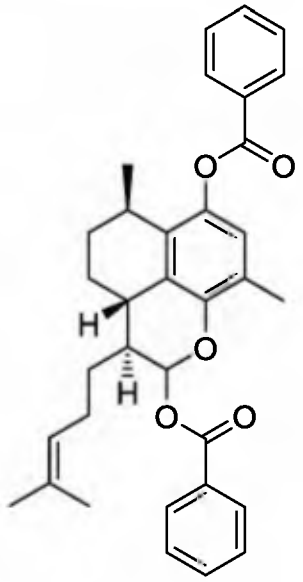
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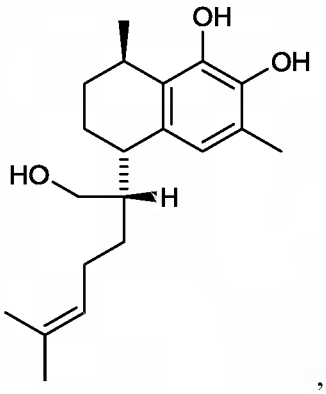
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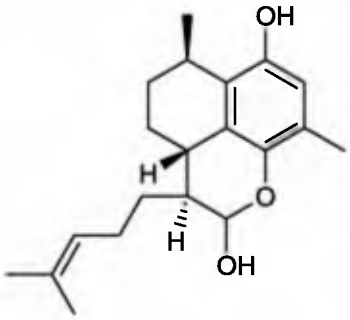




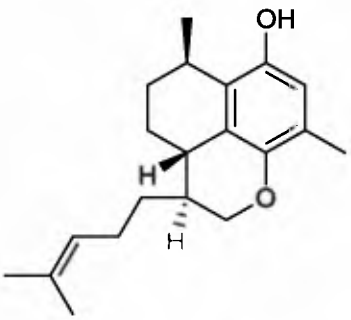
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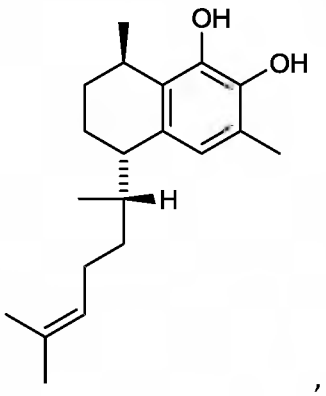


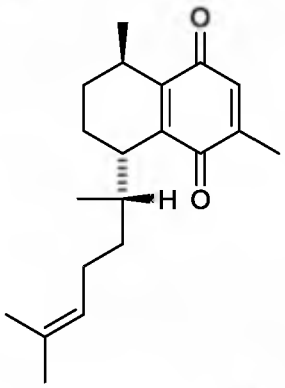
22. The method or use according to example embodiment 21, wherein the compound is selected from the group consisting of:

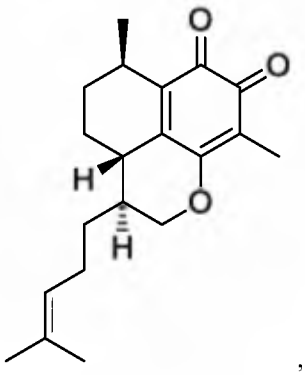


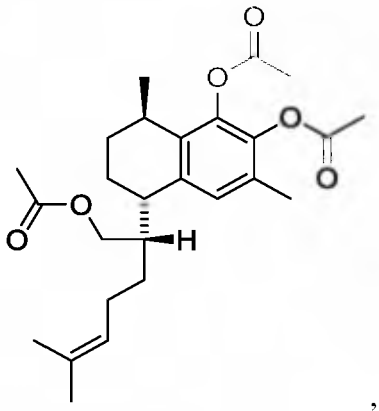
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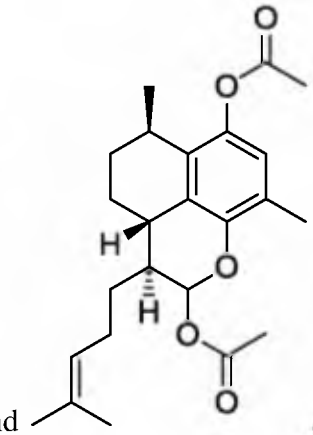
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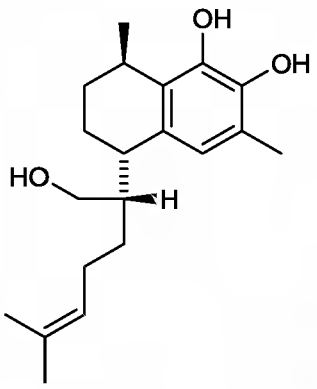
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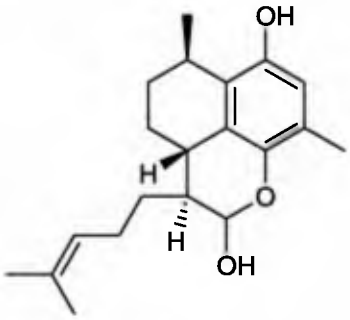
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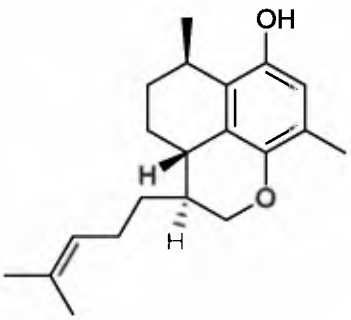


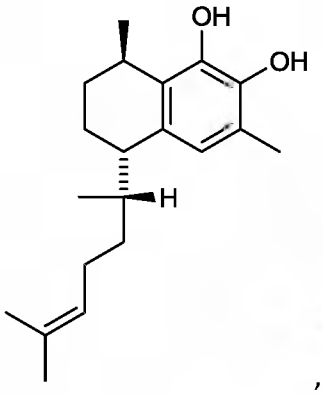
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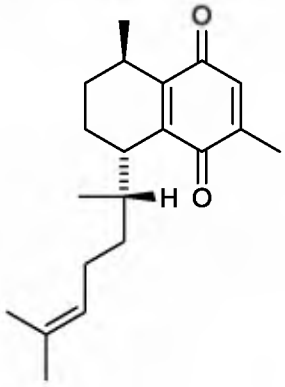
23. The method or use according to example embodiment 22, wherein the compound is selected from the group consisting of:

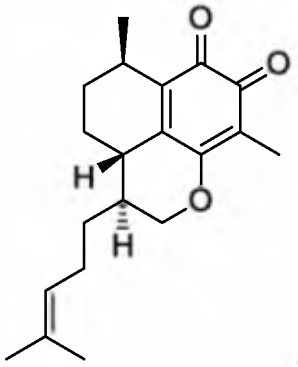


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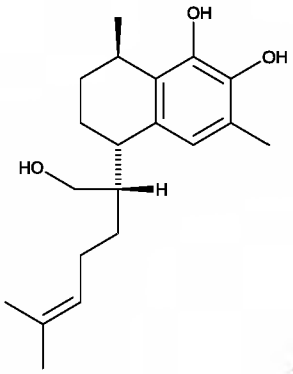


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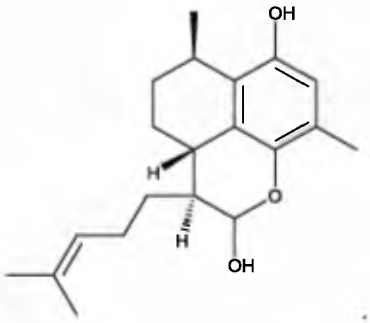
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24. The method or use according to example embodiment 23, wherein the compound is:

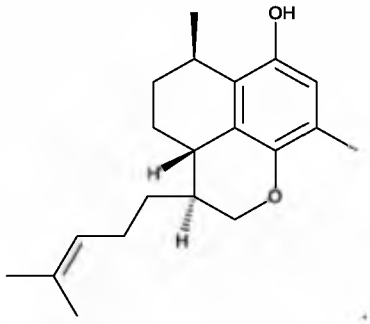


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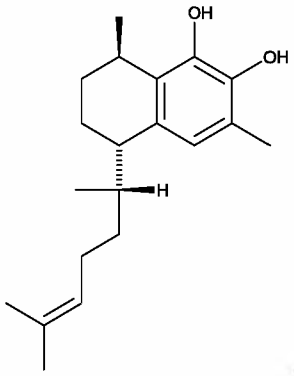
25. The method or use according to example embodiment 23, wherein the compound is:



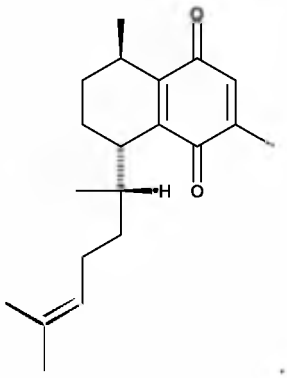
26. The method or use according to example embodiment 23, wherein the compound is:



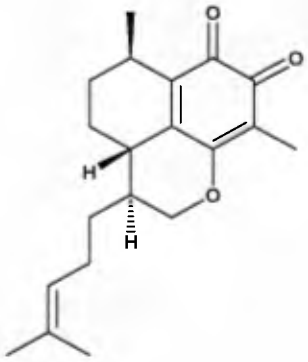
27. The method or use according to example embodiment 23, wherein the compound is:



28. The method or use according to example embodiment 23, wherein the compound is:



29. The method or use according to example embodiment 23, wherein the compound is:



30. The method according to any one of example embodiments 1 to 29 or the use according to any one of example embodiments 2 to 29, wherein the cancer is bladder cancer, bone cancer, brain cancer, breast cancer, a cancer of the central nervous system, cancer of the adrenal glands, cancer of the placenta, cancer of the testis, cervical cancer, colon cancer, kidney cancer, head and neck cancer, myeloma, leukemia, liver cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, stomach cancer, thyroid cancer, uterine cancer, a carcinoma, a lymphoma, a sarcoma, eye cancer, esophageal cancer, bile duct cancer or vulva cancer.

31. The method or use according to example embodiment 30, wherein the cancer of the central nervous system is a glioma.

32. The method or use according to example embodiment 30, wherein the cancer of the central nervous system is a medulloblastoma.

33. The method or use according to example embodiment 30, wherein the cancer of the central nervous system is a neuroblastoma.

34. The method or use according to example embodiment 30, wherein the lung cancer is a non-small cell lung cancer.

35. The method or use according to example embodiment 30, wherein the lung cancer is a small cell lung cancer.

36. The method or use according to example embodiment 30, wherein the carcinoma is adenosquamous cell carcinoma or squamous cell carcinoma.

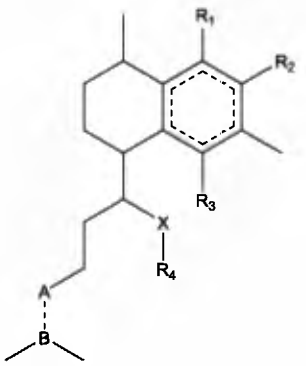
37. The method or use according to example embodiment 30, wherein the sarcoma is a liposarcoma, rhabdomyosarcoma, or fibrosarcoma.

38. The method or use according to example embodiment 30, wherein the sarcoma is a soft tissue sarcoma.

39. The method or use according to example embodiment 38, wherein the soft tissue sarcoma is a soft tissue osteosarcoma.

40. The method according to example embodiment 30, wherein the lymphoma is Burkitt's lymphoma, Hodgkin's lymphoma, or non-Hodgkin's lymphoma.

41. A compound of Formula (**I**),



(**I**)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC_{4\text{-}5}$alkadienyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl, $OC(O)C_{4\text{-}5}$alkadienyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

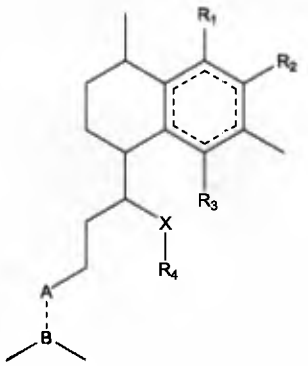
and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH.

42. A compound of Formula (**I**),



(**I**)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl, $OC(O)C_{4-5}$alkadienyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, OC_{4-5}alkadienyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or $OC(O)C_{4-5}$alkadienyl; and

A---B is CH=C or CH_2-CH,

for use in treating a cancer.

43. The compound according to example embodiment 41 or example embodiment 42, wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph, $OC(O)C_{2-5}$alkenyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, OC_{2-5}alkenyl, $OC(O)C_{1-5}$alkyl, OC(O)Ph or $OC(O)C_{2-5}$alkenyl; and

A---B is CH=C or CH_2-CH.

44. The compound according to example embodiment 41 or example embodiment 42, wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl, OC(O)Ph or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph; and

A---B is CH=C or CH_2-CH.

45. The compound according to example embodiment 41 or example embodiment 42, wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

where X is CH_2, CHOH or C(O), R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

46. The compound according to example embodiment 41 or example embodiment 42, wherein:

X is CH_2;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

47. The compound according to example embodiment 41 or example embodiment 42, wherein:

X is CHOH;

R_1 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_2 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

R_3 is independently H, OH, OC_{1-5}alkyl, $OC(O)C_{1-5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, OC_{1-5}alkyl, OCH_2Ph, $OC(O)C_{1-5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or OC_{1-5}alkyl or $OC(O)C_{1-5}$alkyl; and

A---B is CH=C or CH_2-CH.

48. The compound according to example embodiment 41 or example embodiment 42, wherein:

X is C(O);

R_1 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;

R_2 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;

R_3 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;

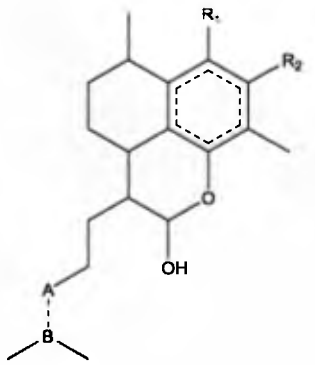
and no more than one of R_1, R_2 and R_3 can be H;

R_4 is H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC(O)C_{1\text{-}5}$alkyl or OC(O)Ph;

or X and R_3 form a six-membered ether ring or lactone ring, or a six membered ring containing a hemiacetal carbon atom or an acetal carbon atom wherein R_4 is respectively OH or $OC_{1\text{-}5}$alkyl or $OC(O)C_{1\text{-}5}$alkyl; and

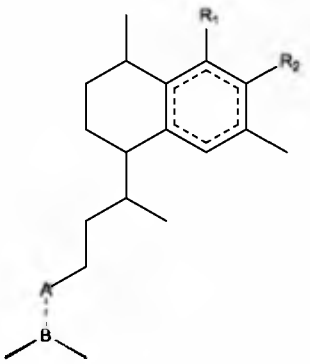
A---B is CH=C or CH_2-CH.

49. The compound according to example embodiment 41 or example embodiment 42, wherein the compound is a compound of Formula (**Ia**):



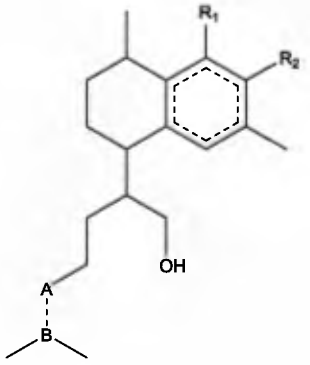
(**Ia**).

50. The compound according to example embodiment 41 or example embodiment 42, wherein the compound is a compound of Formula (**Ib**):



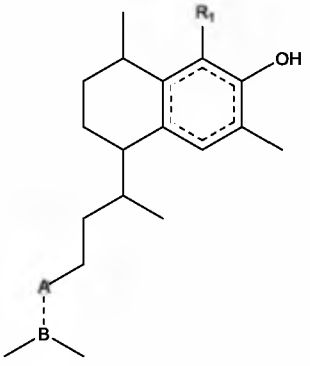
(**Ib**).

51. The compound according to example embodiment 41 or example embodiment 42, wherein the compound is a compound of Formula (**Ic**):



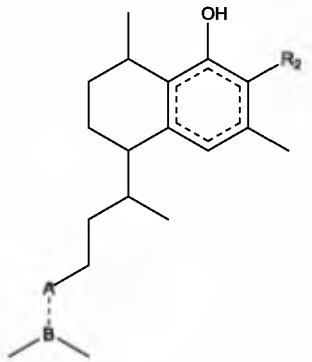
(**Ic**).

52. The compound according to example embodiment 41 or example embodiment 42, wherein the compound is a compound of Formula (**Id**):



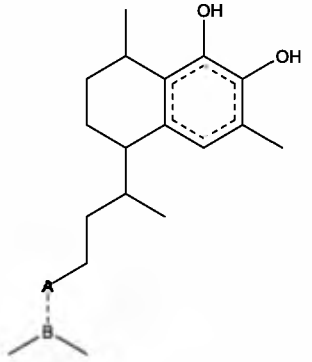
(**Id**).

53. The compound according to example embodiment 41 or example embodiment 42, wherein the compound is a compound of Formula (**Ie**):



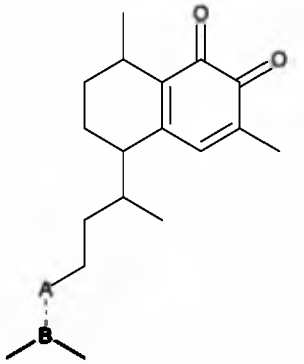
(**Ie**).

54. The compound according to example embodiment 41 or example embodiment 42, wherein the compound is a compound of Formula (**If**):



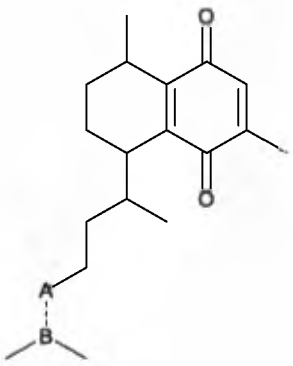
(**If**).

55. The compound according to example embodiment 41 or example embodiment 42, wherein the compound is a compound of Formula (**Ig**):



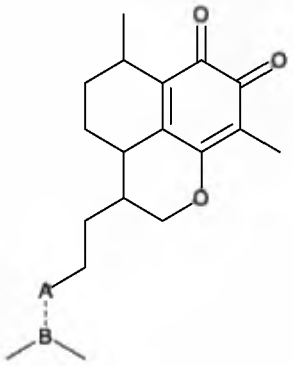
(**Ig**).

56. The compound according to example embodiment 41 or example embodiment 42, wherein the compound is a compound of Formula (**Ih**):



(**Ih**).

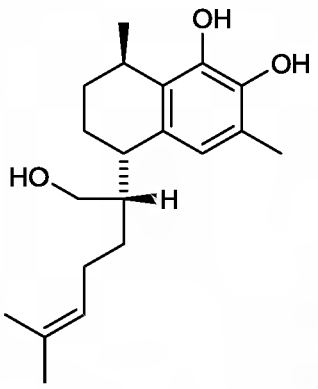
57. The compound according to example embodiment 41 or example embodiment 42, wherein the compound is a compound of Formula (**Ii**):



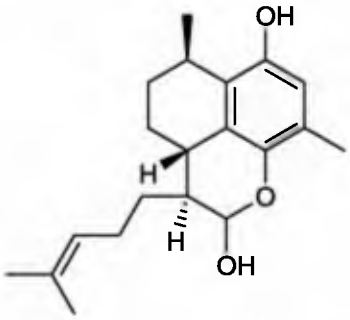
(**Ii**).

58. The compound according to any one of example embodiments 41 to 57, wherein A---B is CH=C.

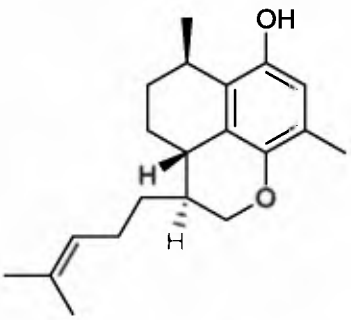
59. The compound according to any one of example embodiments 41 to 58, wherein the compound is selected from the group consisting of:


OH
OH
HO
H

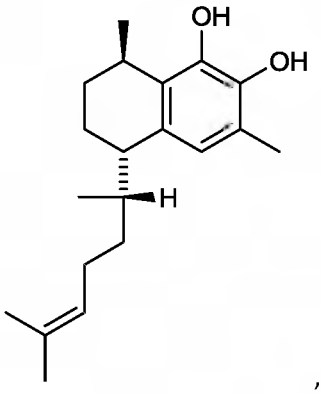
,


OH
H
O
H
OH

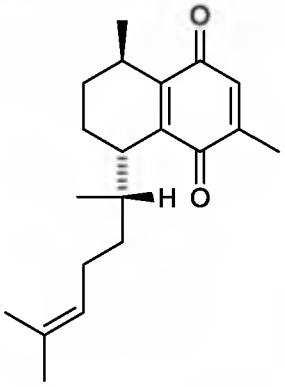
,


OH
H
O
H

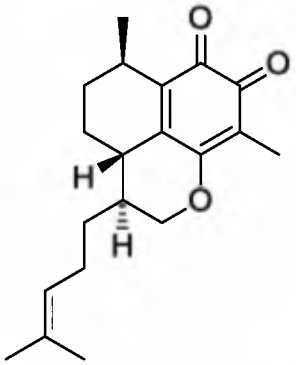
,


OH
OH
H

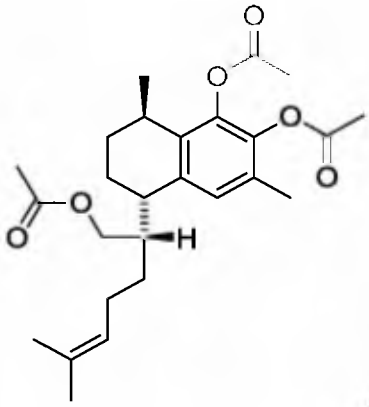
,


O
H
O

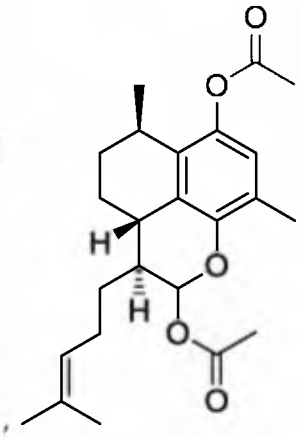
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O
O
H
O
H

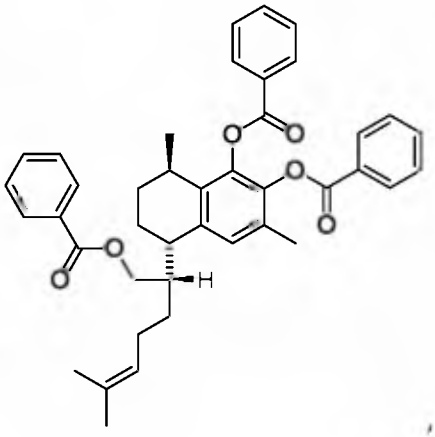
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O
O
O
O
O
H

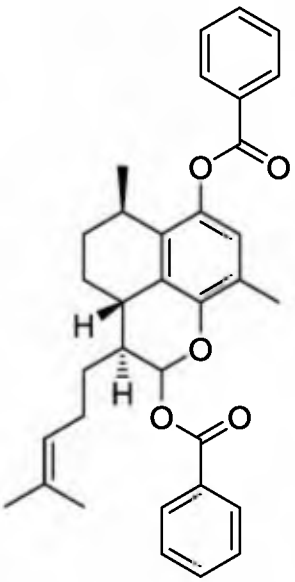
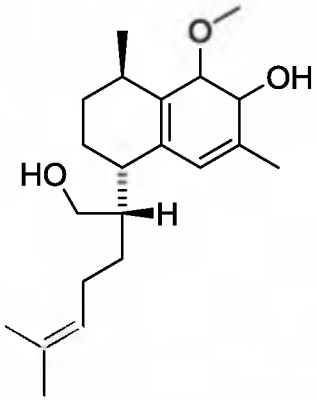
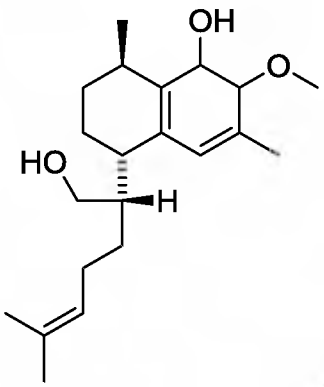
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O
O
H
O
H
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O

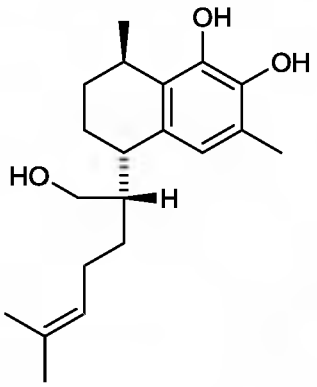
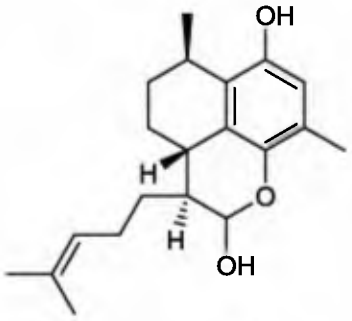
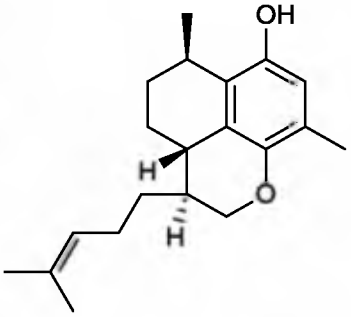
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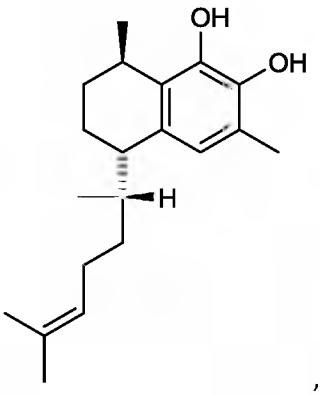
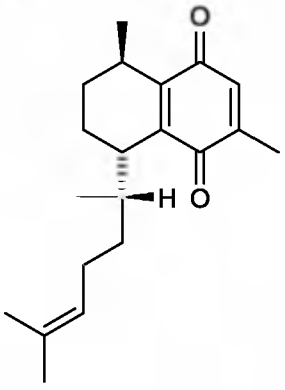
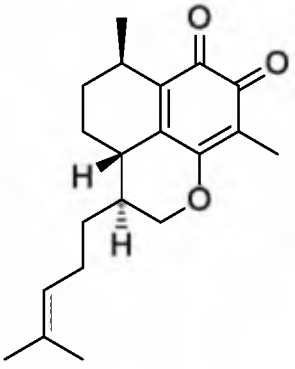

O
O
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O
H

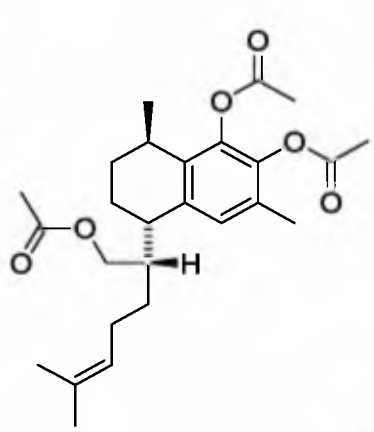
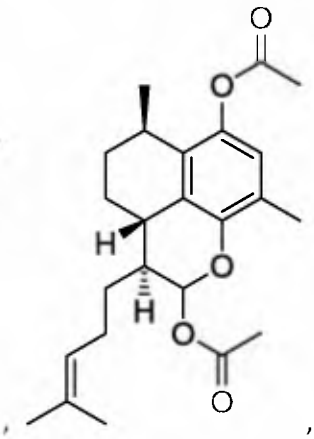
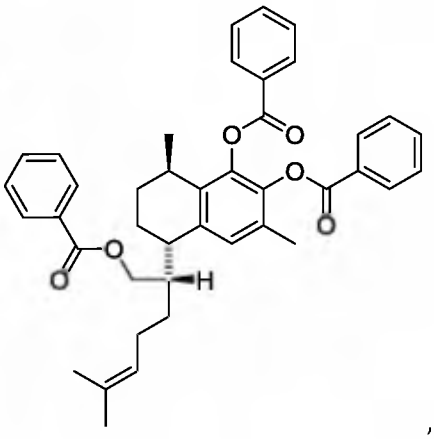
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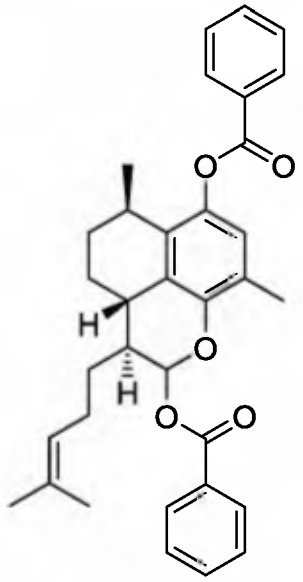
60. The compound according to example embodiment 59, wherein the compound is selected from the group consisting of:


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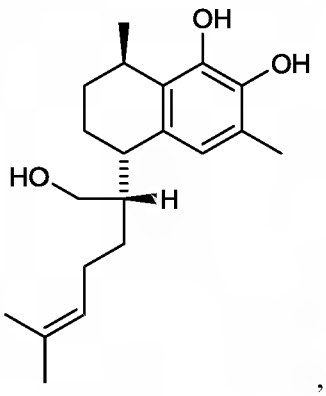

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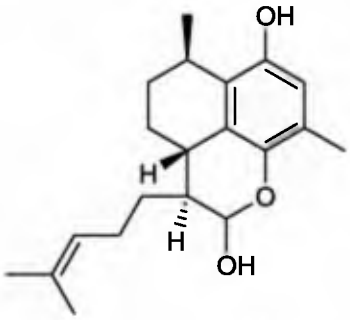




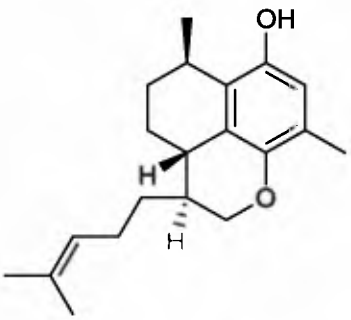
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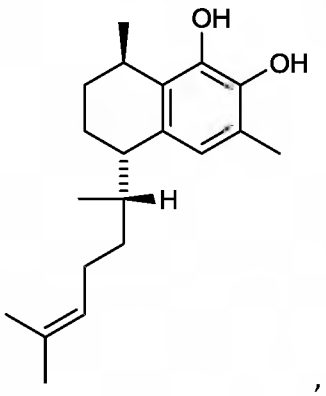


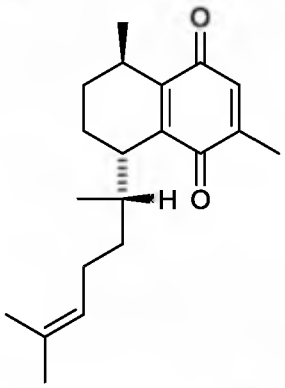
61. The compound according to example embodiment 60, wherein the compound is selected from the group consisting of:

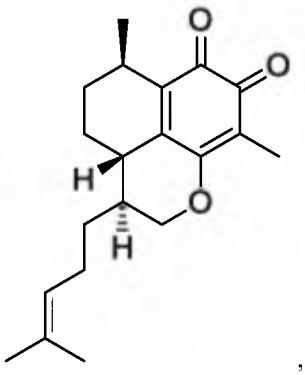


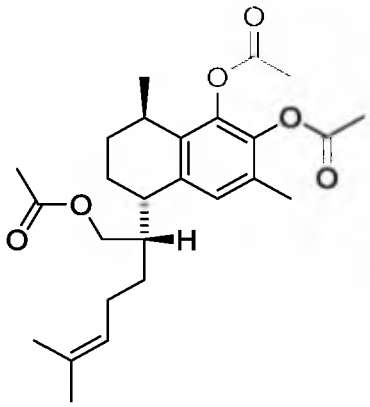
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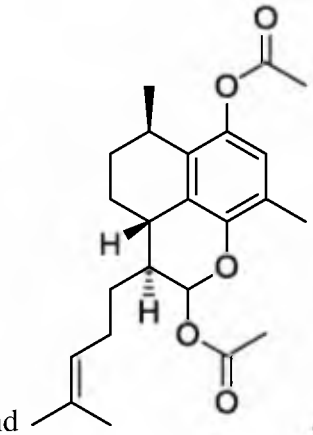
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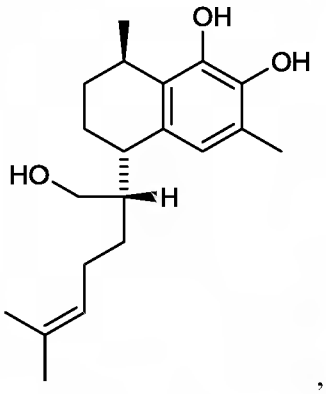
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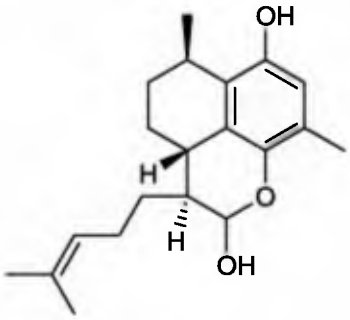
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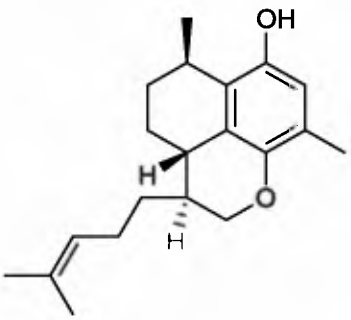


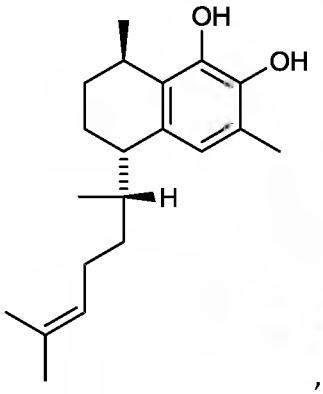
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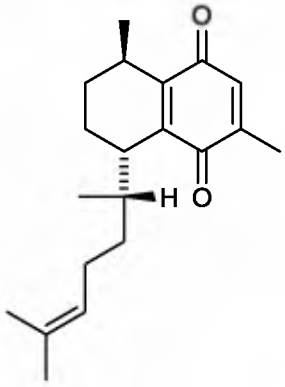
62. The compound according to example embodiment 61, wherein the compound is selected from the group consisting of:

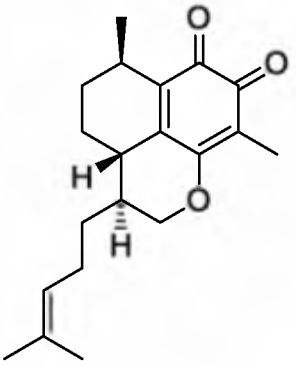


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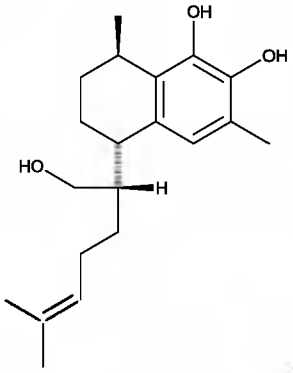


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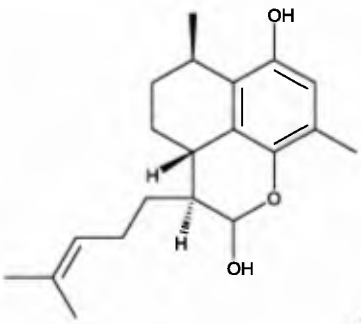
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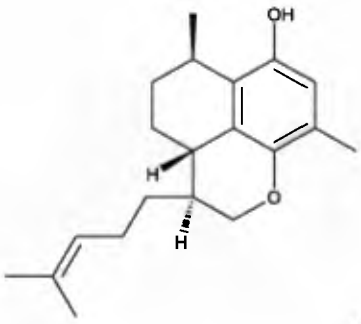
63. The compound according to example embodiment 62, wherein the compound is:



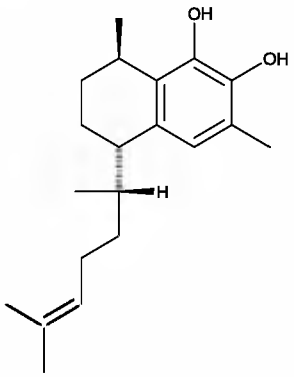
64. The compound according to example embodiment 62, wherein the compound is:



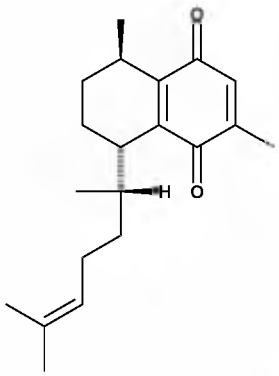
65. The compound according to example embodiment 62, wherein the compound is:



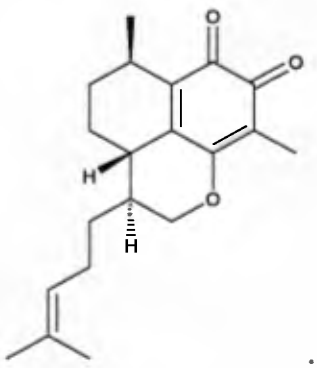
66. The compound according to example embodiment 62, wherein the compound is:



67. The compound according to example embodiment 62, wherein the compound is:



68. The compound according to example embodiment 62, wherein the compound is:



69. The compound according to any one of example embodiments 42 to 68, wherein the cancer is bladder cancer, bone cancer, brain cancer, breast cancer, a cancer of the central nervous system, cancer of the adrenal glands, cancer of the placenta, cancer of the testis, cervical cancer, colon cancer, kidney cancer, head and neck cancer, myeloma, leukemia, liver cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, stomach cancer, thyroid cancer, uterine cancer, a carcinoma, a lymphoma, a sarcoma, eye cancer, esophageal cancer, bile duct cancer or vulva cancer.

70. The compound according to example embodiment 69, wherein the cancer of the central nervous system is a glioma.

71. The compound according to example embodiment 69, wherein the cancer of the central nervous system is a medulloblastoma.

72. The compound or use according to example embodiment 69, wherein the cancer of the central nervous system is a neuroblastoma.

73. The compound according to example embodiment 69, wherein the lung cancer is a non-small cell lung cancer.

74. The compound according to example embodiment 69, wherein the lung cancer is a small cell lung cancer.

75. The compound according to example embodiment 69, wherein the carcinoma is adenosquamous cell carcinoma or squamous cell carcinoma.

76. The compound according to example embodiment 69, wherein the sarcoma is a liposarcoma, rhabdomyosarcoma, or fibrosarcoma.

77. The compound according to example embodiment 69, wherein the sarcoma is a soft tissue sarcoma.

78. The compound according to example embodiment 77, wherein the soft tissue sarcoma is a soft tissue osteosarcoma.

79. The compound according to example embodiment 69, wherein the lymphoma is Burkitt's lymphoma, Hodgkin's lymphoma, or non-Hodgkin's lymphoma.

80. A pharmaceutical composition comprising a compound, geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof, according to example embodiment 41 or any one of example embodiments 43 to 68, and a pharmaceutically acceptable excipient.

81. A pharmaceutical composition comprising a compound, geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof, according to example embodiment 41 or any one of example embodiments 43 to 68, or a mixture thereof, and a pharmaceutically acceptable excipient.

82. The compound according to example embodiment 41 or any one of example embodiments 43 to 68, or the pharmaceutical composition according to example embodiment 80 or example embodiment 81, for use as a medicament.

83. The compound according to example embodiment 41 or any one of example embodiments 43 to 68, or the pharmaceutical composition according to example embodiment 80 or example embodiment 81, for use in therapy.

84. A compound as defined in any one of example embodiments 42 to 68 isolated from propolis, wherein the propolis originates from plants of the *Myoporum* genus.

85. The compound according to example embodiment 84, wherein the propolis originates from *Myoporum insulare*.

86. A compound as defined in example embodiment 41 or any one of example embodiments 43 to 68 isolated from the resin, gum or exudate of *Myoporum* genus.

87. The compound according to example embodiment 86 isolated from the resin, gum or exudate of *Myoporum insulare*.

88. A method of treating a disease or disorder, the method comprising administering a therapeutically effective amount of a compound example embodiment 41 or any one of example embodiments 43 to 68 or a composition according to example embodiment 80 or example embodiment 81.

89. Use of a compound according to example embodiment 41 or any one of example embodiments 43 to 68 in the preparation of a medicament for treating a disease or disorder.

90. Use of a compound according to example embodiment 41 or any one of example embodiments 43 to 68 or a composition according to example embodiment 80 or example embodiment 81 in treating a disease or disorder.

91. A compound according to example embodiment 41 or any one of example embodiments 43 to 68 or a composition according to example embodiment 80 or example embodiment 81 for use in treating a disease or disorder.

92. The method according to example embodiment 88 or use according to example embodiment 89 or example embodiment 90 or compound according to example embodiment 91, wherein the disease or disorder is selected from the group consisting of: acute coronary syndrome, an aging-related disease or disorder; an allergic disease or a related condition; Alzheimer's disease, atherosclerosis, an autoimmune disease; a bacterial infection, cancer; dementia, depression or a related condition; diabetes; dyslipidemia, hyperlipidemia, hypertension, itchytosis, an immune disease; a metabolic disease or disorder; a neurological disease or disorder; obesity; Parkinson's disease; pain; rheumatoid arthritis and a skin disease or disorder.

93. The method or use or compound according to example embodiment 92, wherein the disease or disorder is cancer.

94. The method or use or compound according to example embodiment 93, wherein the cancer is bladder cancer, bone cancer, brain cancer, breast cancer, a cancer of the central nervous system, cancer of the adrenal glands, cancer of the placenta, cancer of the testis, cervical cancer, colon cancer, kidney cancer, head and neck cancer, myeloma, leukemia, liver cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, stomach cancer, thyroid cancer, uterine cancer, a

carcinoma, a lymphoma, sarcoma, eye cancer, esophageal cancer, bile duct cancer or vulva cancer.

95. The method or use or compound according to example embodiment 94, wherein the cancer of the central nervous system is a glioma.

96. The method or use or compound according to example embodiment 94, wherein the cancer of the central nervous system is a medulloblastoma.

97. The method or use or compound according to example embodiment 94, wherein the cancer of the central nervous system is a neuroblastoma.

98. The method or use or compound according to example embodiment 94, wherein the lung cancer is a non-small cell lung cancer.

99. The method or use or compound according to example embodiment 94, wherein the lung cancer is a small cell lung cancer.

100. The method or use or compound according to example embodiment 94, wherein the carcinoma is adenosquamous cell carcinoma or squamous cell carcinoma.

101. The method or use or compound according to example embodiment 94, wherein the sarcoma is a liposarcoma, rhabdomyosarcoma, or fibrosarcoma.

102. The method or use or compound according to example embodiment 94, wherein the sarcoma is a soft tissue sarcoma.

103. The method or use or compound according to example embodiment 102, wherein the soft tissue sarcoma is a soft tissue osteosarcoma.

104. The method or use or compound according to example embodiment 94, wherein the lymphoma is Burkitt's lymphoma, Hodgkin's lymphoma, or non-Hodgkin's lymphoma.

105. The method or use or compound according to example embodiment 92, wherein the skin disease or disorder is selected from the group consisting of: eczema, psoriasis, acne, a scar, inflammation, a burn, sunburn, skin damage and skin irritation.

Examples

In order to better understand the nature of the invention a number of examples will now be described as follows:

Experimental

Materials

Honey bees observed collecting from the boobialla trees and shrubs (*Myoporum insulare*) were captured in plastic tubes, capped and frozen. Sections of the bee hind legs holding propolis were cut and pooled. Plant samples were obtained and dried at 40°C in a ventilated oven (Thermoline, NSW Australia) a few days to provide voucher specimens for identification by botanist, A/Prof Murray Henwood, John Ray Herbarium, University of Sydney, Sydney, Australia, and registered as *Myoporum insulare* voucher number Duke-131202-01. Resin extracted from plant samples was stored at −20°C until analysis or further processing.

Propolis was obtained from apiary sites with from 1 to 10 colonies of European honey bee (*Apis mellifera ligustica*) in standard 10-frame box hives, each fixed with a propolis mat under the hive cover lid. The propolis samples were collected and provided by a few beekeepers in eight apiary sites located in different parts of Kangaroo Island, South Australia. These sites were located in the vicinity of Hanson Bay, Vivonne Bay, Flour Cask Bay, Island Beach, Kingscote, Brownlow, Rainy Creek and Eleanor River. These locations are known to be a habitat for the plant *Myoporum insulare* on Kangaroo Island. This provided 23 propolis samples which, based on TLC analysis and ^{1}H NMR techniques, were estimated to be at least 90% sourced from *M. insulare*. The samples were stored at −20°C until further analysis and processing.

Thin layer chromatography sheets precoated with silica gel 60 F_{254} and silica gel 60H for normal-phase short-column vacuum chromatography (NPSCVC) were purchased from Merck. TLC plates were visualized with a UVGL-58 mineral-light lamp, Multiband UV-2544/366.

All the chemicals used in the isolation and synthesis, including deuterated NMR solvents such as *d*-chloroform, d_4-methanol and d_6-dimethyl sulfoxide were purchased

from Novachem Pty Ltd (Collingwood, Vic, Australia). Solvents including hexane, dichloromethane, ethyl acetate, isopropanol, ethanol, methanol, and acetic acid were of analytical grade and purchased from Chem Supply, Gillman, SA, Australia.

General Methods

Rotavapor model R-114 rotary evaporator with a water bath temperature ranging between 40-60°C was used to evaporate the solvent fraction. Vacuum pump V-700 or Vacuubrand MD 4C NT diaphragm pump (Vacuubrand GMBH, Wertheim, Germany) with vacuum controller V-800 or V-850 is used. Final drying is carried out by a Napco 5831 vacuum oven (NAPCO, Salt Lake City, USA) using a DirectTorr vacuum pump (Sargent-Welch, Buffalo, USA).

Isocratic analytical HPLC was performed on a Shimadzu UFLC, LC-20AD pump, SIL-20A HT autosampler, with a Hewlett-Packard Column, NUCLEOSIL 100 C_{18}, 5 µm, 4 mm × 125 mm, injection volume 20 µl, eluted at 1 ml/min and detected at 230 nm with a UV-Vis detector (Shimadzu SPD-20A). The column was eluted with methanol-water-acetic acid (65:34.8:0.2).

Gradient analytical HPLC was performed on a Shimadzu Nexera X2 LC-30AD system, SIL-30 autosampler, with a Hewlett-Packard Column, NUCLEOSIL 100 C_{18}, 5 µm, 4 mm × 125 mm, injection volume 10 µl, eluted at 1 ml/min and detected at 320 nm with a SPD-M30A UV-Vis diode array detector. The column was eluted with a gradient system made up of methanol (phase A), and methanol: water: acetic acid (40:59.8:0.2) (phase B). A solvent gradient was applied as follows: 0–2 min: 32–50% A, 2–9 min: 50-90% A, 9-12 min: 90–100% A, 12–14 min, 100% A, and finally 14–15 min: 100–32% A, maintained over 5 min.

^{1}H and ^{13}C Nuclear magnetic resonance (NMR) analyses were carried out on Varian 400 MHz System with a SMS autosampler (Palo Alto, California, USA). Chemical shifts (δ) of peaks in NMR spectra are reported in parts per million (ppm) and are referenced to tetramethylsilane ($Si(CH_3)_4$, TMS). ^{1}H NMR data is reported as chemical shift (δ), relative integral, multiplicity (abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *td* = triplet of doublets, *q* = quartet, *dd* = doublet of doublets, *ddd* = doublet of

doublet of doublets, *bs* = broad singlet, *bt* = broad triplet), coupling constant (*J* in Hz) and assignment. ^{13}C NMR data is reported as chemical shift (δ) and assignment.

For low resolution ESI-MS, the samples were analyzed by Finnigan Polaris Ion Trap MS/MS system (Finnigan Corporation, San Jose, USA) using an Xcalibur 1.2 data system, in Electrospray Ionization (ESI) negative and positive modes using infusion technique.

High resolution ESI-MS were measured on a Bruker Daltonics Apex Ultra Fourier Transform Ion Cyclotron Resonance 7 Tesla Mass Spectrometer, mass spectrometry unit, School of Chemistry, The University of Sydney.

Determination of the ^{1}H-NMR chemical profiles of the plant and propolis specimens

Young leaf shoots (25 g), bee hind leg (0.01 g) and beehive propolis (1.0 g) were extracted with dichloromethane at room temperature for 15 min. The extracts were filtered, dried under reduced pressure and analyzed by ^{1}H-NMR and HPLC. Samples were found to contain serrulatane diterpenes. Propolis and plant samples were subsequently selected for isolation of the components.

Preparation of *Myoporum insulare* resin extract

Fresh young leaves and young shoot tips were harvested from several *Myoporum insulare* trees. The leaves were stored in plastic bags on ice until processing within 5 days. To extract the external resin/exudate the leaves and shoot tips (4 Kg) were mixed with dichloromethane (4 litres) and after 1 hour standing the dichloromethane extract was filtered and the dichloromethane was removed from the filtrate by evaporation under reduced pressure using a rotary evaporator to give a brown partially solid dried resin (12.5 g, yield 0.31%).

Isolation and identification of serrulatane diterpenes from *Myoporum insulare* propolis from Kangaroo Island.

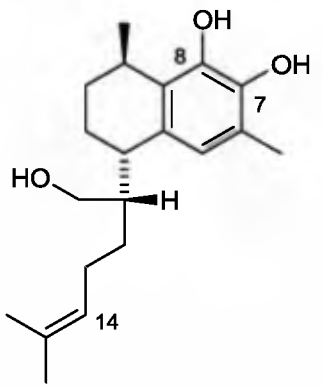
General Method

Propolis (100 g) was extracted with dichloromethane at room temperature with stirring for 1 hr. The extract was subjected to purification using normal-phase short column vacuum chromatography (NPSCVC). A step-wise gradient of mobile phase (2 x 100 mL) consisting of dichloromethane (DCM) and ethyl acetate (EtOAc) at 0, 1, 2, 4, 8,

10, 15, 20, 50 and 100% was employed to elute the components which were analysed by TLC and NMR. Further purification of the compounds, if required, was subsequently carried out on the same NPSCVC with different mobile phases consisting of either hexane and EtOAc or hexane and isopropanol. Structures and identity of these purified compounds were characterized by ^{1}H- and ^{13}C-NMR and mass spectrometry including high resolution mass spectrometry. Detailed structural analyses of the isolated compound were also carried out when needed by 2D-NMR using Gradient Heteronuclear Multiple Bond Coherence (GHMBC). The major serrulatane diterpenoid was determined to be 7,8,18-trihydroxyserrulat-14-ene (**1**).

Isolated serrulatane diterpenes from the plant, *Myoporum insulare.*

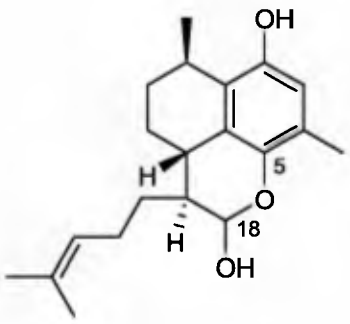
7,8,18-trihydroxyserrulat-14-ene (1)



Yellowish liquid, yield 50 mg, $[\alpha]_D^{20}$ -27.3° (C = 1.0, $CHCl_3$). UV (CH_3OH) λ_{max} nm (log ε) 279 (3.37) and 320 (2.49). IR (ν): 3381, 2924, 2864, 1625, 1581, 1448 cm^{-1}. HRESIMS: 341.2089 m/z $[M+Na]^+$ (calcd 341.2087) $C_{20}H_{30}O_3$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.56, (1H, *s*, H-5), 5.04 (1H, *bt*, *J*= 7.0 Hz, H-14), 3.63 (2H, *d*, *J*= 6.2 Hz, H-18), 3.07 (1H, *pentet* of *d*, *J*= 6.8, 1.6 Hz, H-1), δ 2.76 (1H, *td*, *J*= 5.6, 2.6 Hz, H-4), 2.20 (3H, *s*, H-19), 1.99 (1H, *m* , H-13A), 1.90 (1H, *m*, H-13B), 1.90 (1H, *m*, H-3A), 1.86 (1H, *m*, H-2A), 1.83 (1H, *m*, H-11), 1.68 (3H, *s*, H-16), 1.66 (1H, *m*, H-2B), 1.58 (3H, *s*, H-17), 1.51 (1H, *m*, H-3B), 1.25 (1H, m, H-12A), 1.36 (2H, *m*, H-12B), 1.21 (3H, *d*, *J*= 7.0 Hz, H-20). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.54 (C-19), 17.68 (C-17), 20.51 (C-2), 21.11 (C-20), 25.70 (C-16), 26.16 (C-13), 26.47 (C-3), 26.98 (C-1), 29.85

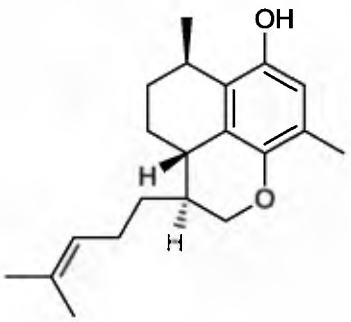
(C-12), 37.91 (C-4), 45.45 (C-11), 64.38 (C-18), 121.31 (C-6), 122.00 (C-5), 124.43 (C-14), 127.18 (C-9), 130.70 (C-10), 131.75 (C-15), 139.74 (C-7), 141.61 (C-8).

5,18-epoxyserrulat-14-en-8,18-diol (2)



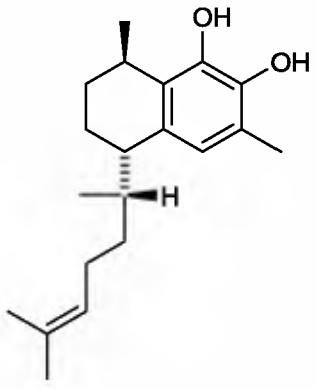
Red liquid, yield 84 mg, $[\alpha]_D^{20}$ -21.5° (C = 1.0, $CHCl_3$). UV (CH_3OH) λ_{max} nm (log ε) 293 (3.36) and 334 (2.91). IR (ν): 3327, 2970, 2926, 2860, 1647, 1558, 1448, 1043 cm^{-1}. HRESIMS: 315.1970 m/z $[M-H]^-$ (calcd 315.1966).$C_{20}H_{28}O_3$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.48 (1H, *s*, H-7), 5.59 (1H, *bs*, H-18), 5.14 (1H, *bt*, *J*= 7.0 Hz, H-14), 3.11 (1H, *sextet*, *J*= 7.6, H-1), 2.54 (1H, *td*, *J*= 11.4, 3.6 Hz, H-4), 2.25 (1H, *m*, H-2A), 2.20 (1H, *m*, H-13A), 2.13 (3H, *s*, H-19), 2.09 (1H, *m* , H-13B), 2.08 (1H, *m*, H-3A), 1.69 (1H, *m*, H-12A), 1.70 (3H, *s*, H-16), 1.63 (3H, *s*, H-17), 1.52 (1H, *m*, H-11), 1.41 (1H, *m*, H-2B), 1.28 (3H, *d*, *J*= 6.9 Hz, H-20), 1.27 (1H, *m*, H-12B), 1.05 (1H, *m*, H-3B). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.88 (C-19), 17.75 (C-17), 22.89 (C-20), 25.36 (C-13), 25.70 (C-16), 26.62 (C-3), 27.79 (C-1), 28.90 (C-12), 31.75 (C-2), 31.99 (C-4), 40.48 (C-11), 91.88 (C-18), 115.94 (C-7), 122.94 (C-6), 124.09 (C-14), 124.29 (C-10), 125.21 (C-9), 131.99 (C-15), 141.71 (C-5), 146.85 (C-8).

5,18-epoxy-8-hydroxyserrulat-14-ene (3)



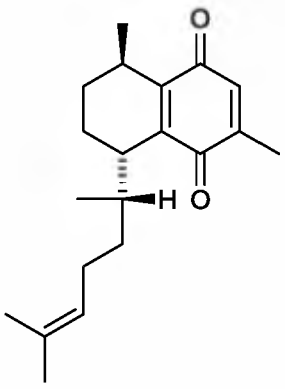
Shiny yellow liquid, yield 87 mg, $[\alpha]_D^{20}$ -8.9° (C = 1.0, $CHCl_3$). UV (CH_3OH) λ_{max} nm (log ε) 296 (3.55) and 334 (2.66). IR (ν): 3502, 2922, 2856, 1622, 1597, 1421, 1230 cm^{-1}. HRESIMS: 301.21635 m/z $[M+H]^+$ (calcd 301.21621) $C_{20}H_{28}O_2$. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.46 (1H, *s*, H-7), 5.13 (1H, *bt*, *J*= 6.9 Hz, H-14), 4.35 (1H, *dd*, *J*= 10.5, 3.7 Hz, H-18A), 3.70 (1H, *t*, *J*= 10.8 Hz, H-18B), 3.13 (1H, *sextet*, *J*= 7.4 Hz, H-1), 2.31 (1H, *m*, H-4), 2.24 (1H, *m*, H-2A), 2.16(1H, *m*, H-13A), 2.15 (1H, *m*, H-3A), 2.12 (3H, *s*, H-19), 2.02 (1H, *m*, H-13B), 1.74 (1H, *m*, H-12A), 1.70 (3H, *s*, H-16), 1.63 (3H, *s*, H-17), 1.55, (1H, *m*, H-11), 1.40 (1H, *m*, H-2B), 1.28 (3H, *d*, *J*= 7.0 Hz, H-20), 1.18 (1H, *m*, H-12B), 1.06 (1H, *td*, *J*= 12.2, 4.4 Hz, H-3B). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.82 (C-19), 17.73 (C-17), 23.12 (C-20), 25.44 (C-13), 25.70 (C-16), 26.97 (C-3), 27.61 (C-1), 29.97 (C-12), 31.47 (C-2), 37.17 (C-11), 39.00 (C-4), 69.52 (C-18), 115.79 (C-7), 122.64 (C-6), 124.12 (C-14), 124.26 (C-9), 125.70 (C-10), 131.99 (C-15), 145.27 (C-5), 146.16 (C-8).

7,8-dihydroxyserrulat-14-ene (4)



Yellowish liquid, yield 56 mg, $[\alpha]_D^{20}$ -21.1° (C = 1.0, $CHCl_3$). UV (CH_3OH) λ_{max} nm (log ε) 278 (3.36) and 329 (2.95). IR (ν): 3396, 2954, 2924, 2868, 1635, 1577, 1456 cm^{-1}. HRESIMS: 325.21413 m/z $[M+Na]^+$ (calcd 325.21380) $C_{20}H_{30}O_2$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.53 (1H, *s*, H-5), 5.00 (1H, *bt*, *J*= 7.0 Hz, H-14), 3.06 (1H, *pentet* of *d*, *J*= 6.7, 2.8 Hz, H-1), 2.53 (1H, *td*, *J*= 5.5, 3.4 Hz, H-4), 2.22 (3H, *s*, H-19), 2.00 (1H, *m* , H-13A), 1.95 (1H, *m*, , H-2A), 1.84 (1H, *m*, H-11), 1.82 (1H, *m*, H-3A), 1.80 (1H, *m* , H-13B), 1.70 (1H, *m*, H-3B), 1.67 (3H, *s*, H-16), 1.59 (3H, *s*, H-17), 1.48 (1H, *m*, H-2B), 1.29 (1H, *m*, H-12A), 1.12 (3H, *d*, *J*= 6.8 Hz, H-20), 1.05 (1H, *m*, H-12B), 0.95 (3H, *d*, *J*=6.8 ,H-18). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.53 (C-19), 17.62 (C-17), 18.66 (C-18), 19.63 (C-3), 21.10 (C-20), 25.71 (C-16), 26.25 (C-13), 27.1 (C-1), 27.43 (C-2), 33.35 (C-12), δ 37.8 (C-11), δ 41.88 (C-4), δ 120.50 (C-6), δ 122.46 (C-5), δ 124.96 (C-14), δ 127.09 (C-9), δ 131.10 (C-15), δ 131.90 (C-10), δ 139.19 (C-7), δ 140.93 (C-8).

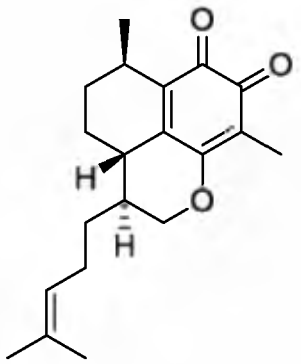
Serrulat-14-en-5,8-dione (5)



Light orange liquid, yield 30 mg. ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, *s*, H-5), 5.02 (1H, *bt*, J= 7.1 Hz, H-14), 2.85 (1H, *m*, H-1), 2.20 (1H, *m*, H-4), 2.12 (1H, *m*, H-3A), 2.03 (1H, *m* , H-13A), 1.95 (3H, *s*, H-19), 1.88 (1H, *m*, H-11), 1.85 (1H, *m* , H-13B), 1.69 (1H, *m*, H-2A), 1.67 (3H, *s*, H-16), 1.58 (3H, *s*, H-17), 1.34 (1H, *m*, H-2B), 1.30 (1H, *m*, H-12A), 1.20 (1H, *m*, H-3B), 1.12 (1H, *m*, H-12B), 1.07 (6H, *d*, *J*= 6.9 Hz, H-

18 and H-20). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.21 (C-19), 17.69 (C-17), 18.67 (C-20), 18.75 (C-18), 20.55 (C-3), 25.71 (C-16), 26.10 (C-13), 26.56 (C-1), 26.59 (C-2), 33.41 (C-12), 34.9 (C-11), 43.83 (C-4), 124.13 (C-14), 132.00 (C-15), 135.36 (C-6), 140.04 (C-7), 140.70 (C-9), 150.13 (C-10), 179.85 (C-5), 181.55 (C-8).

5,18-epoxyserrulat-14-en-7,8-dione (6)

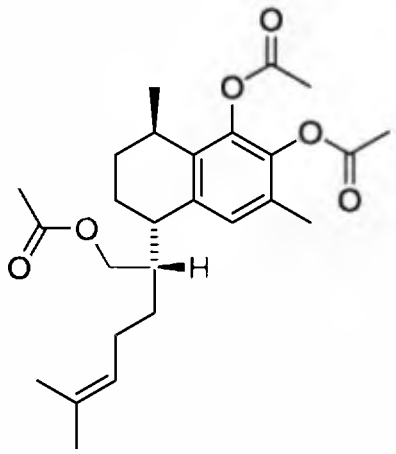


Purple liquid, yield 50 mg, HRESIMS: 315.19573 m/z [M+H]+ (calcd 315.19547) $C_{20}H_{26}O_3$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (1H, *bt*, *J*= 6.8 Hz, H-14), 4.49 (1H, *dd*, *J*= 11.0, 3.8 Hz, H-18A), 3.86 (1H, *t*, *J*= 11.1 Hz, H-18B), 2.82 (1H, *m*, H-1), 2.14 (1H, *m*, H-4), 2.15 (1H, *m*, H-2A), 2.13 (1H, *m* , H-3A), 2.09 (1H, *m* , H-13A), 1.97 (1H, *m* , H-13B), 1.81 (3H, *s*, H-19), 1.76 (1H, *m*, H-12A), 1.74 (1H, *m*, H-11), 1.71 (3H, *s*, H-16), 1.63 (3H, *s*, H-17), 1.23 (1H, *m*, H-2B), 1.19 (1H, *m*, H-12B), 1.13 (3H, *d*, H-20) 1.11 (1H, *m* , H-3B),. ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.57 (C-19), 17.78 (C-17), 21.67 (C-20), 24.66 (C-13), 25.32 (C-3), 25.71 (C-16), 28.74 (C-1), 29.15 (C-12), 30.77 (C-2), 37.07 (C-11), 40.09 (C-4), 71.85 (C-18), 114.44 (C-6), 123.06 (C-14), 132.87 (C-15), 139.43 (C-9), 149.67(C-10), 162.76 (C-5), 179.38 (C-7), 181.91 (C-8).

Compound **6** was observed to be formed from oxidation of compound **1**.

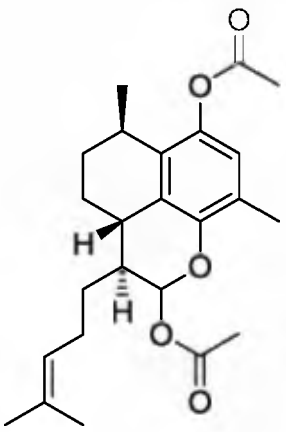
Acetylation of serrulatane diterpenes

7,8,18-triacetyloxyserrulat-14-ene (7)



The serrulatane (**1**) (400 mg) was dissolved in acetic anhydride (1 mL) and in dry pyridine (1 mL) and stirred at room temperature overnight (Davis *et al.*, 1999). The reaction mixture was quenched with distilled water (30 mL), and was extracted with dichloromethane (3 x 40 mL). The dichloromethane solution was extracted with aqueous 0.1 M hydrochloric acid (30 mL) to remove the residual trace of pyridine. The dichloromethane solutions were dried with Na_2SO_4, filtered and concentrated on a rotary evaporator to give a yellow oily residue. Finally, using normal-phase short-column vacuum chromatography (NPSCVC) with dichloromethane and ethyl acetate (100:0 to 90:10, v/v) the compound (**7**) (434 mg, 77%) was purified and isolated as a pale yellow oil, yield 27 mg. HRESIMS: 467.2404 m/z $[M+Na]^+$ (calcd 467.2206). $C_{26}H_{36}O_6$.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (1H, *s*, H-5), 4.97 (1H, *bt*, *J*=7.1 Hz, H-14), 4.11 (2H, *d*, *J*= 6.3 Hz, H-18), 2.92 (1H, *m*, H-1), 2.88 (1H, *m*, H-4), 2.31 (3H, *s*, H-26), 2.29 (3H, *s* , H-24), 2.14 (3H, *s*, H-19), 2.12 (1H, *m*, H-11), 2.06 (3H, *s*, H-22), 1.99 (1H, *m*, H-13A), 1.87 (1H, *m*, H-13B), 1.87 (1H, *m*, H-3A), 1.87 (1H, *m*, H-2A), 1.68 (1H, *m*, H-3B), 1.66 (3H, *s*, H-16), 1.54 (3H, *s*, H-17), 1.50 (1H, *m*, H-2B), 1.33 (1H, *m*, H-12A), 1.23 (1H, *m*, H-12B), 1.15 (3H, *d*, *J*= 7.0 Hz, H-20). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.08 (C-19), 17.60 (C-17), 19.16 (C-3), 20.36 (C-24), 20.51 (C-26), 20.97 (C-22), 21.45 (C-20), 25.68 (C-16), 26.11 (C-13), 26.96 (C-2), 27.58 (C-1), 28.32 (C-12), 36.92 (C-4), 41.92 (C-11), 65.88 (C-18), 123.94 (C-14), 128.09 (C-5), 128.31 (C-6), 132.04 (C-15), 139.26 (C-7), 140.56 (C-8), 134.06 (C-9), 137.11 (C-10), 168.1 (C-23), 168.34 (C-25), 171.18 (C-21).

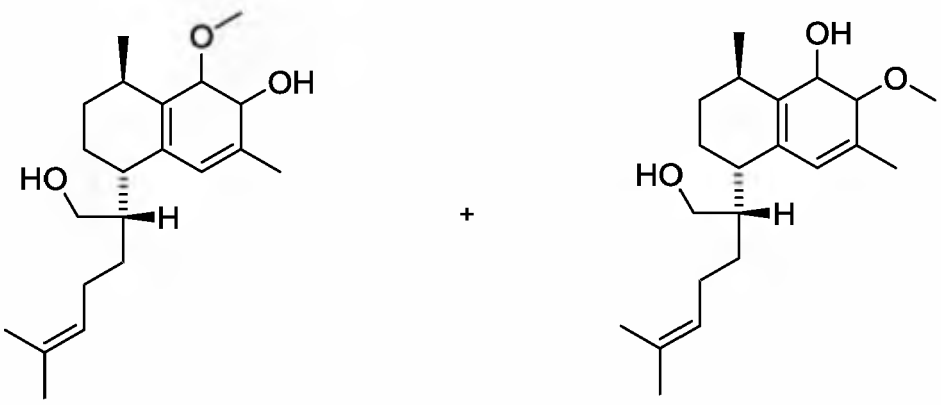
5,18-epoxyserrulat-14-ene-8,18-diacetate (8)



To acetylate compound (**2**), 80 mg of serrulatane (**2**) was dissolved in acetic anhydride (1 mL) and in dry pyridine (1 mL) and stirred at room temperature overnight, and with the same workup procedure and using short-column vacuum chromatography with hexane and ethyl acetate (100:0 to 80:20, v/v) the compound (**8**) (57.8 mg,58%) was purified and isolated. Red coloured liquid, yield 18 mg, HRESIMS: m/z 423.2143 $[M+Na]^+$ calcd 423.2142. $C_{24}H_{32}O_5$. ^1H NMR (400 MHz, $CDCl_3$) δ: 6.69 (1H, *s*, H-7), 6.53 (1H, *d*, *J*= 1.7 Hz, H-18), 5.08 (1H, *bt*, *J*= 6.5 Hz, H-14), 2.96 (1H, *sextet*, *J*= 7.4 Hz, H-1), 2.54 (1H, *td*, *J*= 11.6, 3.8 Hz, H-4), 2.3 (3H, *s*, H-24), 2.19 (1H, *m*, H-13A), 2.19 (1H, *m*, H-2A), 2.14 (3H, *s*, H-19), 2.12 (1H, *m*, H-3A), 2.09 (3H, *s*, H-22), 2.02, (1H, *m*, H-13B), 1.70 (1H, *m*, H-12A), 1.69 (3H, *s*, H-16), 1.62 (3H, *s*, H-17), 1.65 (1H, *m*, H-11), 1.42 (1H, *m*, H-2B), 1.30 (1H, *m*, H-12B), 1.23 (3H, *d*, *J*= 6.8 Hz, H-12), 1.10 (1H, m, H-3B).^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.88 (C-19), 17.68 (C-17), 21.09 (C-22), 21.23 (C-24), 22.78 (C-20), 25.15 (C-13), 25.70 (C-16), 26.22 (C-3), 28.26 (C-1), 28.29 (C-12), 31.41 (C-2), 32.3 (C-4), 38.93 (C-11), 90.18 (C-18), 41.92 (C-11), 122.53 (C-7), 123.48 (C-14), 123.77 (C-10), 123.96 (C-6), 130.9 (C-9), 132.57 (C-15), 142.44 (C-8), 145.63 (C-5), 170.05 (C-23), 170.19 (C-21).

Methylation of serrulatane diterpenes

8-methoxy-7,18-dihydroxyserrulat-14-ene (11) and **7-methoxy-8,18-dihydroxyserrulat-14-ene (12)**



11 **12**

Compound **1** (140 mg) was treated with diazomethane (excess equiv) in diethyl ether at 0°C to room temperature overnight to give an undetermined 4 to 1 (^{1}H-NMR) mixture of mono-methylated products **11** and **12** (35 mg, 88% purity by HPLC).

Compounds **11** and **12**

Yellow oil Mass Spectrum (positive mode) m/z = 333.2 (12%, $(M+H)^+$), 315.2 (100%, $(M+H-H_2O)^+$), 205.2 (18%, $(M+H-C_8H_{16}O)^+$). HPLC analysis: Wavelength, 210 nm, bandwidth 4; Column, SorbTech C18AQ, 2.1 x 50 mm, 3 µm; Retention time 7.474 min; Mobile phase acetonitrile/formic acid/water; Gradient method, 5-95% CAN + 0.1% Formic acid in Water + 0.1% Formic acid in 14 min, hold at 95% CAN + Formic acid for 4 min. UV_{max}, 275 nm and 210 nm, shoulder at 225 nm. ^{1}H-NMR analysis indicated a 4:1 undetermined mixture of **11** and **12** (interchangeable major and minor isomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.74 (1H, *s*, H-5)[minor], 6.56, (1H, *s*, H-5)[major], 5.78 (1H, OH)[major], 5.57 (1H, OH)[minor], 5.01 (1H, *bt*, *J*= 6.3 Hz, H-14), 3.78 (3H, *s*, CH_3O)[minor], 3.77 (3H, *s*, CH_3O)[major], 3.63 (2H, *m*, H-18), 3.14 (1H, *m*, H-1)[major], 3.07 (1H, *m*, H-1)[minor], δ 2.81 (1H, *m*, H-4), 2.25 (3H, *s*, H-19)[major], 2.21 (3H, *s*, H-19)[minor], 2.0 – 1.8 (5H, *m*, H-13, H-3A, H-2A, H-11), 1.7 – 1.6 (1H, *m*, H-2B), 1.66 (3H, *bs*, H-16), 1.55 (3H, *bs*, H-17), 1.52 – 1.46 (1H, *m*, H-3B), 1.35 – 1.23 (2H, *m*, H-12), 1.21 (3H, *d*, *J*= 6.8 Hz, H-20)[major] 1.20 (3H, *d*, *J*=

6.8 Hz, H-20)[minor]. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.50 (C-19)[minor], 15.77 (C-19)[major], 17.62 (C-17), 20.22 (C-2)[major], 20.44 (C-2)[minor], 21.08 (C-20)[major], 22.22 (C-20)[minor], 25.66 (C-16), 26.27 (C-13), 26.81 (C-3), 27.14 (C-1)[major], 27.87 (C-1)[minor], 29.14 (C-12)[minor], 29.26 (C-12)[major], 37.53 (C-4)[minor], 37.55 (C-4)[major], 45.43 (C-11)[minor], 45.53 (C-11)[major], 60.64 (OCH_3)[major], 60.89 (OCH_3)[minor], 64.17 (C-18)[major], 64.30 (C-18)[minor], 121.89 (C-5), 124.55 (C-14), 126.39, 126.70, 127.69, 130.42, 131.63, 131.66, 133.17, 135.11, 143.15, 144.85, 145.26, 146.27.

Figure 1 and **Figure 2** show the ^{1}H NMR (400 MHz, $CDCl_3$) and the ^{13}C NMR (100 MHz, $CDCl_3$) spectra of the 4:1 mixture of compounds **11** and **12**.

Biological evaluation of serrulatane terpene compounds

The serrutalene diterpenes **1** to **3** were evaluated for *in vitro* biological activities using assays for epigenetics (**Tables 3** to **6**). **Table 3** shows the experimental conditions used in epigenetic binding assays. **Table 4** shows the results of inhibition of compounds **1** to **3** on binding of epigenetic interacting protein modules. **Tables 5** to **8** show representative inhibition data for compound **1** on binding example epigenetic targets (**Table 5**: ASH1L (h) bromodomain; **Table 6**: CECR2(h) bromodomain; **Table 7**: SP140 *(h)* bromodomain; **Table 8**: UHRF1(108-286) (h)). Corresponding binding curves for the data displayed in **Tables** 5 to **8** are shown in **Figures 3** to **6**. **Table 9** shows the results of inhibition of compounds **1** to **3** on binding of epigenetic enzymes. **Table 10** shows the results for enzyme and cell-based stimulation assays for compounds **1** to **3.**

Diterpenes **1** to **3** were also evaluated for *in vitro* pharmacological activity (**Tables 11** to **13**). **Table 11** shows the experimental conditions used in the pharmacological assays. **Table 12** shows the pharmacological activity of compounds **1** to **3**. Table **13** shows effects of compounds **1** to **4** on glucose uptake while **Table 14** shows dose response and IC_{50} values for the pharmacological activity of compounds **1** to **3**.

Diterpenes **1** to **4** and *Myoporum insulare* resin were evaluated in a cell viability assay (**Table 15**).

Diterpenes **1**, **2**, **4** and *Myoporum insulare* resin were assayed for cell cancer cell proliferation in an OncoPanel assay (**Table 16** and **Table 17**).

Epigenetic Assays

Epigenetic binding assays were carried out by Eurofins CEREP (France). The conditions used in the assays including: enzymes, source of enzymes, substrate, substrate concentration, ligand, ligand concentration, tracer, incubation, detection method, and reference compound and concentration are detailed in **Table 3**. Appropriate literature references are also provided. The AlphaScreen detection method refers to an Amplified Luminescent Proximity Homogeneous Assay used to study biomolecular interactions (see Ullman *et al.* 1994). LANCE and LanthaScreen assays are based on the principle of time-resolved fluorescence energy transfer (TR-FRET) and are described, for example, in Ma *et al.* 2008.

The IC_{50} values (concentration causing a half-maximal inhibition of control specific activity) were determined by non-linear regression analysis of the inhibition/concentration-response curves generated with mean replicate values using Hill equation curve fitting. Inhibition/concentration-response curve concentrations were 30, 3, 0.3, 0.03 and 0.003 μM.

Table 3. Epigenetic binding assay details

Assay	Main Feature	
Bromodomain		
ATAD2B bromodomain [Filippakopoulos *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 75 nM 30 min/RT AlphaScreen Ischemin sodium salt (IC50:76.6 μM)
ASH1L bromodomain [Filippakopoulos *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 di acetyl Lys 5/8 75 nM 30 min/RT AlphaScreen JQ-1 (IC50:13.8 μM)
BAZ2A bromodomain [Filippakopoulos and Knapp 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 25 nM 30 min/RT AlphaScreen GSK2801 (IC50:1.8 μM)

BRPF1-1 bromodomain [Filippakopoulos *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 10 nM 30 min/RT AlphaScreen Bromosporine (IC50:0.026 μM)
CECR2 bromodomain [Filippakopoulos *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 10 nM 30 min/RT AlphaScreen Bromosporine (IC50:0.062 μM)
EP300 bromodomain [Filippakopoulos and Knapp 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H3 acetyl Lys56 25 nM 30 min/RT AlphaScreen SGC-CBP30 (IC50:0.050 μM)
KAT2A (GCN5L2) bromodomain [Filippakopoulos *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 30 nM 15 min/RT AlphaScreen JQ-1 (IC50:45 μM)
PCAF bromodomain [Filippakopoulos and Knapp 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 100 nM 30 min/RT AlphaScreen JQ-1 (IC50:12 μM)
PB1(2) bromodomain [Filippakopoulos *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H3 acetyl Lys 14 60 nM 15 min/RT AlphaScreen PFI-3 (IC50:68 μM)
PB1(3) bromodomain [Filippakopoulos *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H3 acetyl Lys14 50 nM 30 min/RT AlphaScreen JQ-1 (IC50:47 μM)
PB1(4) bromodomain [Filippakopoulos *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H3 acetyl Lys14 50 nM 30 min/RT AlphaScreen Ischemin sodium salt (IC50:6.8 μM)
PHIP(2) bromodomain [Filippakopoulos *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 diacetyl Lys5/8 100 nM 30 min/RT AlphaScreen SGC-CBP30 (IC50:0.130 μM)

SP140 bromodomain [Filippakopoulos *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H3 acetyl Lys 9 50 nM 30 min/RT AlphaScreen Ischemin (IC50:86 μM)
SMARCA2 bromodomain [Filippakopoulos *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) Biotin H3 mono acetyl Lys 14 5 nM 30 min/RT AlphaScreen PFI-3 (IC50:0.47 μM)
TAF1(1) bromodomain [Filippakopoulos and Knapp 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 100 nM 30 min/RT AlphaScreen GSK2801 (IC50:4.4 μM)
SMARCA4 bromodomain [Filippakopoulos *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) Biotin -H3 mono acetyl Lys14 15 nM 30 min/RT AlphaScreen PFI-3 (IC50:3 μM)
TAF1(2) bromodomain [Filippakopoulos and Knapp 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 100 nM 30 min/RT AlphaScreen GSK2801 (IC50:10 μM)
BAZ2B bromodomain [Philpott *et al.* 2011]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H3 acetyl Lys14 25 nM 30 min/RT AlphaScreen GSK2801 (IC50:1.8 μM)
ATAD2A bromodomain [Filippakopoulos and Knapp 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 100 nM 30 min/RT AlphaScreen JQ-1 (IC50:70 μM)
BRD2(1) bromodomain [Philpott *et al.* 2011]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 50 nM 30 min/RT AlphaScreen JQ-11 (IC50:0.510 μM)
BRD2(2) bromodomain [Filippakopoulos and Knapp 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 50 nM 30 min/RT AlphaScreen JQ-1 (IC50:0.017 μM)

BRD3(1) bromodomain [Filippakopoulos and Knapp 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 25 nM 30 min/RT AlphaScreen JQ-1 (IC50:0.040 μM)
BRD3(2) bromodomain [Filippakopoulos and Knapp 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 di acetyl Lys 5/8 100 nM 30 min/RT AlphaScreen PFI-1 (IC50:0.79 μM)
BRD4(1) bromodomain [Philpott *et al.* 2011]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 50 nM 30 min/RT AlphaScreen JQ-1 (IC50:0.018 μM)
BRD4(2) bromodomain [Filippakopoulos and Knapp 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 50 nM 30 min/RT AlphaScreen PFI-1 (IC50:1.3 μM)
BRDT(1) bromodomain [Filippakopoulos and Knapp 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 25 nM 30 min/RT AlphaScreen JQ-1 (IC50:0.110 μM)
CREBBP bromodomain [Philpott *et al.* 2011]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H3 acetyl Lys56 50 nM 30 min/RT AlphaScreen SGC-CBP30 (IC50:0.120 μM)
FALZ bromodomain [Philpott *et al.* 2011]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H4 tetra acetyl Lys 5/8/12/16 50 nM 30 min/RT AlphaScreen I-CBP112 (IC50:24.5 μM)
Chromodomain		
CBX1 [Kaustov *et al.* 2011]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin- H3 trimethylated Lys9 5 nM 30 min/RT AlphaScreen NA
CBX2 [Kaustov *et al.* 2011]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin- H3 trimethylated Lys27 20 nM 30 min/RT AlphaScreen NA

CBX4 [Kaustov *et al.* 2011]	Source	human recombinant (E. coli)
	Ligand	biotin- H3 trimethylated Lys27
	Ligand concentration	8 nM
	Incubation	30 min/RT
	Detection method	AlphaScreen
	Reference:	NA
CBX6 [Kaustov *et al.* 2011]	Source	human recombinant (E. coli)
	Ligand	biotin- H3 trimethylated Lys27
	Ligand concentration	5 nM
	Incubation	30 min/RT
	Detection method	AlphaScreen
	Reference:	NA
CBX5 [Kaustov *et al.* 2011]	Source	human recombinant (E. coli)
	Ligand	biotin- H3 trimethylated Lys9
	Ligand concentration	6 nM
	Incubation	15 min/RT
	Detection method	AlphaScreen
	Reference:	NA
CBX7 [Kaustov *et al.* 2011]	Source	human recombinant (E. coli)
	Ligand	biotin- H3 trimethylated Lys27
	Ligand concentration	10 nM
	Incubation	30 min/RT
	Detection method	AlphaScreen
	Reference:	NA
CBX8 [Kaustov *et al.* 2011]	Source	human recombinant (E. coli)
	Ligand	biotin- H3 trimethylated Lys27
	Ligand concentration	55 nM
	Incubation	30 min/RT
	Detection method	AlphaScreen
	Reference:	NA
MBT domain		
L3MBTL1 [Kim *et al.* 2006]	Source	human recombinant (E. coli)
	Ligand	biotin- H3 methylated Lys4
	Ligand concentration	50 nM
	Incubation	15 min/RT
	Detection method	AlphaScreen
	Reference:	NA
L3MBTL3 [Kim *et al.* 2006]	Source	human recombinant (E. coli)
	Ligand	biotin-H4 dimethylated lysine 20
	Ligand concentration	60 nM
	Incubation	15 min/RT
	Detection method	AlphaScreen
	Reference:	NA
PHD Domain		
SP140 [Org *et al.* 2008]	Source	human recombinant (E. coli)
	Ligand	Biotin H3K4me
	Ligand concentration	15 nM
	Incubation	30 min/RT
	Detection method	AlphaScreen
	Reference:	NA
TRIM 33 [Venturini *et al.* 1999]	Source	human recombinant (E. coli)
	Ligand	biotin- H3 trimethylated Lys9
	Ligand concentration	8 nM
	Incubation	30 min/RT
	Detection method	AlphaScreen
	Reference:	NA

UHRF1(108-286) [Xie *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H3 trimethylated Lys9 15 nM 15 min/RT AlphaScreen NA
PHF20(1) [Adams-Cioba *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin- H4 dimethylated Lys20 100 nM 30 min/RT AlphaScreen NA
Cell-based detection methyl modifications		
H3K27 ac [Hayashi-Takanaka *et al.* 2011]	Source Incubation Detection method Reference:	HeLa Cells 24h/37 °C AlphaScreen NA
H3K27 me2-1 [Kubicek, S. *et al.* 2007]	Source Incubation Detection method Reference:	MCF7 cells 24h/37 °C AlphaScreen NA
H3K27 me3 [Kubicek, S. *et al.* 2007]	Source Incubation Detection method Reference:	SU-DHL-6 cells 24h/37 °C AlphaScreen NA
H3K36 me2 [Kubicek, S. *et al.* 2007]	Source Incubation Detection method Reference:	HeLa cells 24h/37 °C AlphaScreen NA
H3K4 me2 [Ken-ichi Noma and Grewal 2002]	Source Incubation Detection method Reference:	HeLa cells 24h/37 °C AlphaScreen NA
H3K79 me2 [Kubicek, S. *et al.* 2007]	Source Incubation Detection method Reference:	MCF7 cells 24h/37 °C AlphaScreen NA
H3K9 ac [Hayashi-Takanaka *et al.* 2011]	Source Incubation Detection method Reference:	HeLa cells 24h/37 °C AlphaScreen NA
H3K9 me2 [Kubicek, S. *et al.* 2007]	Source Incubation Detection method Reference:	HeLa cells 24h/37 °C AlphaScreen NA
Demethylases (KDMs)		
FBXL10 (h) [Rotili and Mai 2011]	Source Substrate Incubation Detection method Reference:	human recombinant (Sf9 cells) biotin-H3K36me2 (24 nM) 10 min/RT LANCE 2,4 PDCA (IC50: 0.61 μM)

FBXL11 (h) [Chowdhury 2011]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin- H3K36me2 50 nM 10 min/RT LANCE 2,4 PDCA (IC50: 1.5 μM)
JARID1A (h) [Nottke *et al.* 2009]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) biotin-H3K4me3 100 nM 10 min/RT LANCE 2,4 PDCA (IC50: 0.18 μM)
JARID1B (h) [Kristensen 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) biotin-H3K4me3 60 nM 30 min/RT LANCE 2,4 PDCA (IC50: 0.15 μM)
JARID1C (h) [Nottke *et al.* 2009]	Source Substrate Substrate concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) biotin-H3K4me3 15 nM 30 min/RT LANCE 2,4 PDCA (IC50: 0.23 μM)
JMJD1A (h) [Heightman 2011]	Source Substrate Substrate concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H3K4me1 25 nM 10 min/RT LANCE 2,4 PDCA (IC50: 0.76 μM)
JMJD2A (h) [King *et al.* 2010]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H3K9me3 100 nM 10 min/RT LANCE 2,4 PDCA (IC50: 0.083 μM)
JMJD2B (h) [King *et al.* 2010]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin- H3K9me3 100 nM 10 min/RT LANCE 2,4 PDCA (IC50: 0.14 μM)
JMJD2C (h) [King *et al.* 2010]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin- H3K9me3 100 nM 10 min/RT LANCE 2,4 PDCA (IC50: 0.091 μM)
JMJD2D (h) [Hong *et al.* 2007]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) biotin- H3K27me3 50 nM 10 min/RT LANCE 2,4 PDCA (IC50: 0.091 μM)

JMJD2E (h) [Hong *et al.* 2007]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) biotin-H3K27me3 50 nM 10 min/RT LANCE 2,4 PDCA (IC50: 0.061 μM)
JMJD3 (h) [Hong *et al.* 2007]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) biotin- H3K27me3 50 nM 10 min/RT LANCE 1198 2,4 PDCA (IC50: 52 μM)
LSD1 (h) [Hong *et al.* 2007]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) biotin- H3K27me3 50 nM 10 min/RT LANCE Tranylcypromine (IC50: 22 μM)
PHF8(h) [Hong *et al.* 2007]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) biotin- H3K27me3 50 nM 10 min/RT LANCE 1198 Daminozide (IC50: 0.28 μM)
UTX (h) [Hong *et al.* 2007]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) biotin-H3K27me3 50 nM 10 min/RT LANCE IOX1 (0.15 μM)
DNA methyltransferases (DNMTs)		
DNMT1 (h) [Pradhan *et al.* 1999]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) Poly (dI-dC)-Poly(dIdC) [6 mU/mL] [3H] SAM (50 nM) 30 min/37 °C Scintillation counting SAH (IC50:0.23 μM)
DNMT3b [Hong *et al.* 2007]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) biotin- H3K27me3 50 nM 10 min/RT LANCE SAH (IC50:0.094 μM)
DNMT3B/DNMT3L (h) [Suetake *et al.* 2004]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (Sf9 cells) Poly (dI-dC)-Poly(dIdC) [0.15 mU/mL] [3H] SAM (200 nM) 20 min/37 °C Scintillation counting SAH (IC50:0.045 μM)
hDNMT3a [Aoki *et al.* 2001]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (Sf9 cells) Poly (dI-dC)-Poly(dIdC) [0.15 mU/mL] [3H] SAM (200 nM) 20 min/37 °C Scintillation counting SAH (IC50:0.052 μM)

Histone acetyltransferases (HATs)		
CREBBP(h) [Hong *et al.* 2007]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin- H3K27me3 50 nM 10 min/RT LANCE Garcinol (IC50:1.5 μM)
GCN5L2(h) [Hong *et al.* 2007]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) biotin- H3K27me3 50 nM 10 min/RT LANCE Anacardic acid (IC50:4.7 μM)
HAT1(h) [Zhang *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin-H3K27me3 50 nM 10 min/RT Scintillation counting Garcinol (IC50:1.5 μM)
MYST3(h) [Zhang *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin- H3K27me3 50 nM 10 min/RT Scintillation counting Garcinol (IC50:1.8 μM)
MYST4 (h) [Zhang *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin- H3K27me3 50 nM 10 min/RT Scintillation counting 1293 Curcumin (IC50:11 μM)
pCAF(h) [Zhang *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (E. coli) biotin- H3K27me3 50 nM 10 min/RT Scintillation counting 1293 Garcinol (IC50:2.9 μM)
TIP60 (h) [Zhang *et al.* 2012]	Source Ligand Ligand concentration Incubation Detection method Reference:	human recombinant (Sf 21 cells) biotin- H3K27me3 50 nM 10 min/RT Scintillation counting 1293 Garcinol (IC50:1.5 μM)
Histone deacetylase (HDACs) [Strahl and Allis 2000]		
HDAC1 (h)	Source Substrate Substrate concentration Incubation Detection method Reference:	human recombinant fluorogenic HDAC substrate 20 μM 10 min/RT fluoro-lysine fluorimetry trichostatin A (IC50:0.0052 μM)
HDAC2 (h)	Source Ligand Substrate concentration	human recombinant fluorogenic HDAC substrate NA 20 μM

	Incubation	15 min/RT
	Detection method	fluoro-lysine fluorimetry 896
	Reference:	trichostatin A (IC50:0.024 μM)
HDAC3 (h)	Source	human recombinant
	Substrate	fluorogenic HDAC substrate
	Substrate concentration	50 μM
	Incubation	10 min/RT
	Detection method	fluoro-lysine fluorimetry
	Reference:	trichostatin A (IC50:0.0068 μM)
HDAC4 (h)	Source	human recombinant
	Substrate	fluorogenic HDAC substrate
	Substrate concentration	20 μM
	Incubation	30 min/RT
	Detection method	fluoro-lysine fluorimetry
	Reference:	trichostatin A (IC50:4.0 μM)
HDAC5 (h)	Source	human recombinant
	Ligand	fluorogenic HDAC substrate
	Substrate concentration	20 μM
	Incubation	30 min/RT
	Detection method	fluoro-lysine fluorimetry
	Reference:	trichostatin A (IC50:1.0 μM)
HDAC6 (h)	Source	human recombinant
	Substrate	fluorogenic HDAC substrate
	Substrate concentration	25 μM
	Incubation	30 min/RT
	Detection method	fluoro-lysine fluorimetry
	Reference:	trichostatin A (IC50:0.0074 μM)
HDAC7 (h)	Source	human recombinant
	Substrate	fluorogenic HDAC substrate class 2a
	Substrate concentration	50 μM
	Incubation	45 min/RT
	Detection method	fluoro-lysine fluorimetry
	Reference:	trichostatin A (IC50:1.8 μM)
HDAC8 (h)	Source	human recombinant
	Substrate	fluorogenic HDAC substrate class 2a
	Substrate concentration	50 μM
	Incubation	45 min/RT
	Detection method	fluoro-lysine fluorimetry 896
	Reference:	trichostatin A (IC50:0.41 μM)
HDAC9 (h)	Source	human recombinant
	Substrate	fluorogenic HDAC substrate class 2a
	Substrate concentration	50 μM
	Incubation	30 min/RT
	Detection method	fluoro-lysine fluorimetry 896
	Reference:	trichostatin A (IC50:9.1 μM)
HDAC10 (h)	Source	human recombinant
	Substrate	fluorogenic HDAC substrate class 2a
	Substrate concentration	50 μM
	Incubation	45 min/RT
	Detection method	fluoro-lysine fluorimetry 896
	Reference:	trichostatin A (IC50:0.009 μM)
HDAC11 (h)	Source	human recombinant (E. coli)
	Substrate	fluorogenic HDAC substrate class 2a
	Substrate concentration	50 μM
	Incubation	30 min/37 °C
	Detection method	fluoro-lysine fluorimetry 896
	Reference:	Scriptaid (IC50:8.9 μM)

Sirtuins		
sirtuin 1 (h) (inhibitor effect) [Strahl and Allis 2000]	Source Substrate Substrate concentration Incubation Detection method Reference:	human recombinant (E. coli) fluorogenic HDAC substrate class 2a 50 μM 30 min/37 °C fluoro-lysine fluorimetry Suramin (IC50:7.9 μM)
sirtuin 2 (h) (inhibitor effect) [Michan and Sinclair 2007]	Source Substrate Substrate concentration Incubation Detection method Reference:	human recombinant (E. coli) fluoro-lysine sirtuin 2 deacetylase substrate 150 μM 60 min/RT fluoro-lysine fluorimetry Suramin (IC50:21 μM)
sirtuin 3 (h) (inhibitor effect) [Strahl and Allis 2000]	Source Substrate Substrate concentration Incubation Detection method Reference:	human recombinant (E. coli) fluorogenic HDAC substrate class 2a 50 μM 30 min/37 °C fluoro-lysine fluorimetry Niacinamide (IC50:21 μM)
Sirtuin 6 (h) [Michishita *et al.* 2008]	Source Substrate Substrate concentration Incubation Detection method Reference	human recombinant (E. coli) Fluorogenic HDAC 50 μM 180 min/RT fluoro-lysine fluorimetry EX-527 (IC50:550 μM)
Sirtuin 7 (h) [Kim and Kim 2013]	Source Substrate Substrate concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) fluorogenic HDAC 25 μM 60 min/37 °C fluoro-lysine fluorimetry JFD00244 (IC50:1300 μM)
Methyltransferases (MTs)		
ASH1L [An *et al.* 2011]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) polynucleosome (1.5 μg/mL) [3H] SAM (150 nM) 15 min/RT Scintillation counting SAH (IC50: 9.1 μM)
DOT1L (h) [An *et al.* 2011]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) polynucleosome (2.5 μg/mL) [3H] SAM (150 nM) 15 min/RT Scintillation counting SAH (IC50: 0.14 μM)
EHMT1 (h) [Yost *et al.* 2011]	Source Substrate (concentration) Co-substrate (concentration) Incubation Detection method Reference:	human recombinant (E. coli) histone H3 full length (10 nM) [3H] SAM (25 nM) 120 min/RT Scintillation counting SAH (IC50: 0.18 μM)
EZH1/EED/SUZ12 (h) [Shen *et al.* 2008]	Source Substrate (concentration) Co-substrate (concentration) Incubation Detection method Reference:	human recombinant histone H3 full length (70 nM) [3H] SAM (120 nM) 90 min/RT Scintillation counting SAH (IC50: 8.4 μM)

EZH2/EED/SUZ12 (h) (PRC2 complex) [Philpott *et al.* 2011]	Source Substrate (concentration) Co-substrate (concentration) Incubation Detection method Reference:	human recombinant (Sf9 cells) histone H3 full length (50 nM) [3H] SAM (350 nM) 120 min/RT Scintillation counting SAH (IC50: 22 μM)
G9a (h) [Yost *et al.* 2011]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (E. coli) histone H3 full length (5 nM) [3H] SAM (25 nM) 120 min/RT Scintillation counting SAH (2.1 μM)
hSMYD2 [An *et al.* 2011]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (Sf9 cells) histone H4 full length (25 nM) [3H] SAM 150 nM 10 min/RT Scintillation counting SAH (0.16 μM)
MLL complex (h) [Jiang *et al.* 2013]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) Histone H3 full length (35 nM) [3H] SAM (200 nM) 30 min/RT Scintillation counting SAH (0.97 μM)
MLL2(h) complex [Jiang *et al.* 2013]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) Histone H3 full length (35 nM) [3H] SAM (200 nM) 30 min/RT Scintillation counting SAH (0.97 μM)
MLL3(h) complex [Ali *et al.* 2014]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) Core histone (20 nM) [3H] SAM (200 nM) 20 min/RT Scintillation counting SAH (0.97 μM)
MLL4(h) complex [Ali *et al.* 2014]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) Core histone (30 nM) [3H] SAM (200 nM) 10 min/RT Scintillation counting SAH (0.97 μM)
NSD1 (h) [Allali-Hassani *et al.* 2014]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) Histone H3 full length (35 nM) [3H] SAM (200 nM) 30 min/RT Scintillation counting SAH (0.97 μM)
NSD3 / WHSC1L1 (h) [Selvi *et al.* 2010]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) Histone H3 full length (35 nM) [3H] SAM (200 nM) 30 min/RT Scintillation counting SAH (0.97 μM)
PRDM9 (h) [Munoz-Fuentes *et al.* 2011]	Source Substrate Co-Substrate	human recombinant (E. coli) Histone H3 full length (250 nM) [3H] SAM (60 nM)

	Incubation Detection method Reference:	30 min/RT Scintillation counting SAH (370 μM)
PRMT1 (h) [Cheng *et al.* 2004]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (E. coli) histone H4 full length (25 nM) [3H] SAM (60 nM) 90 min/RT Scintillation counting SAH (0.094 μM)
PRMT3 (h) [Li *et al.* 2012]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (E. coli) histone H4 full length (25 nM) [3H] SAM (60 nM) 90 min/RT Scintillation counting SAH (0.86 μM)
PRMT4 (h) [Selvi *et al.* 2010]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (Sf9 cells) histone H4 full length (25 nM) [3H] SAM (60 nM) 120 min/RT Scintillation counting SAH (0.094 μM)
PRMT5 complex (h) [Yost *et al.* 2011]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (Sf9 cells) histone H4 full length (250 nM) [3H] SAM (600 nM) 120 min/RT Scintillation counting SAH (0.65 μM)
PRMT6 (h) [Iberg *et al.* 2007]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (Sf9 cells) histone H4 full length (250 nM) [3H] SAM (600 nM) 120 min/RT Scintillation counting SAH (0.65 μM)
PRMT7 (h) [Zurita-Lopez *et al.* 2012]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (Sf9 cells) histone H2B (21-41) biotin labeled (4 nM) [3H] SAM (250 nM) 90 min/RT Scintillation counting SAH (0.65 μM)
PRMT8 (h) [Lee *et al.* 2005]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (Sf9 cells) histone H4 full length (250 nM) [3H] SAM (600 nM) 120 min/RT Scintillation counting SAH (0.65 μM)
SETD2(h) [Du *et al.* 2008]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (E. coli) Nucleosome (0.5 μg/mL) [3H] SAM (250 nM) 10 min/RT Scintillation counting SAH (1.2 μM)
SETD7 (h) [Li *et al.* 2012]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (E. coli) histone H3 full length (120 nM) [3H] SAM (850 nM) 30 min/RT Scintillation counting SAH (24 μM)

SETD8 (h) [Yost *et al.* 2011]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (E. coli) histone H3 full length (120 nM) [3H] SAM (850 nM) 30 min/RT Scintillation counting SAH (24 μM)
SETDB1 (h) [Schultz *et al.* 2002]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (Sf9 cells) histone H3 full length (15 nM) [3H] SAM (25 nM) 120 min/RT Scintillation counting SAH (1.8 μM)
SUV39H2 (h) [Yost *et al.* 2011]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (Sf9 cells) histone H3 full length (500 nM) [3H] SAM (350 nM) 120 min/RT Scintillation counting SAH (24 μM)
SUV4-20H2 (h) [Li *et al.* 2012]	Source Substrate Co-substrate Incubation Detection method Reference:	human recombinant (E. coli) Nucleosome (1.5 μg/ml) [3H] SAM (75 nM) 15 min/RT Scintillation counting SAH (24 μM)
WHSC1(h) (NSD2(h)) [Kang *et al.* 2009]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) Core Histone (1500 nM) [3H] SAM (250 nM) 15 min/RT Scintillation counting Chaetocin (IC50: 0.48 μM)
Kinases		
Aurora B (h) (substrate histone H3 full length) [Sabbattini *et al.* 2007]	Source Substrate Tracer Incubation Detection method Reference:	Baculovirus Histone H3 full length (150nM) [33P] ATP 10 min/RT Scintillation counting Staurosporine (0.038 μM)
DAPK3/ZIP (substrate histone H3 full length) [Preuss *et al.* 2003]	Source Substrate Tracer Incubation Detection method Reference:	Baculovirus Histone H3 full length (50nM) [33P] ATP 10 min/RT Scintillation counting Staurosporine (IC50: 0.0073 μM)
Haspin (h) (substrate histone H3 full length) [Han *et al.* 2011]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) baculovirus Histone H3 full length (250nM) [33P] ATP 10 min/RT Scintillation counting Staurosporine (IC50: 0.0073 μM)
IKK alpha(h) (substrate histone H3 full length) [Baek 2011]	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (Sf21 cells) Histone H3 full length (50nM) [33P] ATP 10 min/RT Scintillation counting Staurosporine (IC50: 0.03 μM)
MSK1(h) (substrate histone H3 full length) [Baek 2011]	Source Substrate	human recombinant insect cells Histone H3 full length (100nM)

	Tracer	[33P] ATP
	Incubation	10 min/RT
	Detection method	Scintillation counting
	Reference:	Staurosporine (IC50: 0.015 μM)
MSK2(h) (substrate histone H3 full length) [Baek 2011]	Source	human recombinant (insect cells)
	Substrate	Histone H3 full length (20nM)
	Tracer	[33P] ATP
	Incubation	10 min/RT
	Detection method	Scintillation counting
	Reference:	Staurosporine (IC50: 0.0058 μM)
PIM1(h) (histone H3 full length substrate) [Baek 2011]	Source	human recombinant (Sf21 cells)
	Substrate	Histone H3 full length (50nM)
	Tracer	[33P] ATP
	Incubation	10 min/RT
	Detection method	Scintillation counting
	Reference:	Staurosporine (IC50: 0.03 μM)
PKBalpha/AKT1(h) (substrate histone H3 full length) [Barnett *et al.* 2005]	Source	human recombinant (Sf21 cells)
	Substrate	Histone H3 full length (50nM)
	Tracer	[33P] ATP
	Incubation	10 min/RT
	Detection method	Scintillation counting
	Reference:	Staurosporine (IC50: 0.03 μM)
PKBbeta/AKT2(h) (substrate histone H3 full length) [Barnett *et al.* 2005]	Source	human recombinant (baculovirus)
	Substrate	Histone H3 full length (100nM)
	Tracer	[33P] ATP
	Incubation	10 min/RT
	Detection method	Scintillation counting
	Reference:	Staurosporine (IC50: 0.03 μM)
PKBgamma/AKT3(h) (substrate histone H3 full length) [Baek 2011]	Source	human recombinant (baculovirus)
	Substrate	Histone H3 full length (150nM)
	Tracer	[33P] ATP
	Incubation	10 min/RT
	Detection method	Scintillation counting
	Reference:	Staurosporine (IC50: 0.03 μM)
Rsk2(h) (substrate histone H3 full length) [Baek 2011]	Source	human recombinant (baculovirus)
	Substrate	Histone H3 full length (250nM)
	Tracer	[33P] ATP
	Incubation	10 min/RT
	Detection method	Scintillation counting
	Reference:	Staurosporine (IC50: 0.007 μM)
Small molecule methyltransferases		
Catechol O-methyltransferase (h)	Source	human recombinant (E. coli)
	Substrate	Pyrocatechol (250nM)
	Tracer	SAM (10 μM)
	Incubation	15 min/37 °C
	Detection method	MS
	Reference:	SAH-d4 (IC50: 14 μM)
Glycine N-methyltransferase (h)	Source	human recombinant (E. coli)
	Substrate	Glycine (100 μM)
	Tracer	SAM (20 μM)
	Incubation	30 min/22 °C
	Detection method	MS
	Reference:	SAH-d4 (IC50: 17 μM)
Guanidinoacetate N-methyltransferase (h)	Source	human recombinant (E. coli)
	Substrate	Guanidineacetic acid (4 μM)
	Tracer	SAM (7 μM)

	Incubation Detection method Reference:	30 min/22 °C MS SAH-d4 (IC50: 2.3 μM)
Histamine N-methyltransferase (h)	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) Histamine (4 μM) SAM (4 μM) 30 min/22 °C MS SAH-d4 (IC50: 13 μM)
Nicotinamide N-methyltransferase (h)	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) Nicotinamide (8 μM) SAM (6 μM) 15 min/22 °C MS SAH-d4 (IC50: 13 μM)
Phenylethanolamine N-methyltransferase (h)	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) DL-Normetanephrine SAM (35 μM) SAM (6 μM) 45 min/22 °C MS SAH-d4 (IC50: 13 μM)
Thiopurine S-methyltransferase (h)	Source Substrate Tracer Incubation Detection method Reference:	human recombinant (E. coli) 6-mercaptopurine (1.5 μM) SAM (1.5 μM) 30 min/22 °C MS SAH-d4 (IC50: 2.3 μM)
Ubiquitin modifying enzymes		
BAP1 (h) [Misaghi *et al.* 2009]	Source Substrate Substrate concentration Incubation Detection method Reference:	human recombinant (E. coli) LanthaScreen DUB substrate 20 nM 180 min/RT LanthaScreen Ubiquitin aldehyde (IC50: 0.23 μM)
USP 10 (h) [Horton *et al.* 2007]	Source Substrate Substrate concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) LanthaScreen DUB substrate 10 nM 60 min/22 °C LanthaScreen Ubiquitin aldehyde (IC50: 0.23 μM)
USP 14 (h) [Hu *et al.* 2005]	Source Substrate Substrate concentration Incubation Detection method Reference:	human recombinant (Sf9 cells) LanthaScreen DUB substrate 10 nM 240 min/RT LanthaScreen Ubiquitin Aldehyde (0.004 μM)
USP 16 (h) [Horton *et al.* 2007]	Source Substrate Substrate concentration Incubation Detection method Reference:	Human recombinant HEK 293 cells LanthaScreen DUB substrate 20 nM 180 min/22 °C LanthaScreen Iodoacetamide (3.5 μM)
USP 21 (h) [Ye *et al.* 2011]	Source Substrate Substrate concentration Incubation	human recombinant (E. coli) LanthaScreen DUB substrate 10 nM 15 min/RT

	Detection method Reference:	LanthaScreen Ubiquitin aldehyde (IC50: 0.17 μM)
USP 7 (h) [Tian *et al.* 2011]	Source Substrate Substrate concentration Incubation Detection method Reference:	human recombinant (Sf21 cells) LanthaScreen DUB substrate 10 nM 60 min/RT LanthaScreen Ubiquitin Aldehyde (0.11 μM)

Results for the binding assays are shown below in **Table 4**.

Table 4. Inhibition of Compounds **1** to **3** at 10 μM on binding of epigenetic interacting protein modules against reference compounds.

Binding Assay	**% Inhibition[A]**			**Reference**	
	Comp 1	**Comp 2**	**Comp 3**	**Compound**	**IC_{50} μM**
Bromodomain					
ATAD2B (h)	52	25	28	Ischemin sodium salt	76.6
ASH1L (h)	95	59	42	JQ-1	13.8
BAZ2A (h)	56	17	16	GSK2801	1.8
BRPF1-1 (h)	-25	-25	-4	Bromosporine	0.026
CECR2 (h)	100	25	15	Bromosporine	0.062
EP300 (h)	89	37	40	SGC-CBP30	0.050
KAT2A (GCN5L2) (h)	76	19	18	JQ-1	45
PCAF (h)	37	16	3	JQ-1	12
PB1(2) (h)	31	22	13	PFI-3	68
PB1(3) (h)	38	13	6	JQ-1	47
PB1(4) (h)	41	-3	16	Ischemin sodium salt	6.8
PHIP(2) (h)	61	30	23	SGC-CBP30	0.130
SP140 (h)	84	43	1	Ischemin	86
SMARCA2 (h)	83	21	18	PFI-3	0.47
TAF1(1) (h)	48	17	17	GSK2801	4.4
SMARCA4 (h)	53	16	13	PFI-3	3
TAF1(2)(h)	62	28	22	GSK2801	10
BAZ2B (h)	58	23	21	GSK2801	1.8
ATAD2A (h)	100	16	9	JQ-1	70
BRD2(1) (h)	60	89	19	JQ-1	0.510
BRD2(2) (h)	58	22	18	JQ-1	0.017
BRD3(1) (h)	47	17	13	JQ-1	0.040
BRD3(2) (h)	35	25	1	PFI-1	0.79
BRD4(1) (h)	49	11	8	JQ-1	0.018
BRD4(2) (h)	76	16	13	PFI-1	1.3
BRDT(1) (h)	43	23	29	JQ-1	0.110
CREBBP (h)	65	21	17	SGC-CBP30	0.120

FALZ (h)	42	18	5	I-CBP112	24.5
Chromodomain					
CBX1 (h)	15	0	-1	NA	
CBX2 (h)	17	6	3	NA	
CBX4 (h)	25	29	40	NA	
CBX6 (h)	-1	27	58	NA	
CBX5 (h)	25	24	25	NA	
CBX7 (h)	25	33	43	NA	
CBX8 (h)	27	31	23	NA	
MBT domain					
L3MBTL1	41	61	59	NA	
L3MBTL3 (h)	22	29	33	NA	
PHD domain					
SP140 (h)	74	0	2	NA	
TRIM 33 (h)	59	3	-2	NA	
UHRF1(108-286) (h)	73	34	29	NA	
Tudor domain					
PHF20(1)	7	2	2	NA	

[A] % Inhibition of Control Specific Binding

NA Not-applicable

Representative inhibition data for compound **1** on binding example epigenetic targets is shown in **Tables 5** to **8**.

Table 5. ASH1L (h) bromodomain

Conc.	**1st**	**2nd**	**Mean**
3.0E-09 M	-2.6	-8.2	-5.4
3.0E-08 M	-12.3	1.8	-5.2
3.0E-07 M	-0.2	-2.9	-1.6
3.0E-06 M	17.0	28.0	22.5
3.0E-05 M	100.6	99.6	100.1

Table 6. CECR2(h) bromodomain binding curve

Conc.	**1st**	**2nd**	**Mean**
3.0E-09 M	5.9	2.4	4.2
3.0E-08 M	-0.9	-1.7	-1.3
3.0E-07 M	-1.5	0.9	-0.3
3.0E-06 M	7.3	8.6	7.9
3.0E-05 M	99.4	99.6	99.5

Table 7. SP140 *(h)* bromodomain binding curve.

Conc.	1st	2nd	Mean
3.0E-09 M	-6.0	-8.6	-7.3
3.0E-08 M	-9.7	-14.6	-12.1
3.0E-07 M	-14.1	-11.0	-12.6
3.0E-06 M	8.4	11.3	9.9
3.0E-05 M	102.3	102.3	102.3

Table 8. UHRF1(108-286) (h) binding curve.

Conc.	1st	2nd	Mean
3.0E-09 M	-11.9 -	13.1	-12.5
3.0E-08 M	-13.3	-12.6	-12.9
3.0E-07 M	-12.1	-13.2	-12.7
3.0E-06 M	-1.8	-0.1	-0.9
3.0E-05 M	81.5	83.3	82.4

Table 9. IC_{50} values from inhibition/concentration-response curves of compounds **1** and **2** for binding of epigenetic interacting protein modules against reference compounds.

	Compound			
	1	2	Reference	Reference
	IC_{50} (μM)	IC_{50} (μM)	Comp.	IC_{50} (μM)
Bromodomain				
ASH1L (h)	4.2		JQ-1	8.7
ATAD2A (h)	3.1		Ischemin	5.2
BRD2(1) (h)		22	1-BET 151	0.028
BRD4(2) (h)	5.6		PFI-1	1.1
CECR2(h)	5		Bromosporine	0.14
CREBBP (h)	3.4		SGC-CBP30	0.046
EP300 (h)	4.5		SGC-CBP30	0.068
KAT2A (GCN5L2) (h)	3.9		GSK2801	10
SP140 (h)	3.8		Ischemin	11
PHD domain				
SP140 (h)	4.6		NA	NA
UHRF1(108-286) (h)	11		NA	NA

Table 10. Inhibition of compounds **1** to **3** at 10 μM on activity of epigenetic enzymes against references.

	% Inhibition[A]			Reference	
Assay	**Comp 1**	**Comp 2**	**Comp 3**	**Compound**	**IC_{50} μM**
Cell-based detection methyl modifications					
H3K27 ac	-16	-12	-11	(Not-applicable) NA	
H3K27 me2-1	-2	3	2	NA	
H3K27 me3	-8	-7	0	NA	
H3K36 me2	10	7	-8	NA	
H3K4 me2	-5	-1	-9	NA	
H3K79 me2	-2	-16	-5	NA	
H3K9 ac	17	3	-1	NA	
H3K9 me2	1	11	20	NA	
Demethylases (KDMs)					
FBXL10 (h)	37	7	22	2,4 PDCA	0.61
FBXL11 (h)	34	2	11	2,4 PDCA	1.5
JARID1A (h)	64	-9	3	2,4 PDCA	0.18
JARID1B (h)	70	6	-2	2,4 PDCA	0.15
JARID1C (h)	49	-13	25	2,4 PDCA	0.23
JMJD1A (h)	80	37	-1	2,4 PDCA	0.76
JMJD2A (h)	29	-10	12	2,4 PDCA	0.083
JMJD2B (h)	65	16	8	2,4 PDCA	0.14
JMJD2C (h)	35	2	8	2,4 PDCA	0.091
JMJD2D (h)	36	-17	18	2,4 PDCA	0.091
JMJD2E (h)	65	10	6	2,4 PDCA	0.061
JMJD3 (h)	91	9	11	2,4 PDCA	52
LSD1 (h)	10	10	-3	Tranylcypromine	22
PHF8(h)	36	-11	13	Daminozide	0.28
UTX (h)	68	5	27	IOX1	0.15
DNA methyltransferases (DNMTs)					
DNMT1 (h)	10	4	-5	SAH	0.23
DNMT3b	-3	-17	-4	SAH	0.094
DNMT3B/DNMT3L (h)	23	27	-20	SAH	0.045
hDNMT3a	3	3	-31	SAH	0.052
Histone acetyltransferases (HATs)					
CREBBP(h)	74	78	43	Garcinol	1.5
GCN5L2(h)	11	5	1	Anacardic Acid	4.7
HAT1(h)	-3	3	-3	Garcinol	1.5
MYST3(h)	18	11	3	Garcinol	1.8
MYST4(h)	25	39	71	Curcumin	11
pCAF(h)	-25	-26	-20	Garcinol	2.9

TIP60(h)	20	10	-3	Garcinol	1.5
Histone deacetylase (HDACs)					
HDAC1 (h)	-2	-1	-1	trichostatin A	0.0052
HDAC2 (h)	1	0	-2	trichostatin A	0.024
HDAC3 (h)	1	1	3	trichostatin A	0.0068
HDAC4 (h)	-73	-20	-11	trichostatin A	4.0
HDAC5 (h)	-3	-2	-1	trichostatin A	1.0
HDAC6 (h)	12	2	-18	trichostatin A	0.0074
HDAC7 (h)	-111	-6	16	trichostatin A	1.8
HDAC8 (h)	-8	-19	0	trichostatin A	0.41
HDAC9 (h)	-50	-1	-9	trichostatin A	9.1
HDAC10 (h)	1	3	6	trichostatin A	0.0090
HDAC11 (h)	27	-47	-130	scriptaid	8.9
Sirtuins					
sirtuin 1 (h) (inhibitor effect)	2	-3	-5	suramin	7.9
sirtuin 2 (h) (inhibitor effect)	-4	6	-19	suramin	21
sirtuin 3 (h) (inhibitor effect)	-14	-8	-3	niacinamide	21
Sirtuin 6 (h)	2	6	-4	EX-527	550
Sirtuin 7 (h)	7	-2	-8	JFD00244	1300
Methyltransferases (MTs)					
ASH1L	3	20	-54	SAH	9.1
DOT1L (h)	-5	18	13	SAH	0.14
EHMT1 (h)	13	9	63	SAH	0.18
EZH1/EED/SUZ12 (h)	-1	3	-12	SAH	8.4
EZH2/EED/SUZ12 (h) (PRC2 complex)	19	26	4	SAH	22
G9a (h)	86	64	49	SAH	2.1
hSMYD2	12	5	-12	SAH	0.16
MLL complex (h)	2	22	11	SAH	0.97
MLL2(h) complex	6	3	-15	SAH	24
MLL3(h) complex	-22	-21	-33	SAH	9.0
MLL4(h) complex	-16	-18	-4	SAH	0.55
NSD1 (h)	69	29	-10	chaetocin	0.13
NSD3 / WHSC1L1 (h)	-17	11	-35	Suramin	1.5
PRDM9 (h)	9	5	4	SAH	370
PRMT1 (h)	16	26	-1	SAH	0.094
PRMT3 (h)	22	50	14	SAH	0.86
PRMT4 (h)	90	84	77	SAH	0.094
PRMT5 complex (h)	8	-8	9	SAH	0.65
PRMT6 (h)	49	57	34	SAH	0.053
PRMT7 (h)	-2	0	-36	SAH	0.86

PRMT8 (h)	5	24	-26	SAH	0.14
SETD2(h)	-9	-4	-11	SAH	1.2
SETD7 (h)	12	16	-2	SAH	24
SETD8 (h)	4	25	-10	mercurochrome	2.4
SETDB1 (h)	53	43	52	SAH	1.8
SUV39H2 (h)	-8	-16	14	SAH	24
SUV4-20H2 (h)	11	20	-45	SAH	4.7
WHSC1(h) (NSD2(h))	3	14	7	Chaetocin	0.48
Kinases					
Aurora B (h) (substrate histone H3 full length)	6	4	-1	Staurosporine	0.038
DAPK3/ZIP (substrate histone H3 full length)	4	9	8	Staurosporine	0.0073
Haspin (h) (substrate histone H3 full length)	2	11	7	Staurosporine	0.032
IKK alpha(h) (substrate histone H3 full length)	26	28	14	staurosporine	0.03
MSK1(h) (substrate histone H3 full length)	6	2	10	Staurosporine	0.015
MSK2(h) (substrate histone H3 full length)	9	12	-1	Staurosporine	0.0058
PIM1(h) (histone H3 full length substrate)	22	11	5	Staurosporine	0.025
PKBalpha/AKT1(h) (substrate histone H3 full length)	-1	-19	-15	Staurosporine	0.0073
PKBbeta/AKT2(h) (substrate histone H3 full length)	13	11	12	Staurosporine	0.021
PKBgamma/AKT3(h) (substrate histone H3 full length)	5	-7	3	Staurosporine	0.03
Rsk2(h) (substrate histone H3 full length)	5	7	-4	Staurosporine	0.007
Small molecule methyltransferases					
Catechol O-methyltransferase (h)	6	1	0	SAH-d4	14
Glycine N-methyltransferase (h)	55	5	-11	SAH-d4	17
Guanidinoacetate N-methyltransferase (h)	8	-1	-1	SAH-d4	2.3
Histamine N-methyltransferase (h)	18	-2	18	SAH-d4	13
Nicotinamide N-methyltransferase (h)	13	-2	-2	SAH-d4	13
Phenylethanolamine N-methyltransferase (h)	23	9	5	SAH-d4	3.9
Thiopurine S-methyltransferase (h)	40	28	19	SAH-d4	2.3
Ubiquitin modifying enzymes					
BAP1 (h)	1	-9	24	Ubiquitin Aldehyde	0.23
USP 10 (h)	7	2	-7	N-Methylmaleimide	1000
USP 14 (h)	1	0	-24	Ubiquitin Aldehyde	0.004

USP 16 (h)	11	14	12	Iodoacetamide	3.5
USP 21 (h)	-18	3	3	Ubiquitin aldehyde	0.17
USP 7 (h)	-18	-14	9	Ubiquitin Aldehyde	0.11

[A] % Inhibition of Control Values

Table 11. IC_{50} values from inhibition/concentration-response curves of compounds **1**, **2** and **4** for inhibition of epigenetic enzymes against reference compounds.

	Compound				
	1	**2**	**4**	Reference	Reference
Enzyme and Cell-based assays	IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)	Compound	IC_{50} (μM)
Demethylases					
JARID1A (h)	9.6			2,4 PDCA	0.099
JARID1B (h)	3.6			2,4 PDCA	0.12
JMJD1A (h)	4.5			2,4 PDCA	3.9
JMJD2B (h)	12			2,4 PDCA	0.095
JMJD2E (h)	4.7			2,4 PDCA	0.11
JMJD3 (h)	14			2,4 PDCA	73
UTX (h)	6.7			IOX1	0.056
Histone acetyltransferases					
CREBBP(h)	3.9	6.1		Garcinol	5.4
MYST4 (h)			4.2	Curcumin	8.9
Histone methyltransferases					
G9a (h)	11	5.4		SAH	4.6
NSD1 (h)	4.9			chaetocin	0.24
PRMT4 (h)	4.7	5.4	4.7	SAH	0.056

Results: epigenetic targets, diseases and cancer

Epigenetic modifications can have a role in the development of a variety of diseases. Epigenetic regulation involves hierarchical covalent modification of DNA and proteins that package such as histones. DNA is regulated by methylation and demethylation on the cytosine residues. DNA methylation is mediated by members of the DNA-methyl transferase family (DNMT1, DNMT3A and DNMT3B) whereas demethylation is mediated by the family ten-eleven translocation (TET1-3). Besides methylation and demethylation, histone is also regulated by acetylation and deacetylation. The key proteins that mediate epigenetic signaling though acetylation and methylation of histones comprise histone acetyltransferases (HATs), histone deacetylases (HDMs), protein methyltransferases (PMTs) including lysine methyltransferases (KMTs) protein

arginine methyltransferases (PRMTs), and bromodomain-containing proteins and proteins that bind to methylated histones (Arrowsmith *et al.*, 2012; Plass *et al.*, 2013; Tough *et al.*, 2014; Biggar and Li, 2015).

Bromodomain containing proteins

Compound **1** showed significant inhibitory activity towards many of the bromodomain containing proteins (**Table 10**), in particular ASH1L, CECR2, EP300, KAT2A, PHIP(2), SP140, SMARCA2, TAF1(2), ATAD2A, BRD2(1), BRD4(2) and CREBBP. Compound **2** only showed significant activity towards BRD2(1). Recent studies have implicated bromodomain (BRD) containing proteins in a wide range of human diseases, including cancer (Taverna *et al.*, 2007; Prinjha *et al.*, 2012; Biggar and Li, 2015). The most investigated member of BRD containing proteins (BCPs) as drug targets is the BET family proteins. Currently, there are several BET inhibitors in various stages of clinical trials including RVX-208, I-BET 762, OTX 015, CPI-0610 and TEN-010 (see Table 14 in Tough *et al.*, 2014).

In addition, JQ1 and I-BET have been shown to interact with NF-κB and induce apoptosis in drug resistant leukemia (Ciceri *et al.*, 2014). NF-κB plays a central role inflammation and unresolved inflammation is involved in many disease states including cancer.

Several bromodomain containing proteins, including ASH1L,ATAD2A/B, BAZ2A/B, CECR2, EP300, KAT2A, PHIP(2), PB1, SMARCA2/4, BRD2/4 and CREBBP, have been shown to be up-regulated in many types of cancers (Tough *et al.*, 2014; Fu *et al.*, 2015). Hence, BRDs are therefore therapeutic targets for cancer. BRD-containing domains have been linked to the development of a number of extremely aggressive tumours containing BRD4-NUT and BRD3-NUT. CREBBP mutations have been identified in relapsed acute lymphoblastic leukaemia and are very common in diffuse large B-cell lymphoma and follicular lymphoma, Hodgkin's lymphoma. CREBBP and the related HAT are highly expressed in advanced prostate cancer and expression levels have been linked with patient survival. ATAD2 is over expressed in more than 70% of breast tumours and higher protein levels correlate with poor overall survival and disease recurrence (Ciro *et al.*, 2009). ATAD2B is highly expressed in glioblastoma

and oligodendroglioma as well as breast carcinoma (Krakstad *et al.*, 2015). BRD4 is linked to development of cervical cancer (Weidner-Glunde *et al.*; 2010).

Compound **1** showed good inhibitory activity against domain PHD (plant homology domain) containing domain proteins SP140, TRIM 33, UHRF1 (108-286)).

Methyltransferases

Compound **1** was a strong inhibitor of the lysine methyltransferase enzyme G9a whereas compounds **2** and **3** were weaker (**Table 10**). G9a is a multipotent regulator of gene expression which has been shown to be over expressed in many different types of cancers (See reviews for details: Shankar *et al.*, 2013; Casciello *et al.*, 2015).

Compounds **1** to **3** strongly inhibited the activity of PRMT4 and moderately inhibited the activity of PRMT6. Dysregulated PRMT expression and activity have been observed in a variety of cancers and PRMT1-5 and 7 have been shown to be overexpressed or otherwise contribute to tumorigenesis whereas PRMT8, and 9 have not been implicated in oncogenesis (Fuhrmann *et al.*, 2015). PRMT4 (CARM1) is necessary for NFκB target gene expression. Further study showed a link between PRMT4 and p300 acetyltransferase activity in NFκB recruitment and gene activation.

Demethylases

Compound **1** showed significant inhibitory activity towards many of the lysine demethylase enzymes (**Table 10**), in particular JARID1A, JARID1B, JMJD1A, JMJD2B, JMJD2E, JMJD3 and UTX. Aberrant expression and mutations of lysine demethylases have been linked to various cancers (Hojfeldt *et al.*, 2013; Tough *et al.*, 2014). Mutation of lysine demethylases including FBXL10, JMJD2A, JMJDB, JMJD2C, JARID1B and PHF2 have been shown to be overexpressed in breast, colorectal, lung, prostrate, bladder and other tumours; the functional significance of JMJD2C overexpression is further suggested by the presence of the JMJD2C gene within an amplified region of a chromosome in multiple cancers (Xiang *et al.*, 2007; Couvelard *et al.*, 2008; Roesch *et al.*, 2010; He *et al.*, 2011a; Berry and Janknecht, 2013; Kogure *et al.*, 2013; Tzatsos *et al.*, 2013).

Histone acetyltransferases

The serrulatanes diterpenes showed significant inhibitory activity on histone acetyltransferases CREBBP and MYST4 (**Table 10**). Misregulation of histone acetyltransferase activity has been linked to many different pathogenic states including cancers, neurodegenerative disorders, and metabolic, respiratory, inflammatory and cardiovascular diseases (Adcock and Lee, 2006; Avvakumov and Cote, 2007; Grabiec *et al.*, 2008; Ghizzo *et al.*, 2011, Iyer *et al.*, 2011; Pirooznia and Elefant, 2013).

Table 12. Enzyme and Cell-based stimulation assays for compounds **1** to **3** at 10 μM concentration

	% Stimulation Relative to Control			Reference	
Assay	**Comp 1**	**Comp 2**	**Comp 3**	**Compound**	**EC_{50} (μM)**
H3K9 ac (increase)	-21	-26	-8	(Not-applicable) NA	
noneH3K27 ac (increase)	-28	-17	-25	NA	
sirtuin 1 (h) (activator effect)	-5	-3	-4	Resveratrol	27

Pharmacology Assays

The *in vitro* pharmacological studies were conducted by Eurofins PanLab (Taiwan) using the parameters shown in Table **13** with respect to appropriate literature references.

Table 13. Pharmacology assay methods.

Angiotensin system	
Angiotensin AT2 [Lee *et al.* 2001]	
Source	Human recombinant CHO-K1 cells
Vehicle	1.00% DMSO
Ligand	0.050 nM [^{125}I] CGP-42112A
Non-Specific Ligand	10.0 μM (Sar^1, Ile^8)-Angiotensin II
Incubation (Time/ Temperature)	3 hours @ 37°C
Incubation Buffer	50 mM Tris-HCl, pH 7.4, 5 mM MgCl2, 1 mM EDTA, 0.1% BSA
Quantitation Method	Radio ligand Binding
Angiotensin, AT_1/ACE [Rubin *et al.* 1978]	
Source	Dunkin Hartley Guinea pig 600 ± 80.0 g ileum
Vehicle	0.10% DMSO
Incubation (Time/ Temperature)	5 minutes @ 32°C
Incubation Buffer	Krebs, pH 7.4
Quantitation Method	Isotonic (cm changes)
Peptidase, Angiotensin Converting Enzyme [Bunning *et al.* 1983]	
Source	Rabbit lung
Substrate	500 μM (N-3-[2-furyl] acryloyl)-Phe-Gly- Gly (FAPGG)

Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 25°C
Incubation (Time/ Temperature)	30 minutes @ 25°C
Incubation Buffer	50 mM HEPES, pH 7.5, 300 mM NaCl
Quantitation Method	Spectrophotometric quantitation of FAPGG
Chemokines	
Chemokine CCR1 [Hesselgesser *et al.* 1998]	
Source	Human recombinant Chem-2 cells
Vehicle	1.00% DMSO
Ligand	0.10 nM [^{125}I] MIP-1α
Non-Specific Ligand	0.10 µM MCP-3
Incubation (Time/ Temperature)	3 hours @ 25°C
Incubation Buffer	50 mM HEPES, pH 7.4, 5 mM MgCl2, 1 mM CaCl2, 0.2% BSA
Quantitation Method	Radio ligand Binding
Chemokine CCR2B [Gong *et al.* 1997]	
Source	Human recombinant CHO-K1 cells
Vehicle	1.00% DMSO
Ligand	0.10 nM [^{125}I] MCP-1
Non-Specific Ligand	0.030 µM MCP-1
Incubation (Time/ Temperature)	60 minutes @ 25°C
Incubation Buffer	50 mM Tris-HCl, pH 7.4, 5 mM MgCl2, 1 mM EDTA, 0.1% BSA
Quantitation Method	Radio ligand Binding
Chemokine CX3CR1 [Combadiere *et al.* 1998]	
Source	Human recombinant Chem-1 cells
Vehicle	1.00% DMSO
Ligand	20.0 pM [^{125}I] Fractalkine
Non-Specific Ligand	10 nM Fractalkine
Incubation (Time/ Temperature)	90 minutes @ 25°C
Incubation Buffer	50 mM HEPES, pH 7.5, 1 mM CaCl2, 5 mM MgCl2, 0.5% BSA, 0.1% NaN3
Quantitation Method	Radio ligand Binding
Chemokine CXCR1/2 (IL-8, Non-Selective) [Grob *et al.* 1990]	
Source	Human neutrophils
Vehicle	1.00% DMSO
Ligand	15.0 pM [^{125}I] IL-8
Non-Specific Ligand	10 nM IL-8
Incubation (Time/ Temperature)	2 hours @ 4°C
Incubation Buffer	50 mM Tris-HCl, pH 7.4, 1 mM EDTA, 5 mM MgCl2, 5 mg/ml BSA
Quantitation Method	Radio ligand Binding
Chemokine CXCR2 (IL-8RB) [Ahuja and Murphy 1996]	
Source	Human recombinant CHO-K1 cells
Vehicle	1.00% DMSO
Ligand	15.0 pM [^{125}I] IL-8
Non-Specific Ligand	10 nM IL-8
Incubation (Time/ Temperature)	60 minutes @ 25°C
Incubation Buffer	25 mM HEPES, pH 7.4, 2 mM CaCl2, 1 mM MgCl2, 0.2% BSA
Quantitation Method	Radio ligand Binding
Chemokine CXCR4 [Valenzuela-Fernandez 2002]	
Source	Human recombinant Chem-1 cells

Vehicle	1.00% DMSO
Ligand	0.030 nM [^{125}I] SDF-1α
Non-Specific Ligand	0.030 µM SDF-1α
Incubation (Time/ Temperature)	90 minutes @ 25°C
Incubation Buffer	50 mM HEPES, pH 7.4, 5 mM MgCl2, 1 mM CaCl2, 0.2% BSA
Quantitation Method	Radio ligand Binding
Histone Deacetylases (HDACs)	
Deacetylase, Histone 1 [Strahl and Allis 2000]	
Source	Human recombinant Insect Sf9 cells
Substrate	25.0 µM Fluor-de-Lys deacetylase
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 25°C
Incubation (Time/ Temperature)	60 minutes @ 25°C
Incubation Buffer	25 mM Tris-HCl, pH 8.0, 2.7 mM KCl, 1 mM MgCl2, 137 mM NaCl
Quantitation Method	Spectrofluorimetric quantitation of Fluor- de-Lys deacetylsubstrate
Deacetylase, Histone 2 [Strahl and Allis 2000]	
Source	Human recombinant Insect Sf9 cells
Substrate	25.0 µM Fluor-de-Lys deacetylase
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 25°C
Incubation (Time/ Temperature)	60 minutes @ 25°C
Incubation Buffer	25 mM Tris-HCl, pH 8.0, 2.7 mM KCl, 1 mM MgCl2, 137 mM NaCl
Quantitation Method	Spectrofluorimetric quantitation of Fluor- de-Lys deacetylsubstrate
Growth Factor	
Epidermal Growth Factor (EGF) [Dittadi *et al.* 1990]	
Source	Human A431 cells
Vehicle	1.00% DMSO
Ligand	0.080 nM [^{125}I] EGF (human)
Non-Specific Ligand	0.10 µM EGF (human)
Incubation (Time/ Temperature)	60 minutes @ 25°C
Incubation Buffer	50 mM HEPES, pH 7.7, 0.1% BSA, 1.2 mM CaCl2, 5 mM KCl, 1.2 mM MgSO4, 138 mM NaCl
Quantitation Method	Radio ligand Binding
Other classes	
Catechol-O-Methyl Transferase (COMT) [Muller-Enoch *et al.* 1976]	
Source	Porcine liver
Substrate	1.0 µM Esculetin
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 37°C
Incubation (Time/ Temperature)	30 minutes @ 37°C
Incubation Buffer	36 mM Tris-HCl, pH 8.0, 1.35 mM DTT, 0.54 mM MgCl2, 30.6 µM SAM
Quantitation Method	Spectrofluorimetric quantitation of scopoletin
Phospholipase sPLA2-V [Tietge *et al.* 2005]	
Source	Human E. coli
Substrate	250 µM diheptanoyl thio-PC
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 25°C

Incubation (Time/ Temperature)	30 minutes @ 25°C
Incubation Buffer	16.25 mM Tris-HCl, 6.5 mM CaCl2, 65 mM KCl, 0.2 mM Triton X-100
Quantitation Method	Spectrophotometric quantitation of heptanoyl thio-PC
Protein Tyrosine Phosphatase, PTPN1 (PTP1B) [Montalibet *et al.* 2005]	
Source	Human recombinant E. coli
Substrate	10.0 µM DiFMUP
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 37°C
Incubation (Time/ Temperature)	60 minutes @ 37°C
Incubation Buffer	50 mM HEPES, pH 7.2, 0.1% BSA, 1 mM DTT
Quantitation Method	Spectrofluorimetric quantitation of DiFMU
Steroid 5α-Reductase [Sun and Tu 1998]	
Source	Wistar Rat liver
Substrate	0.90 µM Testosterone
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 37°C
Incubation (Time/ Temperature)	30 minutes @ 37°C
Incubation Buffer	40 mM Potassium Phosphate, pH 6.5, containing 1 mM DTT, 50 µM NADPH
Quantitation Method	EIA quantitation of Testosterone
Thioredoxin Reductase [Becker *et al.* 2000]	
Source	E. coli
Substrate	1.0 mM 5,5'-Dithiobis (2-nitrobenzoic acid) (DTNB)
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 25°C
Incubation (Time/ Temperature)	60 minutes @ 25°C
Incubation Buffer	100 mM Potassium Phosphate, pH 7.4, 2 mM EDTA, 0.2 mg/ml BSA
Quantitation Method	Spectrophotometric quantitation of 5- Mercapto-2-nitrobenzoic acid
Xanthine Oxidase [Hatano *et al.* 1990]	
Source	Bovine buttermilk
Substrate	165 µM Xanthine
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 25°C
Incubation (Time/ Temperature)	30 minutes @ 25°C
Incubation Buffer	33.3 mM Potassium Phosphate, pH 7.5
Quantitation Method	Spectrophotometric quantitation of Uric acid
Histamine H1 [De Backer *et al.*, 1993]	
Source	Human recombinant Chem-1 cells
Substrate	1.00% DMSO
Vehicle	1.20 nM [^{3}H] Pyrilamine
Pre incubation (Time/ Temperature)	1.0 µM Pyrilamine
Incubation (Time/ Temperature)	3 hours @ 25°C
Incubation Buffer	50 mM Tris-HCl, pH 7.4, 5 mM MgCl2
Quantitation Method	Radio ligand Binding
Histamine H2 [Ruat *et al.*, 1990]	
Source	Human recombinant CHO-K1 cells
Vehicle	1.00% DMSO
Ligand	0.10 nM [^{125}I] Aminopotentidine
Non-Specific Ligand	3.0 µM Tiotidine

Incubation (Time/ Temperature)	2 hours @ 25°C
Incubation Buffer	50 mM Phosphate, pH 7.4
Quantitation Method	Radio ligand Binding
Histamine H3 [Krueger *et al.*, 2005]	
Source	Human recombinant Chem-1 cells
Substrate	1.00% DMSO
Vehicle	0.40 nM [^{3}H] N-α-Methylhistamine (NAMH)
Pre incubation (Time/ Temperature)	1.0 µM R(-)-α-Methylhistamine (RAMH)
Incubation (Time/ Temperature)	2 hours @ 25°C
Incubation Buffer	50 mM Tris-HCl, pH 7.4, 5 mM MgCl2, 0.1% BSA
Quantitation Method	Radio ligand Binding
Histamine H4 [Liu *et al.*, 2001]	
Source	Human recombinant Chem-1 cells
Substrate	1.00% DMSO
Vehicle	8.20 nM [^{3}H] Histamine
Pre incubation (Time/ Temperature)	1.0 µM Histamine
Incubation (Time/ Temperature)	90 minutes @ 25°C
Incubation Buffer	50 mM Tris-HCl, pH 7.4, 1.25 mM EDTA
Quantitation Method	Radio ligand Binding
HMG-CoA Reductase [Kubo and Strott, 1987]	
Source	Human recombinant E. coli
Substrate	2.50 µM [^{14}C]HMG-CoA
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 37°C
Incubation (Time/ Temperature)	20 minutes @ 37°C
Incubation Buffer	100 mM KH2PO4, pH 7.5, 8 mM G-6-P, 1 mM NADP, 4 mM EDTA, 2 mM DTT, 0.6 U/ml G-6-P-DH
Quantitation Method	Quantitation of [^{14}C] Mevalonate
5-Lipoxygenase [Pufahl *et al.*, 2007]	
Source	Human recombinant Insect Sf9 cells
Substrate	25.0 µM Arachidonic acid
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	5 minutes @ 25°C
Incubation (Time/ Temperature)	20 minutes @ 25°C
Incubation Buffer	50 mM Tris-HCl, pH 7.4, 5 mM CaCl2, 2 mM EDTA, 1 µM ATP
Quantitation Method	Spectrofluorimetric quantitation of rhodamine 123
Lipid Peroxidase [Mansuy *et al.*, 1986]	
Source	Dunkin Hartley Guinea pig liver microsomes
Substrate	Polyunsaturated fatty acid
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 37°C
Incubation (Time/ Temperature)	20 minutes @ 37°C
Incubation Buffer	0.25 M Potassium Phosphate, pH 7.4, 0.1 mM EDTA
Quantitation Method	Spectrophotometric quantitation of Malondialdehyde

Lipoxygenase 12-LO [Romano *et al.*, 1993]	
Source	Human platelets
Substrate	30.0 μM Arachidonic acid
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 25°C
Incubation (Time/ Temperature)	15 minutes @ 25°C
Incubation Buffer	50 mM Tris-HCl, pH 7.4, 0.1% Triton X-100
Quantitation Method	Spectrophotometric quantitation of 12- HETE
Monoamine Oxidase MAO-A [Urban *et al.*, 1991]	
Source	Human recombinant Insect Hi5 cells
Substrate	50.0 μM Kynuramine
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 37°C
Incubation (Time/ Temperature)	60 minutes @ 37°C
Incubation Buffer	100 mM Potassium Phosphate, pH 7.4
Quantitation Method	Spectrofluorimetric quantitation of 4- hydroxyquinoline
Monoamine Oxidase MAO-B [Urban *et al.*, 1991]	
Source	Human recombinant Insect Hi5 cells
Substrate	50.0 μM Kynuramine
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 37°C
Incubation (Time/ Temperature)	60 minutes @ 37°C
Incubation Buffer	100 mM Potassium Phosphate, pH 7.4
Quantitation Method	Spectrofluorimetric quantitation of 4- hydroxyquinoline
Myeloperoxidase [Svensson *et al.*, 1987]	
Source	Human PMN leukocytes
Substrate	20.0 mM Guaiacol
Vehicle	1.00% DMSO
Pre incubation (Time/ Temperature)	15 minutes @ 25°C
Incubation (Time/ Temperature)	5 minutes @ 25°C
Incubation Buffer	0.1 M Sodium Phosphate, pH 7.4
Quantitation Method	Spectrophotometric quantitation of Tetraguaiacol
[3H]-2-Deoxy-D-glucose uptake[Yamamoto *et al.*, 2006]	
Source	Rat L6 skeletal muscle cells
Substrate	0.10% DMSO
Vehicle	24 hours @ 37°C
Pre incubation (Time/ Temperature)	15 minutes @ 37°C
Incubation (Time/ Temperature)	KRPH, pH 7.4
Incubation Buffer	Radiometric quantitation of insulin-induced 2-DG uptake
Quantitation Method	Rat L6 skeletal muscle cells
Adhesion and Transcription response	
Adhesion, ICAM-1-Mediated [Cobb *et al.* 1992]	
Source	Human
Vehicle	0.40% DMSO
Ligand	0.030 nM [^{125}I] SDF-1α
Non-Specific Ligand	0.030 μM SDF-1α
Incubation (Time/ Temperature)	30 minutes @ 37°C
Incubation Buffer	25 mM HEPES, pH 7.4, RPMI-1640,

	1% FBS
Quantitation Method	Spectrofluorimetric quantitation of adhesion
Adhesion, VCAM-1-Mediated [Stoltenborg *et al*. 1994]	
Source	Human
Vehicle	0.40% DMSO
Incubation (Time/ Temperature)	60 minutes @ 37°C
Incubation Buffer	25 mM HEPES, pH 7.4, RPMI-1640, 1% FBS
Quantitation Method	Spectrofluorimetric quantitation of adhesion
Transcription Response, NF-κB [Lenardo and Baltimore 1989]	
Source	Human
Vehicle	0.50% DMSO
Incubation (Time/ Temperature)	4 hours @ 37°C
Incubation Buffer	RPMI-1640, pH 7.4
Quantitation Method	Spectrofluorimetric quantitation of β- galactosidase

The results of pharmacological assays are shown in **Table 14**.

Table 14. Pharmacological activity of compounds **1** to **3** at 10 μM.

	% Control Response			Assay
Ascii Assay Name	**1**	**2**	**3**	**Year**
Angiotensin system				
Angiotensin AT2	29	18	9	2015
Angiotensin, AT 1/ACE - Agonist	0	0	0	2015
Angiotensin, AT 1/ACE - Antagonist	34	10	17	2015
Peptidase, Angiotensin Converting Enzyme	0	-3	-3	2015
Chemokines				
Chemokine CCR1	33	-3	-5	2015
Chemokine CCR2B	1	-23	-10	2015
Chemokine CX3CR1	-1	5	7	2015
Chemokine CXCR1/2 (IL-8, Non-Selective)	30	-28	-1	2015
Chemokine CXCR2 (IL-8RB)	12	-7	1	2015
Chemokine CXCR4	14	-27	-13	2015
Histone Deacetylases (HDACs)				
Deacetylase, Histone 1	17	23	NA	2014
Deacetylase, Histone 1	-27	-18	-26	2015
Deacetylase, Histone 2	56	44	NA	2014
Deacetylase, Histone 2	34	21	12	2015
Deacetylase, Histone 3	-5	25	NA	2014
Deacetylase, Histone 4	4	-5	NA	2014
Deacetylase, Histone 5	-9	-11	NA	2014
Deacetylase, Histone 6	0	-17	NA	2014
Deacetylase, Histone 7	1	-16	NA	2014

Deacetylase, Histone 8	29	13	NA	2014
Deacetylase, Histone 9	-14	-13	NA	2014
Deacetylase, Histone 10	11	9	NA	2014
Deacetylase, Histone 11	9	5	NA	2014
Sirtuins				
Deacetylase, Sirtuin SIRT1	6	-3	NA	2014
Deacetylase, Sirtuin SIRT2	0	26	NA	2014
Deacetylase, Sirtuin SIRT3	-6	-9	NA	2014
Deacetylase, Sirtuin SIRT5	-16	24	NA	2014
Deacetylase, Sirtuin SIRT6	35	18	NA	2014
Growth Factor				
Epidermal Growth Factor (EGF)	-8	-9	4	2015
Nitric Oxide Synthases				
Nitric Oxide Synthase, Endothelial (eNOS)	6	5	NA	2014
Nitric Oxide Synthase, Inducible (iNOS)	16	7	NA	2014
Nitric Oxide Synthase, Neuronal (nNOS)	14	5	NA	2014
Other classes				
Catechol-O-Methyl Transferase (COMT)	0	-1	3	2015
Histamine H1	85	66	NA	2014
Histamine H1	97	60	50	2015
Histamine H2	67	24	NA	2014
Histamine H2	73	-5	66	2015
Histamine H3	-10	-5	NA	2014
Histamine H3	12	24	1	2015
Histamine H4	50	16	NA	2014
Histamine H4	12	-1	10	2015
HMG-CoA Reductase	29	27	24	2015
5-Lipoxygenase	79	53	67	2015
Lipid Peroxidase	98	53	74	2015
Lipoxygenase 12-LO	60	40	29	2015
Monoamine Oxidase MAO-A	91	34	27	2015
Monoamine Oxidase MAO-B	75	39	18	2015
Myeloperoxidase	52	5	NA	2014
Myeloperoxidase	27	1	-7	2015
Phospholipase sPLA2-V	4	3	0	2015
Protein Tyrosine Phosphatase, PTPN1 (PTP1B)	20	3	-3	2015
Steroid 5alpha-Reductase	2	-6	3	2015
Thioredoxin Reductase	71	6	NA	2014
Thioredoxin Reductase	35	12	9	2015
Xanthine Oxidase	14	20	27	2015

Pharmacological Assays: further lipoxygenase, lipid peroxidase and monoamine oxidase assays

Further *in vitro* pharmacological studies were conducted by Eurofins Panlabs (Taiwan) Ltd. using the parameters shown in **Table 3** with respect to appropriate literature references.

For the compound **1** 5-lipoxygenase, lipid peroxidase and monoamine oxidase MAO-A assays, the inhibition/concentration-response curve concentrations were 10, 3, 1, 0.3, 0.01, 0.03 and 0.01 μM (**Table 15**).

Table 15. Activity of compound **1** against 5-lipoxygenase, lipid peroxidase and monoamine oxidase (MAO-A) IC_{50} (μM) and reference compounds

	Compound		
	1	Reference	
Assay	IC_{50} μM	Compound	IC_{50} μM
5-Lipoxygenase	2.31	NDGA	0.64
Lipid Peroxidase	1.47	N-Propyl Gallate	206
Monoamine oxidase A (MAO-A)	6.74	Clorgyline	0.00143

Compounds **1** to **3** are potent to moderately potent inhibitors of lipid oxidation (**Table 10**). Therefore, they can be used in blocking inflammation induced by oxidative damage in cancer.

5-Lipoxygenase promotes lipid oxidation and produces leukotrienes. Compounds **1** to **3** are potent to moderately potent inhibitor of 5-lipoxygenase (**Table 10**). Therefore, they can be used in blocking inflammation induced by oxidative damage and inflammatory pathophysiology in cancer.

12-Lipoxygenase promotes lipid oxidation and produces leukotrienes. Compounds **1** to **3** are moderately potent inhibitor of 12-lipoxygenase (**Table 10**). Therefore, they can be used in blocking inflammation induced by oxidative damage and inflammatory pathophysiology in cancer.

Compound **1** is a potent inhibitor of monoamine oxidase A and B (**Table 10**). Therefore, it can be used in blocking oxidative damage induced by oxidation of monoamines and as an antidepressant in cancer.

Compounds **1** to **3** inhibit binding of the radioligand to histamine H1 and H2 receptors (**Table 10**). Therefore, they can be used in blocking inflammation induced by histamine resulting in anti-inflammatory action useful in cancer treatment.

Compound **1** inhibited the activity of thioredoxin reductase (**Table 10**). Inhibition of thioredoxin reductase activity can be used to selectively increasing oxidative stress in cancer cell while reducing oxidative stress in normal cells and

Compound **1** inhibited the activity of myeloperoxidase (**Table 10**). Inhibition of myeloperoxidase activity can be used to selectively reduce oxidative stress in immune cells during cancer therapy.

Curves showing binding against 5-lipoxygenase; lipid peroxidase; and monoamine oxidase (MAO-A) for compound 1 are presented in **Figures 7** to **9**.

Pharmacology Assays: 2-deoxy-D-glucose uptake into muscle cells

Table 16. Effect of compounds **1** to **4** at 10 μM on 2-deoxy-D-glucose uptake into muscle cells.

	% Control Response				Assay
Ascii Assay Name	**1**	**2**	**3**	**4**	**Year**
[3H]-2-Deoxy-D-glucose uptake – agonist*	-61	15	-52	-45	2016
[3H]-2-Deoxy-D-glucose uptake – antagonist*	152	67	195	151	2016
* agonist - Increase in 2-DG uptake relative to insulin response * antagonist - Inhibition of insulin-induced 2-DG uptake					

Table 17. Oncopanel cell proliferation results for Compounds **11** and **12**.

		Compound **11** and **12**		
Cell Line	Type	Cell Count EC_{50} (μM)	Cell Count IC_{50} (μM)	Cell Count GI_{50} (μM)
647-V	Bladder	> 30	> 30	> 30
AU565	Breast	16.4	17.1	16.9
CAMA-1	Breast	> 30	> 30	> 30

MCF7	Breast	27.5	27.5	27
MDA MB 231	Breast	> 30	> 30	> 30
MDA MB 453	Breast	10.6	10.6	10.4
MDA-MB-415	Breast	17.8	17.8	15.7
Hs 683	CNS - Glioma	27	27	25.6
M059J	CNS - Glioma	> 30	> 30	> 30
HuTu 80	Colon	8.61	8.7	8.65
LS-174T	Colon	> 30	> 30	> 30
HeLa	Female GU - Cervix	> 30	> 30	> 30
OVCAR3	Female GU - Ovary	> 30	> 30	> 30
AN3 CA	Female GU - Uterus	10.8	13.3	13.1
MEG01	Leukemia	17.5	17.5	17.3
MOLT-16	Leukemia	21.8	21.8	21.7
MOLT-3	Leukemia	11.8	14.1	14
MV-4-11	Leukemia	> 30	> 30	> 30
MX1	Leukemia	14.9	14.9	14.9
A427	Lung - NSCLC	16	16	15.8
Calu1	Lung - NSCLC	> 30	> 30	> 30
Calu6	Lung - NSCLC	> 30	> 30	> 30
Hs 229.T	Lung - NSCLC	> 30	> 30	> 30
NCI-H292	Lung - NSCLC	12.1	> 30	> 30
NCI-H520	Lung - NSCLC	> 30	> 30	> 30
NCI-H596	Lung - NSCLC	> 30	> 30	> 30
DOHH-2	Lymphoma	12.2	13.4	13.4
EB2	Lymphoma	> 30	> 30	> 30
Jiyoye	Lymphoma	> 30	> 30	> 30
L-428	Lymphoma	21.3	21.3	21.1
NAMALWA	Lymphoma	> 30	> 30	> 30
Raji	Lymphoma	> 30	> 30	> 30
SUP-T1	Lymphoma	> 30	> 30	> 30
PSN-1	Pancreas	> 30	> 30	> 30
Hs 934.T	Skin (Melanoma)	21.9	> 30	16.3
HOS	Soft Tissue - Osteosarcoma	> 30	> 30	> 30
KHOS-240S	Soft Tissue - Osteosarcoma	> 30	> 30	> 30
SW1353	Soft Tissue - Osteosarcoma	> 30	> 30	> 30
Hs 729	Soft Tissue - Sarcoma	26.4	> 30	> 30
HT-1080	Soft Tissue - Sarcoma	12.7	12.7	12.7

Pharmacology Assays: adhesion and transcription response

Table 18. Dose response and IC_{50} values for the pharmacological activity of representative serrulatane diterpenes.

		Compound 1		Compound 2		Compound 3	
Ascii Assay Name	Conc µM	Resp Av %	IC_{50} µM	Resp Av %	IC_{50} µM	Resp Av %	IC_{50} µM
Adhesion, ICAM-1-Mediated	10	6	>10	5	>10	7	>10
Adhesion, ICAM-1-Mediated	1	3	>10	4	>10	6	>10
Adhesion, ICAM-1-Mediated	0.1	-2	>10	3	>10	-4	>10
Adhesion, ICAM-1-Mediated	0.01	1	>10	0	>10	-5	>10
Adhesion, ICAM-1-Mediated	0.001	-4	>10	7	>10	-7	>10
Adhesion, VCAM-1-Mediated - Antagonist	10	-7	>10	-18	>10	-4	>10
Adhesion, VCAM-1-Mediated - Antagonist	1	-9	>10	-18	>10	7	>10
Adhesion, VCAM-1-Mediated - Antagonist	0.1	3	>10	-8	>10	13	>10
Adhesion, VCAM-1-Mediated - Antagonist	0.01	0	>10	-17	>10	18	>10
Adhesion, VCAM-1-Mediated - Antagonist	0.001	13	>10	-7	>10	13	>10
Transcription Response, NF-kappaB - Antagonist	10	103	1.4	34	>10	-19	>10
Transcription Response, NF-kappaB - Antagonist	1	17	1.4	10	>10	1	>10
Transcription Response, NF-kappaB - Antagonist	0.1	0	1.4	-3	>10	-7	>10
Transcription Response, NF-kappaB - Antagonist	0.01	-5	1.4	-7	>10	-11	>10
Transcription Response, NF-kappaB - Antagonist	0.001	-25	1.4	-7	>10	-16	>10

Nuclear factor kappa B (NF-κB) was first discovered as a factor in the nucleus of B lymphocytes that binds to the enhancer of kappa light chain of immunoglobulin and is also a lymphoid specific (Sen and Baltimore, 1986). The NF-κB family includes RelA/p65, NF-κB1 p50/p105, NF-κB2 p52/p100, C-Rel and RelB. These proteins contain an N-terminal Rel homology domain (RHD) that is responsible for binding to DNA and other proteins and harbour a nuclear leading sequence (NLS). NF-κB proteins function as a dimeric transcription factor that regulates the expression of genes influencing a broad range of biological processes including innate and adaptive immunity, inflammation, stress responses, B-cell development and lymphoid organogenesis (Pantano *et al.*, 2006; Brigelius-Fohê and Fohê 2011; Ghosh *et al.*, 2012; Akdis *et al.*, 2017).

NF-κB has been shown to have diverse and complex roles in cancer and immune modulation (Perkins, 2012; Sethi *et al.*, 2012; Parri and Chiarugi, 2013; D'Ignazio *et al.*, 2015). Based on significant inhibitory activity against NF-κB (IC_{50} 0. 69 μM) and cytokines (IC_{50} 6.6, 8.8, 4.3, 8.9 μM, for IL1β, IL-6, IL10, TNFα respectively, compound **1** can potentially influence the expression of the aforementioned biological processes as well as modulation of immune responses. In support for these results, Eurofins Oncopanel Genomic analysis showed compound **1** clustered near to ABT-199, a BH3 domain inhibitor of BCL-2. ABT-199 blocked anti-apoptotic of BCL-2 leading to programmed cell death. In addition to antitumor effect of BCL-2 therapeutics, the BH3 mimetics have been proposed in the context of immune modulation (Ludwig *et al.*, 2016). Taken together, compound **1** could target cancer cell death as well as immune modulation. **Figure 10** shows transcription response and binding against NF-κB for compound **1**.

In vitro cell viability assay of serrulatane terpenes

Four serrulatane diterpenes, namely compounds **1** to **4**, and *Myoporum insulare* resin were evaluated for *in vitro* inhibition of cell growth in 43 cancer cell lines and one normal cell line as shown in **Table 19**. The assay is a 72 hour (three day) assay.

Methodology of the in vitro cell viability assay

Cell viability assays were carried out by Eurofins PanLab (Taiwan). The assays are based on the established principle that cell viability (survival) can be evaluated by measuring the intracellular levels of adenosine triphosphate (ATP) by bioluminescence in metabolically active cells (Xia, M *et al.* 2008). Assays are carried out by seeding cells in two plates (T_0 and T_{72}). At time "zero" cell plate (T_0) is harvested, treated, and incubated for 72h (three days) when the T_{72} plate will be harvested. The intracellular levels of ATP are measured and represent the amount of viable cells.

Cell viability assay results for compounds **1** to **4** and *Myoporum insulare* resin/exudate extract towards 43 cancer cell lines and 1 normal cell line are shown in **Table 19**.

Table 19. Inhibition of cell growth at 10.5 μg/mL of *Myoporum insulare* resin and 10 μM of compounds **1** to **4**.

Cell lines	**% Cell growth**				
	***Myoporum insulare* resin**	**1**	**2**	**3**	**4**
Normal					
HUVEC, Endothelium	32	-90	97	91	37
Brain					
U-87 MG	36	7	101	111	81
SK-N-MC	4	-87	73	82	-92
Leukemia					
HL-60 (TB)	13	-62	-35	138	-83
K-562	-20	-55	69	93	60
MV-411	-96	-96	37	76	-94
MOLT-4	-97	-94	38	77	-93
Non-Small Cell Lung Cancer					
A549/ATCC	60	-92	102	106	93
LL/2	41	-62	105	111	98
NCI-H460	63	-37	88	100	93
PC-6	30	-62	92	96	4
Colon Cancer					
CT26.WT	36	2	120	103	33
SW-620	-94	-89	97	107	74
DLD-1	29	-65	95	101	68
HCT-15	15	-62	94	116	69
HCT-116	45	-74	81	99	64
HT-29	69	-66	107	101	91
Melanoma					
B16-F0	84	7	123	116	56
SK-MEL-5	-69	-96	95	118	88
Ovarian Cancer					
OVCAR-3	-33	-93	67	86	60

SK-OV-3	6	-35	82	98	74
Prostrate Cancer					
LNCaP	-5	-86	73	84	56
PC-3		-87	70	99	64
Breast Cancer					
BT474	56	-67	118	108	64
MCF7	-51	-71	114	112	77
MCF-7 AdrR	-43	-90	92	101	77
MDA-MB-231	-38	-92	97	100	84
MDA-MB-468	-69	-92	37	85	52
T-47D	102	20	104	119	47
4T1	75	52	60	99	26
Kidney Cancer					
A-498	43	-43	91	92	89
ACHN	34	-41	101	105	105
Liver Cancer					
HC-4	80	-91	104	105	91
Hep3B	20	-84	87	84	93
HepG2	27	-23	95	103	90
Lymphoma					
Ramos	-94	-92	33	129	-82
H33HJ-JA1	-73	-90	57	90	-87
U937	28	-86	102	105	20
Pancreas					
MIA PaCa-2	20	3	92	106	92
PANC-1	64	36	87	116	82
Skin					
A-431	64	-89	100	102	107
A375	9	-5	74	100	65

Stomach					
KATO III	12	-91	84	105	83
Uterus					
MES-SA	-57	-88	75	94	68

Cell Viability Assay Results

At 10 μM compound **1** showed potent reduction in cell viability (-80 to -100%) towards 20 cancer cell lines. Moderate reduction in cell viability (-40 to -80%) was observed towards 12 cancer cell lines and weak effect towards cell viability for 4 cell lines. Growth inhibition was observed for the remaining cell lines.

At 10 μM compound **2** showed weak reduction in cell viability (-35%) towards the HL-60 leukemia cells and no significant effect on the remaining cell lines. At 10 μM compound **3** showed no significant effect on all 44 cell lines. At 10 μM compound **4** showed potent reduction in cell viability (-82 to -94%) towards six lymphoma, leukemia and brain cancer cell lines: Ramos and H33HJ-JA1 (lymphoma); HL-60 (TB), MOLT-4 and MV-411 (leukemia), and SK-N-MC (brain). Compound **4** was selective with no significant reduction in the growth of HUVEC endothelium cells (normal cell line).

At 10.5 μg/mL *Myoporum insulare* resin showed potent reduction in cell viability (-80 to -100%) towards four cancer cell lines: SW-620 (colon); Ramos (lymphoma); and MV-411 and MOLT4 (leukemia). Moderate reduction in cell viability (-40 to -80%) was observed towards six cancer cell lines: MCF-7, MCF7 AdrR, MDA-MB-468 (breast); H33HJ-JA1 (lymphoma); SK-MEL-5 (melanoma); and MES-SA (uterus). Weak cell viability reduction (-5 to -38%) towards five cell lines: K-562 (leukemia); OVCAR-3 (ovarian); LNCaP (prostrate); MDA-MB-231 (breast); and A375 (skin). No significant effect was observed towards HUVEC endothelium cells (normal cell line).

OncoPanel Cell Proliferation Assay

The OncoPanel cell proliferation assay measures the proliferation response of cancer cell lines to drug treatments through high-content fluorescence imaging or bioluminescence. Whereas the cell viability assay described above is a three-day assay, the OncoPanel assay is a 10-day assay.

Experimental procedure

Cells were grown in RPMI 1640, 10% FBS, 2 mM L-alanyl-L-glutamine, 1 mM Na pyruvate or a special medium. Cells were seeded into 384-well plates and incubated in a humidified atmosphere of 5% CO_2 at 37°C. Compounds were added the day following cell seeding. At the same time, a time zero untreated cell plate was generated. After a 10-day incubation period, cells were fixed and stained to allow fluorescence imaging of nuclei. At 7 days post-seeding, the growth media were replaced and the plates were re-dosed with the test compound.

Compounds were serially diluted in half-log steps from the highest test concentration specified in the above table, and assayed over 10 concentrations with a maximum assay concentration of 0.1% DMSO. Automated fluorescence microscopy was carried out using a Molecular Devices ImageXpress Micro XL high-content imager, and images were collected with a 4X objective. 16-bit TIFF images were acquired and analyzed with MetaXpress 5.1.0.41 software.

Data Analysis

Cell proliferation was measured by the fluorescence intensity of an incorporated nuclear dye. The output is referred to as the relative cell count, where the measured nuclear intensity is transformed to percent of control (POC) using the following formula:

$$\mathrm{POC} = \frac{I_x}{I_0} \times 100$$

Where I_x is the nuclear intensity at concentration x, and I_0 is the average nuclear intensity of the untreated vehicle wells.

Cellular response parameters were calculated using nonlinear regression to a sigmoidal single-site dose response model:

$$y = A + \frac{B - A}{1 + \left(C/x\right)^{D}}$$

Where y is a response measured at concentration x, A and B are the lower and upper limits of the response, C is the concentration at the response midpoint (EC_{50}), and D is the Hill Slope (Fallahi-Sichani, M., S. *et al.* 2013).

Time zero non-treated plates were used to determine the number of doublings during the assay period, using the formula:

$$\text{Doublings} = \log_2\left(\frac{N}{N_{T0}}\right)$$

Where N is the cell number in untreated wells at the assay end point and N_{T0} is the cell number at the time of compound addition.

Cell count IC_{50} is the test compound concentration at 50% of maximal possible response. EC_{50} is the test compound concentration at the curve inflection point or half the effective response (parameter C of the fitted curve solution). GI_{50} is the concentration needed to reduce the observed growth by half (midway between the curve maximum and the time zero value). Activity area is an estimate of the integrated area above the curve (Barretina, J. G. *et al.* 2012). Activity area values range from 0-10, where a value of zero indicates no inhibition of proliferation at all concentrations, and a value of 10 indicates complete inhibition of proliferation at all concentrations. In rare instances, values <0 or >10 may be observed. In these instances, values <0 should be considered as equivalent to 0, whereas values >10 should be considered equivalent to 10.

Curve-fitting, calculations, and report generation were performed using a custom data reduction engine and MathIQ based software (AIM).

The OncoPanel cell proliferation results (OncoPanel, Eurofins PanLab, USA, across 280 human cancer cell lines) for compounds **1**, **2** and **4** are shown below in **Table 20**.

Tables 21 to **28** show representative proliferation response data (**Table 21**: MDA-MB-415; **Table 22**: RKO-AS45-1; **Table 23**: SW480; **Table 24**: 639-V; **Table 25**: Hs 729; **Table 26**: Hs 852.T; **Table 27**: HCT-8; **Table 28**: IM-9) and the cell proliferation results for *Myoporum insulare* resin are shown below in **Table 29**.

Table 20. OncoPanel cell proliferation results for compounds **1**, **2** and **4**.

		Compound **1**			Compound **2**			Compound **4**		
Cell Line	Type	Cell Count EC_{50} (μM)	Cell Count IC_{50} (μM)	Cell Count GI_{50} (μM)	Cell Count EC_{50} (μM)	Cell Count IC_{50} (μM)	Cell Count GI_{50} (μM)	Cell Count EC_{50} (μM)	Cell Count IC_{50} (μM)	Cell Count GI_{50} (μM)
5637	Bladder	3.38	3.38	3.32	> 30	> 30	> 30	15.20	15.20	15.10
639-V	Bladder	2.01	2.01	2.01	6.54	8.00	7.98	12.00	12.00	12.00
647-V	Bladder	3.12	3.12	3.11	11.30	11.30	11.20	5.99	6.00	5.99
BFTC-905	Bladder	1.79	1.79	1.78	8.03	8.03	8.01	9.70	9.70	9.68
HT-1197	Bladder	2.31	2.34	2.28	10.70	10.70	10.30	15.60	15.60	15.20
HT1376	Bladder	1.45	1.46	1.43	4.71	4.71	4.47	14.10	14.10	13.80
J82	Bladder	1.06	1.06	1.05	12.90	12.90	12.70	6.22	6.22	6.09
SCaBER	Bladder	3.12	3.12	3.10	11.50	11.50	11.40	16.90	16.90	16.80
T24	Bladder	1.44	1.44	1.44	20.40	20.40	20.30	12.20	12.20	12.20
TCCSUP	Bladder	1.75	1.75	1.72	8.20	8.20	7.78	8.91	8.91	8.67
UM-UC-3	Bladder	1.85	1.85	1.84	5.30	5.75	5.74	3.83	3.83	3.82
AU565	Breast	1.62	1.62	1.61	6.40	6.40	6.29	10.10	10.10	10.00
BT20	Breast	1.59	1.61	1.53	12.20	12.70	12.30	14.10	14.30	13.90
BT474	Breast	5.41	5.46	4.95	> 30	> 30	> 30	25.50	25.70	25.00
BT-549	Breast	3.14	3.14	3.12	25.80	25.90	25.80	15.30	15.30	15.10
CAMA-1	Breast	3.51	3.51	3.40	> 30	> 30	> 30	> 30	> 30	> 30
EFM-19	Breast	1.61	1.61	1.54	11.20	11.20	10.60	11.90	11.90	11.30
Hs 578T	Breast	4.74	4.76	4.68	28.70	28.70	28.20	15.00	15.00	14.90
KPL-1	Breast	0.81	0.81	0.81	4.70	4.73	4.70	4.18	4.18	4.13
MCF7	Breast	1.37	1.37	1.35	10.40	10.40	9.96	12.10	12.10	11.90
MDA MB 231	Breast	1.47	1.48	1.47	4.39	4.39	4.36	11.40	11.40	11.30
MDA MB 453	Breast	0.78	0.78	0.77	3.68	3.69	3.65	3.76	3.76	3.68
MDA MB 468	Breast	2.75	2.76	2.74	8.07	8.08	8.00	7.41	7.43	7.34
MDA-MB-415	Breast	1.02	1.02	1.00	11.50	11.50	10.80	28.50	28.50	27.40
MDA-MB-436	Breast	2.68	2.69	2.67	9.72	9.77	9.73	10.30	10.30	10.20
SK-BR-3	Breast	1.79	1.80	1.76	12.20	12.20	11.90	10.30	10.30	9.97
T47D	Breast	4.63	4.63	4.28	10.20	10.20	9.40	3.28	3.28	2.92
A172	CNS - Glioma	1.12	1.15	1.14	9.02	9.02	8.93	8.08	8.08	8.03
CCF-STTG1	CNS - Glioma	5.79	6.60	5.24	> 30	> 30	> 30	19.70	19.70	16.00
DBTRG-05MG	CNS - Glioma	2.65	2.66	2.64	12.20	13.00	12.80	17.60	17.60	17.40
DK-MG	CNS - Glioma	6.16	6.41	6.12	1.64	> 30	> 30	17.20	17.20	16.40
H4	CNS - Glioma	2.77	2.77	2.77	3.06	> 30	> 30	13.00	13.00	13.00
Hs 683	CNS - Glioma	4.90	4.91	4.76	29.80	29.80	28.30	24.50	24.60	24.30
M059J	CNS - Glioma	3.09	3.09	3.02	9.98	15.80	14.20	13.00	13.00	12.90
PFSK-1	CNS - Glioma	4.32	4.33	4.31	14.70	14.70	14.60	3.82	3.82	3.80
SNB-19	CNS - Glioma	1.66	1.66	1.65	17.30	17.30	16.80	13.00	13.00	12.90
SW1088	CNS - Glioma	2.44	2.44	2.43	10.70	10.70	10.50	8.77	8.77	8.69
SW1783	CNS - Glioma	3.19	3.19	3.09	10.20	11.00	10.50	12.30	12.30	12.10
T98G	CNS - Glioma	2.05	2.05	2.05	19.10	19.10	19.00	24.50	24.50	24.50

U-118 MG	CNS - Glioma	4.56	4.58	4.49	29.60	29.60	29.40	13.90	13.90	13.60
U-138MG	CNS - Glioma	6.29	6.33	6.15	> 30	> 30	> 30	25.00	25.00	24.90
U-87 MG	CNS - Glioma	2.12	2.12	2.04	> 30	> 30	> 30	13.80	13.80	13.60
D341 Med	CNS - Medulloblastoma	9.09	9.46	9.37	19.20	19.20	18.70	8.57	8.57	8.40
Daoy	CNS - Medulloblastoma	1.06	1.06	1.06	8.64	8.65	8.64	3.19	3.19	3.19
BE(2)C	CNS - Neuroblastoma	4.23	4.23	4.18	6.91	7.52	7.48	13.10	13.10	13.00
CHP-212	CNS - Neuroblastoma	1.43	1.43	1.41	11.40	11.40	11.10	9.77	9.78	9.74
MC-IXC	CNS - Neuroblastoma	4.01	4.01	4.00	16.90	16.90	16.90	6.88	6.88	6.88
SK-N-AS	CNS - Neuroblastoma	3.58	3.58	3.54	6.23	7.92	7.70	5.86	5.86	5.75
SK-N-DZ	CNS - Neuroblastoma	3.16	3.16	2.94	> 30	> 30	> 30	11.90	11.90	11.50
SK-N-FI	CNS - Neuroblastoma	7.31	7.31	6.32	> 30	> 30	> 30	21.50	21.50	20.60
Colo 201	Colon	0.92	0.92	0.92	8.51	8.51	8.45	4.07	4.07	4.04
Colo 205	Colon	1.31	1.31	1.31	10.70	10.70	10.70	11.90	11.90	11.90
Colo 320 HSR	Colon	3.09	3.13	3.13	11.60	11.60	11.60	5.15	5.16	5.15
Colo 320DM	Colon	3.20	3.20	3.18	7.72	7.72	7.67	7.91	7.91	7.87
DLD-1	Colon	2.96	2.96	2.96	10.70	11.20	11.20	15.70	15.70	15.70
HCT-116	Colon	1.75	1.75	1.75	6.68	6.68	6.67	10.30	10.30	10.30
HCT-15	Colon	1.84	1.84	1.83	8.64	9.49	9.48	13.40	13.40	13.40
HCT-8	Colon	1.23	1.23	1.23	6.27	6.27	6.24	12.90	12.90	12.90
HT-29	Colon	4.01	4.01	4.00	19.50	19.50	19.40	17.00	17.00	17.00
LS1034	Colon	1.87	1.87	1.83	12.70	12.70	12.00	23.60	23.60	23.50
LS123	Colon	1.13	1.16	1.03	6.57	18.40	13.40	12.00	12.00	10.70
LS411N	Colon	8.72	8.72	8.51	23.90	23.90	23.40	23.10	23.10	22.60
MT-3	Colon	3.67	3.67	3.66	16.90	16.90	16.80	23.90	23.90	23.80
NCI-H508	Colon	14.40	14.40	14.30	> 30	> 30	> 30	> 30	> 30	> 30
NCI-H747	Colon	3.09	3.11	3.10	12.30	> 30	> 30	28.10	28.20	28.10
RKO	Colon	1.69	1.69	1.69	7.22	7.92	7.92	12.00	12.00	12.00
RKO-AS45-1	Colon	1.50	1.50	1.50	9.64	9.64	9.62	12.80	12.80	12.80
RKOE6	Colon	1.72	1.72	1.72	6.95	6.95	6.93	6.79	6.79	6.76
SW1417	Colon	3.15	3.15	3.07	22.80	22.80	21.80	> 30	> 30	29.30
SW1463	Colon	3.73	3.75	3.71	> 30	> 30	> 30	29.40	29.60	29.50
SW403	Colon	8.09	8.11	7.89	> 30	> 30	> 30	> 30	> 30	> 30
SW48	Colon	1.33	1.33	1.32	8.73	8.73	8.65	13.00	13.00	13.00
SW480	Colon	1.21	1.21	1.20	10.10	10.10	9.93	12.30	12.30	12.30
SW620	Colon	1.48	1.48	1.48	13.20	13.20	13.20	11.30	11.30	11.30
SW837	Colon	2.35	2.37	2.33	> 30	> 30	> 30	18.90	18.90	18.70
SW948	Colon	2.21	2.21	2.20	14.70	14.70	14.50	29.70	> 30	> 30
WiDr	Colon	2.32	2.32	2.31	14.50	14.50	14.40	12.80	12.80	12.80
NCI-H295R	Endocrine - Adrenal gland	14.70	14.70	13.50	> 30	> 30	> 30	25.60	25.60	21.60
BHT-101	Endocrine - Thyroid	2.16	2.17	2.17	14.00	14.00	13.90	6.80	6.80	6.77
CAL-62	Endocrine - Thyroid	1.69	1.69	1.69	5.60	5.79	5.78	5.36	5.36	5.36
CGTH-W-1	Endocrine - Thyroid	1.20	1.20	1.20	5.83	5.83	5.81	3.45	3.48	3.47
SW579	Endocrine - Thyroid	1.71	1.71	1.69	12.30	12.30	12.20	11.00	11.00	11.00
Y79	Eye	5.60	5.60	5.33	6.57	7.65	7.41	5.65	5.65	5.34
C-33A	Female GU - Cervix	7.18	7.18	7.08	12.00	12.00	11.90	9.57	9.57	9.42
C-4 II	Female GU - Cervix	1.09	1.10	1.09	8.94	9.03	9.00	12.60	12.60	12.50

HeLa	Female GU - Cervix	2.99	2.99	2.98	16.60	16.60	16.50	21.10	21.10	21.10
HT-3	Female GU - Cervix	3.88	3.89	3.84	17.60	19.30	18.60	14.50	14.50	14.30
SiHa	Female GU - Cervix	5.22	5.23	5.17	28.30	28.30	25.80	11.30	13.50	13.20
Ca Ski	Female GU - Ovary	5.28	5.29	5.24	> 30	> 30	> 30	17.60	17.60	17.60
CaOV3	Female GU - Ovary	1.91	1.92	1.85	10.20	10.20	9.61	10.20	10.30	10.20
ME-180	Female GU - Ovary	2.25	2.26	2.21	> 30	> 30	> 30	25.30	25.30	25.20
MS751	Female GU - Ovary	2.23	2.23	2.21	7.55	8.78	8.72	12.10	12.10	12.00
OVCAR3	Female GU - Ovary	1.53	1.57	1.52	14.40	14.40	13.70	15.60	15.60	14.90
PA-1	Female GU - Ovary	4.21	4.21	4.21	11.60	16.30	16.20	7.89	7.90	7.89
SKOV3	Female GU - Ovary	1.58	1.58	1.56	15.40	15.40	15.20	8.43	8.43	8.33
AN3 CA	Female GU - Uterus	1.52	1.52	1.49	11.30	11.30	11.10	9.62	9.62	9.43
HEC-1-A	Female GU - Uterus	2.57	2.57	2.56	12.10	12.10	12.00	12.30	12.30	12.20
KLE	Female GU - Uterus	3.70	3.82	3.56	26.30	26.30	20.50	18.20	18.20	16.60
SW954	Female GU - Vulva	7.63	7.63	7.60	> 30	> 30	> 30	21.70	21.70	21.60
BV-173	Leukemia	3.80	3.80	3.79	9.33	9.33	9.33	3.56	3.56	3.55
CCRFCEM	Leukemia	4.73	4.73	4.71	11.50	11.50	11.40	4.92	4.93	4.91
CEM-C1	Leukemia	1.96	1.96	1.95	3.26	3.26	3.26	1.47	1.47	1.47
CML-T1	Leukemia	1.93	1.93	1.93	3.69	3.69	3.68	3.93	3.93	3.93
EM-2	Leukemia	2.39	2.39	2.37	10.80	10.80	10.80	3.99	4.00	4.00
HEL-92-1-7	Leukemia	13.90	13.90	13.90	13.40	13.40	13.40	4.05	4.05	4.05
J-RT3-T3-5	Leukemia	0.01	0.01	0.010	2.08	2.08	2.06	2.71	2.71	2.71
Jurkat	Leukemia	2.25	2.25	2.24	2.66	2.66	2.65	3.59	3.59	3.58
K562	Leukemia	4.60	4.60	4.58	10.20	10.20	10.10	12.20	12.20	12.20
KG-1	Leukemia	0.12	0.12	0.11	11.30	12.00	11.90	13.30	13.30	13.10
KU812	Leukemia	2.81	2.81	2.57	6.52	6.52	5.66	9.50	9.50	9.13
MEG01	Leukemia	7.35	7.35	7.22	13.80	13.80	13.70	8.39	8.39	8.37
MHH-PREB-1	Leukemia	6.17	6.17	6.17	7.85	7.85	7.85	5.71	5.71	5.71
MOLT-16	Leukemia	1.84	1.84	1.84	13.30	13.30	13.30	4.02	4.02	4.01
MOLT-3	Leukemia	2.13	2.13	2.11	1.27	1.27	1.26	3.15	3.15	3.13
MV-4-11	Leukemia	3.58	3.58	3.57	8.56	8.56	8.52	3.81	3.81	3.80
MX1	Leukemia	1.29	1.29	1.29	10.80	10.80	10.80	2.46	2.46	2.46
NALM-6	Leukemia	1.81	1.81	1.81	1.67	1.68	1.68	2.61	2.61	2.61
RS4;11	Leukemia	1.77	1.77	1.71	6.43	6.43	6.30	4.15	4.23	4.16
TF-1	Leukemia	2.11	2.11	1.98	2.75	2.75	2.44	6.57	6.57	6.26
Thp1	Leukemia	1.38	1.38	1.34	5.32	5.69	5.61	12.00	12.00	11.90
BC-1	Lymphoma	1.52	1.52	1.51	7.95	7.95	7.93	4.16	4.16	4.16
BCP-1	Lymphoma	3.18	3.18	3.14	8.48	8.48	8.40	8.82	8.82	8.75
CA46	Lymphoma	2.27	2.27	2.26	3.83	3.83	3.82	4.06	4.06	4.06
CRO-AP2	Lymphoma	5.72	5.72	5.66	6.38	6.38	6.36	9.94	9.94	9.88
Daudi	Lymphoma	1.84	1.84	1.84	3.93	3.93	3.92	2.28	2.28	2.28
DB	Lymphoma	2.10	2.10	2.09	3.23	3.25	3.24	3.85	3.85	3.84
DOHH-2	Lymphoma	1.41	1.41	1.41	3.24	3.24	3.24	2.24	2.24	2.24
DoTc2 4510	Lymphoma	1.03	1.03	1.01	6.07	6.07	5.84	9.23	9.23	9.09
EB2	Lymphoma	6.47	6.49	6.45	23.30	23.30	23.00	8.35	8.38	8.32
EB-3	Lymphoma	3.56	3.56	3.56	9.72	9.72	9.71	3.93	3.93	3.93
GA-10	Lymphoma	1.93	1.94	1.94	3.72	3.73	3.73	1.23	1.23	1.23
Hs 445	Lymphoma	1.30	1.32	1.31	4.34	4.34	4.23	5.80	5.80	5.74

Hs 611.T	Lymphoma	2.92	2.94	2.91	10.70	10.70	10.60	5.11	5.11	5.05
HT	Lymphoma	1.52	1.53	1.51	6.51	6.51	6.43	4.49	4.49	4.46
JeKo-1	Lymphoma	5.23	5.23	5.21	4.48	4.48	4.47	3.91	3.91	3.91
Jiyoye	Lymphoma	5.88	5.88	5.87	17.80	17.80	17.70	3.55	3.55	3.55
L-428	Lymphoma	1.08	1.09	1.08	8.87	8.87	8.83	2.07	2.07	2.06
MC116	Lymphoma	3.79	3.79	3.78	13.80	13.80	13.80	12.50	12.50	12.40
NAMALWA	Lymphoma	3.39	3.39	3.39	5.71	5.71	5.70	3.91	3.91	3.90
Raji	Lymphoma	4.60	4.60	4.59	8.04	8.04	8.04	3.92	3.92	3.92
Ramos (RA 1)	Lymphoma	2.96	2.96	2.96	4.39	4.39	4.39	4.17	4.17	4.17
RPMI 6666	Lymphoma	3.53	3.53	3.44	10.40	10.70	10.70	23.10	23.10	23.00
SR	Lymphoma	3.80	3.80	3.80	10.70	10.70	10.70	4.39	4.39	4.39
ST486	Lymphoma	1.09	1.09	1.08	3.87	3.87	3.86	2.66	2.66	2.65
SU-DHL-10	Lymphoma	3.94	3.94	3.93	9.92	9.92	9.90	7.68	7.68	7.67
SU-DHL-4	Lymphoma	2.01	2.01	2.01	4.20	4.20	4.20	5.74	5.74	5.74
SU-DHL-5	Lymphoma	1.20	1.20	1.19	4.28	4.28	4.27	3.80	3.80	3.80
SU-DHL-8	Lymphoma	1.77	1.77	1.77	7.40	7.40	7.40	3.90	3.90	3.90
SUP-T1	Lymphoma	3.96	3.96	3.95	12.10	12.10	12.00	6.51	6.51	6.49
TUR	Lymphoma	5.09	5.09	5.08	2.63	> 30	> 30	8.98	8.98	8.98
ARH-77	Myeloma	1.95	1.97	1.95	9.50	9.60	9.57	13.50	13.50	13.40
IM-9	Myeloma	0.42	0.42	0.42	3.92	3.92	3.92	6.71	6.71	6.71
RPMI 8226	Myeloma	0.68	0.68	0.67	2.02	2.02	1.95	3.03	3.04	3.03
SKO-007	Myeloma	0.99	0.99	0.93	1.59	1.59	1.42	4.66	4.71	4.55
U266B1	Myeloma	3.22	3.22	3.08	9.15	9.28	9.01	10.10	10.10	9.81
A-253	Head and Neck	4.13	4.14	4.13	28.50	28.70	28.70	18.20	18.20	18.10
A388	Head and Neck	1.66	1.67	1.66	13.50	13.50	13.40	7.66	7.66	7.59
A431	Head and Neck	2.80	2.81	2.80	> 30	> 30	> 30	24.80	24.80	24.80
Cal 27	Head and Neck	2.16	2.16	2.15	7.64	7.64	7.62	12.30	12.30	12.20
Detroit 562	Head and Neck	1.96	1.97	1.96	14.50	14.50	14.40	25.00	25.00	25.00
FaDu	Head and Neck	0.87	0.87	0.87	8.66	8.66	8.66	8.28	8.28	8.28
OE19	Head and Neck	3.23	3.23	3.21	> 30	> 30	> 30	20.70	20.70	20.50
OE21	Head and Neck	3.68	3.68	3.67	> 30	> 30	> 30	12.70	12.70	12.70
SCC-25	Head and Neck	3.94	3.96	3.95	> 30	> 30	> 30	25.00	25.00	25.00
SCC-4	Head and Neck	4.66	4.72	4.63	> 30	> 30	> 30	15.80	15.80	15.50
SCC-9	Head and Neck	3.44	3.45	3.44	26.70	27.30	27.30	16.50	16.50	16.40
769-P	Kidney	0.85	0.85	0.85	6.95	6.95	6.94	3.72	3.72	3.71
786-O	Kidney	2.05	2.05	2.05	27.90	27.90	27.90	14.00	14.00	13.90
A498	Kidney	1.29	1.29	1.29	13.30	13.30	13.20	12.30	12.30	12.20
A-704	Kidney	1.57	1.60	1.54	> 30	> 30	> 30	5.70	5.70	5.41
ACHN	Kidney	1.74	1.74	1.74	8.79	8.79	8.76	9.50	9.50	9.47
Caki-1	Kidney	2.86	2.86	2.75	0.17	> 30	> 30	14.40	14.40	14.10
Caki-2	Kidney	4.38	4.38	4.35	28.80	29.10	28.90	13.10	13.60	13.50
G-401	Kidney	4.00	4.00	3.99	26.00	26.20	26.20	8.08	8.08	8.05
SK-NEP-1	Kidney	0.01	0.01	0.006	0.06	0.06	0.06	9.62	9.63	9.62
HepG2	Liver	0.82	0.82	0.81	6.74	6.95	6.86	25.60	25.70	25.60
HLE	Liver	4.62	4.63	4.59	10.00	16.40	16.00	7.24	7.24	7.15
HLF	Liver	4.47	4.48	4.45	13.70	15.70	15.60	8.72	8.74	8.70
HuCCT1	Liver	2.48	2.48	2.48	22.60	22.60	22.60	24.80	24.80	24.80
HUH-6 Clone 5	Liver	1.52	1.52	1.51	15.50	15.50	15.30	9.63	9.63	9.46
OCUG-1	Liver	4.30	4.30	4.29	> 30	> 30	29.90	15.60	15.60	15.50
SNU-423	Liver	1.48	1.49	1.46	5.29	5.31	5.26	9.30	9.31	9.28
A427	Lung - NSCLC	4.52	4.52	4.50	11.20	11.20	11.20	10.00	10.00	9.98
A549	Lung - NSCLC	1.66	1.67	1.66	22.00	22.00	21.90	10.90	10.90	10.80
Calu1	Lung - NSCLC	3.10	3.10	3.07	13.90	13.90	13.80	8.88	8.88	8.77
Calu6	Lung - NSCLC	9.24	9.24	8.59	14.50	16.60	15.70	25.00	25.00	24.50
ChaGoK1	Lung - NSCLC	1.53	1.54	1.53	8.32	8.32	8.26	8.92	8.92	8.82

COR-L105	Lung - NSCLC	1.44	1.45	1.42	4.76	4.76	4.61	8.66	8.66	8.47
COR-L23	Lung - NSCLC	7.18	7.18	7.14	23.80	23.80	23.60	13.30	13.30	13.20
Hs 229.T	Lung - NSCLC	2.88	2.94	2.89	29.30	29.80	28.60	25.90	26.30	25.20
NCI-H292	Lung - NSCLC	3.20	3.20	3.18	16.70	16.70	16.60	9.21	9.21	9.19
NCIH441	Lung - NSCLC	12.10	12.10	11.70	> 30	> 30	> 30	4.76	> 30	> 30
NCI-H460	Lung - NSCLC	2.34	2.34	2.33	5.57	5.92	5.91	12.20	13.00	13.00
NCI-H520	Lung - NSCLC	2.43	2.43	2.41	9.03	9.20	9.17	20.80	20.80	20.60
NCI-H596	Lung - NSCLC	8.78	8.78	8.41	12.00	15.10	14.40	28.20	> 30	> 30
NCI-H661	Lung - NSCLC	2.28	2.29	2.28	9.51	9.51	9.51	5.94	5.94	5.86
SKMES1	Lung - NSCLC	1.06	1.06	1.06	7.80	7.80	7.67	11.60	11.60	11.50
DMS114	Lung - SCLC	2.77	2.77	2.57	11.50	13.80	13.10	11.50	11.60	11.40
DMS53	Lung - SCLC	0.81	0.81	0.77	5.91	5.95	5.75	8.95	8.95	8.60
NCIH446	Lung - SCLC	10.30	10.30	10.00	9.75	9.85	9.77	7.81	7.81	7.62
NCI-H69	Lung - SCLC	6.30	6.44	5.84	16.20	16.20	14.90	15.90	15.90	15.10
SHP-77	Lung - SCLC	0.89	0.90	0.89	8.01	8.01	7.90	6.83	6.83	6.75
SW900	Lung - SCLC	3.29	3.33	3.24	26.60	26.80	26.70	23.30	23.30	23.10
AsPC-1	Pancreas	2.87	2.87	2.84	14.10	14.10	13.80	14.70	14.70	14.50
BxPC-3	Pancreas	3.29	3.30	3.29	13.00	> 30	> 30	13.40	13.40	13.40
Capan-1	Pancreas	> 30	> 30	> 30	> 30	> 30	> 30	> 30	> 30	> 30
Capan-2	Pancreas	1.33	1.33	1.32	8.64	8.64	8.48	24.80	24.80	24.70
CFPAC-1	Pancreas	3.65	3.66	3.65	12.30	13.50	13.40	25.20	25.20	25.10
HPAF-II	Pancreas	1.38	1.38	1.37	9.46	9.62	9.60	12.40	12.50	12.40
Hs 766T	Pancreas	1.61	1.61	1.54	28.40	28.40	26.20	9.34	9.34	9.08
HuP-T4	Pancreas	4.52	4.54	4.53	> 30	> 30	> 30	13.70	13.70	13.60
Mia PaCa-2	Pancreas	2.97	2.97	2.97	16.30	16.30	16.20	11.00	11.00	11.00
PANC-1	Pancreas	2.87	2.87	2.83	7.06	7.06	7.01	11.70	11.70	11.60
PSN-1	Pancreas	2.32	2.32	2.32	12.00	12.00	12.00	5.04	5.04	5.04
SU.86.86	Pancreas	7.61	7.63	7.58	13.10	> 30	> 30	> 30	> 30	> 30
YAPC	Pancreas	1.91	1.91	1.90	13.00	13.00	12.90	18.00	18.20	18.20
BeWo	Placenta	9.06	9.06	8.92	7.68	> 30	> 30	15.60	15.60	15.50
JAR	Placenta	12.20	12.20	12.20	> 30	> 30	> 30	6.53	6.53	6.49
JEG-3	Placenta	4.33	4.33	4.32	> 30	> 30	> 30	6.50	6.51	6.48
22Rv1	Prostate	4.08	4.08	4.06	11.40	11.40	11.30	9.08	9.08	9.00
BM-1604	Prostate	2.58	2.58	2.56	19.10	19.10	18.90	> 30	> 30	> 30
BPH1	Prostate	5.24	5.24	5.20	> 30	> 30	> 30	17.30	17.30	17.30
DU145	Prostate	2.80	2.80	2.78	21.00	21.00	20.70	18.10	18.10	18.10
LNCaP	Prostate	3.90	3.90	3.47	0.86	0.86	0.28	11.50	12.90	12.40
PC-3	Prostate	3.88	3.88	3.86	12.00	12.00	11.80	7.71	7.71	7.64
A101D	Skin (Melanoma)	8.42	8.42	8.25	> 30	> 30	> 30	> 30	> 30	> 30
A375	Skin (Melanoma)	1.05	1.05	1.05	6.45	6.45	6.44	5.74	5.74	5.74
A7	Skin (Melanoma)	0.94	0.94	0.94	5.54	5.63	5.60	10.50	10.50	10.50
C32	Skin (Melanoma)	2.11	2.11	1.81	19.20	19.20	15.50	7.84	7.84	6.37
CHL-1	Skin (Melanoma)	1.37	1.37	1.36	14.30	14.30	14.20	11.90	11.90	11.80
COLO 829	Skin (Melanoma)	0.68	0.68	0.62	5.35	5.35	4.93	3.71	3.71	3.29
G-361	Skin (Melanoma)	1.79	1.79	1.77	11.70	11.80	11.80	13.80	13.90	13.80
HMCB	Skin (Melanoma)	1.37	1.37	1.36	6.68	6.68	6.57	9.49	9.49	9.38
Hs 294T	Skin (Melanoma)	2.64	2.64	2.59	7.01	7.01	6.72	8.33	8.33	8.23
Hs 688(A).T	Skin (Melanoma)	1.33	1.44	1.27	11.60	13.20	12.20	7.43	7.68	6.88
Hs 695T	Skin (Melanoma)	1.18	1.27	1.16	9.07	9.48	8.99	5.00	5.18	4.02
Hs 852.T	Skin (Melanoma)	2.49	2.56	2.42	15.40	15.40	14.70	12.00	12.00	11.60
Hs 934.T	Skin (Melanoma)	2.53	3.27	2.34	> 30	> 30	24.10	11.10	11.60	10.20
Hs 936.T(C1)	Skin (Melanoma)	2.00	2.00	1.97	3.62	3.76	3.74	9.10	10.40	10.20
MALME3M	Skin (Melanoma)	1.79	1.79	1.66	19.80	19.80	17.30	20.60	20.60	17.80
MeWo	Skin (Melanoma)	1.32	1.32	1.31	9.45	9.97	9.91	9.66	9.66	9.51
RPMI-7951	Skin (Melanoma)	0.70	0.70	0.70	5.77	6.15	6.13	9.98	9.98	9.96

SH-4	Skin (Melanoma)	1.95	1.95	1.94	9.60	11.90	11.80	11.60	11.60	11.50
SK-MEL-1	Skin (Melanoma)	4.29	4.41	4.11	15.70	15.70	14.70	> 30	> 30	> 30
SK-MEL-28	Skin (Melanoma)	1.54	1.54	1.53	9.46	9.89	9.85	11.20	11.20	11.10
SK-MEL-3	Skin (Melanoma)	4.37	4.38	4.28	22.00	22.00	20.80	> 30	> 30	> 30
WM-266-4	Skin (Melanoma)	1.15	1.15	1.14	6.39	6.39	6.25	10.90	10.90	10.80
G-292, clone A141B1	Soft Tissue - Osteosarcoma	4.55	4.57	4.41	8.80	8.80	8.57	6.23	6.25	6.07
HOS	Soft Tissue - Osteosarcoma	0.96	0.96	0.96	4.82	4.82	4.81	3.08	3.08	3.08
Hs 888.Sk	Soft Tissue - Osteosarcoma	2.20	2.38	2.05	28.30	28.50	27.90	12.30	12.70	12.10
KHOS-240S	Soft Tissue - Osteosarcoma	0.95	0.95	0.95	4.59	4.59	4.58	4.96	4.96	4.96
MG-63	Soft Tissue - Osteosarcoma	9.24	9.24	9.16	> 30	> 30	> 30	11.20	11.20	11.10
SaOS2	Soft Tissue - Osteosarcoma	1.98	2.10	2.04	15.70	15.70	15.10	10.60	10.70	10.70
SJSA1	Soft Tissue - Osteosarcoma	1.41	1.41	1.41	7.11	7.11	7.02	7.45	7.45	7.45
SW1353	Soft Tissue - Osteosarcoma	1.00	1.00	0.99	9.49	9.49	9.46	4.15	4.15	4.14
U2OS	Soft Tissue - Osteosarcoma	1.66	1.66	1.65	12.70	12.70	12.70	4.21	4.21	4.20
A204	Soft Tissue - Sarcoma	0.52	0.54	0.52	8.46	8.54	8.50	0.72	0.72	0.68
A-673	Soft Tissue - Sarcoma	1.54	1.55	1.54	10.80	11.10	11.10	2.88	2.88	2.87
Hs 729	Soft Tissue - Sarcoma	2.77	2.78	2.67	23.30	23.30	21.80	11.90	11.90	11.60
Hs 821.T	Soft Tissue - Sarcoma	4.22	4.22	1.80	> 30	> 30	13.90	12.60	12.90	9.99
HT-1080	Soft Tissue - Sarcoma	0.96	0.96	0.96	3.31	3.31	3.30	4.42	4.42	4.42
MES-SA	Soft Tissue - Sarcoma	1.23	1.23	1.22	9.26	9.26	9.22	6.49	6.49	6.44
RD	Soft Tissue - Sarcoma	0.81	0.81	0.81	2.98	2.98	2.96	5.19	5.19	5.17
SJRH30	Soft Tissue - Sarcoma	1.42	1.42	1.41	5.09	5.10	5.07	3.68	3.68	3.68
SK-LMS-1	Soft Tissue - Sarcoma	1.57	1.57	1.56	6.79	11.30	11.20	9.04	9.04	8.98
SK-UT-1	Soft Tissue - Sarcoma	2.23	2.23	2.22	11.70	11.70	11.60	5.49	5.49	5.46
SW684	Soft Tissue - Sarcoma	9.37	9.37	8.28	> 30	> 30	> 30	> 30	> 30	> 30
SW872	Soft Tissue - Sarcoma	0.96	0.96	0.96	4.46	4.46	4.45	4.39	4.39	4.38
SW982	Soft Tissue - Sarcoma	1.07	1.07	1.07	7.63	7.63	7.53	7.29	7.30	7.26
TE 125.T	Soft Tissue - Sarcoma	6.47	9.21	1.48	> 30	> 30	28.70	23.60	23.60	17.00
TE 381.T	Soft Tissue - Sarcoma	1.62	1.62	1.59	8.14	8.14	7.99	6.28	6.28	6.08
VA-ES-BJ	Soft Tissue - Sarcoma	3.67	3.67	3.55	> 30	> 30	> 30	15.20	15.20	15.00
AGS	Stomach	0.70	0.70	0.70	4.69	4.69	4.69	5.25	5.25	5.24
HS 746T	Stomach	5.58	5.74	4.64	> 30	> 30	> 30	20.00	20.00	17.10
KATO III	Stomach	3.28	3.28	3.27	8.98	16.80	16.60	10.90	11.10	11.10
SK-PN-DW	Stomach	4.66	4.66	4.63	10.80	10.90	10.90	4.91	4.91	4.88
SNU-1	Stomach	1.25	1.25	1.25	8.51	9.42	9.41	6.99	6.99	6.98
SNU-16	Stomach	1.31	1.31	1.31	9.96	9.96	9.91	11.00	11.00	11.00
SNU-5	Stomach	3.92	3.92	3.87	> 30	> 30	> 30	14.40	14.40	14.20
NTERA-2 cl.D1	Testis	2.25	2.25	2.20	12.50	12.50	12.30	7.41	7.41	7.39

Table 21. Representative data for proliferation response when cell line MDA-MB-415 is treated with compound **1**

Concentration (microM)	Relative cell count (%)	
	Mean	StdDev
9.55E-04	90.2	1.3
3.02E-03	100.0	6.4
9.53E-03	98.0	8.7
3.01E-02	93.4	2.7
9.52E-02	98.1	10.3
3.01E-01	100.2	8.6
9.51E-01	62.3	5.3
3.00E+00	1.3	0.2
9.49E+00	0.3	0.0
3.00E+01	0.2	0.0

The data displayed in **Table 21** is graphed in **Figure 11.**

Table 22. Representative data for proliferation response when cell line RKO-AS45-1 is treated with compound **1**

Concentration (microM)	Relative cell count (%)	
	Mean	StdDev
9.55E-04	95.4	2.0
3.02E-03	83.7	7.7
9.53E-03	88.3	3.7
3.01E-02	86.2	5.6
9.52E-02	80.5	4.7
3.01E-01	90.0	6.9
9.51E-01	72.1	9.7
3.00E+00	7.6	3.5
9.49E+00	0.1	0.0
3.00E+01	0.1	0.0

The data displayed in **Table 22** is graphed in **Figure 12**.

Table 23. Representative data for proliferation response when cell line SW480 is treated with compound **1**

Concentration (microM)	Relative cell count (%)	
	Mean	StdDev
9.55E-04	111.8	7.0
3.02E-03	116.5	19.3
9.53E-03	103.7	9.4
3.01E-02	99.5	0.5
9.52E-02	94.1	10.2
3.01E-01	93.5	6.4

9.51E-01	69.9	17.0
3.00E+00	4.1	4.6
9.49E+00	0.2	0.0
3.00E+01	0.4	0.4

The data displayed in **Table 23** is graphed in **Figure 13**.

Table 24. Representative data for proliferation response when cell line 639-V is treated with compound **1**

Concentration (microM)	Relative cell count (%)	
	Mean	StdDev
9.55E-04	92.0	14.3
3.02E-03	96.1	1.9
9.53E-03	101.2	5.0
3.01E-02	103.6	8.6
9.52E-02	91.6	9.6
3.01E-01	92.6	14.1
9.51E-01	91.9	12.2
3.00E+00	15.8	4.2
9.49E+00	0.3	0.1
3.00E+01	0.0	0.0

The data displayed in **Table 24** is graphed in **Figure 14.**

Table 25. Representative data for proliferation response when cell line Hs 729 is treated with compound **1**

Concentration (microM)	Relative cell count (%)	
	Mean	StdDev
9.55E-04	100.6	7.6
3.02E-03	103.0	10.5
9.53E-03	108.7	4.1
3.01E-02	107.0	2.1
9.52E-02	99.9	0.7
3.01E-01	99.4	7.7
9.51E-01	98.9	1.2
3.00E+00	46.0	8.8
9.49E+00	3.2	0.2
3.00E+01	1.0	0.3

The data displayed in **Table 25** is graphed in **Figure 15**.

Table 26. Representative data for proliferation response when cell line Hs 852.T is treated with compound **1**

Concentration (microM)	Relative cell count (%)	
	Mean	StdDev

9.55E-04	104.3	9.1
3.02E-03	104.5	5.1
9.53E-03	100.2	6.2
3.01E-02	94.5	5.6
9.52E-02	92.2	2.4
3.01E-01	95.3	2.9
9.51E-01	85.5	4.3
3.00E+00	41.6	5.1
9.49E+00	13.1	1.7
3.00E+01	2.7	0.5

The data displayed in **Table 26** is graphed in **Figure 16.**

Table 27. Representative data for proliferation response when cell line HCT-8 is treated with compound **1**

Concentration (microM)	Relative cell count (%)	
	Mean	StdDev
9.55E-04	102.6	3.7
3.02E-03	104.1	9.7
9.53E-03	91.0	10.1
3.01E-02	91.8	3.5
9.52E-02	100.8	2.6
3.01E-01	94.9	4.8
9.51E-01	72.6	2.3
3.00E+00	1.9	0.5
9.49E+00	0.0	0.0
3.00E+01	0.0	0.0

The data displayed in **Table 27** is graphed in **Figure 17**.

Table 28. Representative data for proliferation response when cell line IM-9 is treated with compound **1**

Concentration (microM)	Relative cell count (%)	
	Mean	StdDev
9.55E-04	94.9	34.7
3.02E-03	102.8	9.5
9.53E-03	103.1	2.4
3.01E-02	107.3	9.3
9.52E-02	97.7	3.4
3.01E-01	97.5	8.6
9.51E-01	0.0	0.0
3.00E+00	0.1	0.0
9.49E+00	0.1	0.1
3.00E+01	0.0	0.0

The data displayed in **Table 28** is graphed in **Figure 18**.

Table 29. Oncopanel cell proliferation results for *Myoporum insulare* resin extract.

		M. insulare resin extract			
Cell Line	Type	Cell Count EC_{50} (µg/mL)	Cell Count IC_{50} (µg/mL)	Cell Count GI_{50} (µg/mL)	
5637	Bladder	3.71	3.75	3.75	A
639-V	Bladder	3.18	3.18	3.17	B
647-V	Bladder	2.69	2.69	2.69	C
BFTC-905	Bladder	3.28	3.28	3.28	B
HT-1197	Bladder	3.18	3.20	3.17	C
HT1376	Bladder	1.31	1.31	1.27	C
J82	Bladder	1.26	1.26	1.26	D
SCaBER	Bladder	2.74	2.74	2.73	C
T24	Bladder	1.70	1.70	1.70	A
TCCSUP	Bladder	2.76	2.77	2.73	B
UM-UC-3	Bladder	0.98	0.98	0.97	C
AU565	Breast	1.62	1.62	1.61	A
BT20	Breast	1.57	1.61	1.50	B
BT474	Breast	5.60	5.60	4.94	A
BT-549	Breast	3.25	3.25	3.16	A
CAMA-1	Breast	3.57	3.57	3.50	A
EFM-19	Breast	1.59	1.59	1.50	A
Hs 578T	Breast	8.96	9.00	8.96	A
KPL-1	Breast	0.61	0.61	0.61	A
MCF7	Breast	1.72	1.73	1.71	C
MDA MB 231	Breast	2.03	2.03	2.03	A
MDA MB 453	Breast	0.53	0.53	0.52	A
MDA MB 468	Breast	2.86	2.86	2.84	A
MDA-MB-415	Breast	1.12	1.12	1.05	A
MDA-MB-436	Breast	2.70	2.70	2.67	A
SK-BR-3	Breast	2.15	2.16	2.10	C
T47D	Breast	4.80	4.80	4.59	B
A172	CNS - Glioma	1.46	1.46	1.45	B
CCF-STTG1	CNS - Glioma	9.00	9.00	7.35	C
DBTRG-05MG	CNS - Glioma	3.23	3.24	3.22	C
DK-MG	CNS - Glioma	5.99	6.23	6.06	C
H4	CNS - Glioma	3.32	3.32	3.32	C
Hs 683	CNS - Glioma	5.01	5.01	4.87	B
M059J	CNS - Glioma	4.62	4.62	4.55	B

PFSK-1	CNS - Glioma	3.89	3.89	3.85	B
SNB-19	CNS - Glioma	1.39	1.41	1.41	C
SW1088	CNS - Glioma	1.79	1.79	1.78	C
SW1783	CNS - Glioma	3.06	3.06	2.96	B
T98G	CNS - Glioma	3.06	3.06	3.06	B
U-118 MG	CNS - Glioma	4.20	4.24	4.20	B
U-138MG	CNS - Glioma	5.92	5.92	5.74	C
U-87 MG	CNS - Glioma	2.46	2.50	2.45	C
D341 Med	CNS - Medulloblastoma	3.78	3.96	3.92	B
Daoy	CNS - Medulloblastoma	1.10	1.11	1.10	A
BE(2)C	CNS - Neuroblastoma	3.07	3.07	3.05	B
CHP-212	CNS - Neuroblastoma	1.19	1.19	1.14	B
MC-IXC	CNS - Neuroblastoma	3.32	3.32	3.30	B
SK-N-AS	CNS - Neuroblastoma	3.18	3.20	3.19	A
SK-N-DZ	CNS - Neuroblastoma	3.35	3.42	3.39	B
SK-N-FI	CNS - Neuroblastoma	3.37	5.39	4.66	C
Colo 201	Colon	1.08	1.08	1.08	D
Colo 205	Colon	1.46	1.46	1.46	D
Colo 320 HSR	Colon	2.45	2.45	2.44	B
Colo 320DM	Colon	3.19	3.19	3.17	B
DLD-1	Colon	3.19	3.19	3.19	A
HCT-116	Colon	1.44	1.44	1.44	B
HCT-15	Colon	1.92	1.92	1.92	C
HCT-8	Colon	2.56	2.56	2.55	D
HT-29	Colon	4.31	4.31	4.31	A
LS1034	Colon	1.96	1.96	1.93	B
LS123	Colon	1.28	1.38	1.29	B
LS411N	Colon	6.41	6.41	6.30	B
MT-3	Colon	4.10	4.10	4.10	A
NCI-H508	Colon	>10.5	>10.5	>10.5	B
NCI-H747	Colon	3.64	3.71	3.68	B
RKO	Colon	1.88	1.88	1.87	C
RKO-AS45-1	Colon	2.78	2.78	2.78	C
RKOE6	Colon	2.49	2.49	2.49	B
SW1417	Colon	3.27	4.03	3.92	D
SW1463	Colon	3.64	3.68	3.64	B
SW403	Colon	9.10	9.42	9.31	B

SW48	Colon	1.14	1.14	1.14	C
SW480	Colon	1.04	1.04	1.03	C
SW620	Colon	2.32	2.32	2.32	B
SW837	Colon	2.92	3.20	3.14	C
SW948	Colon	>10.5	>10.5	>10.5	D
WiDr	Colon	1.12	1.12	1.11	B
NCI-H295R	Endocrine - Adrenal gland	>10.5	>10.5	>10.5	A
BHT-101	Endocrine - Thyroid	2.72	2.72	2.71	C
CAL-62	Endocrine - Thyroid	1.18	1.18	1.18	A
CGTH-W-1	Endocrine - Thyroid	1.03	1.03	1.03	B
SW579	Endocrine - Thyroid	3.01	3.01	3.00	C
Y79	Eye	3.08	3.10	3.02	D
C-33A	Female GU - Cervix	4.27	4.27	4.24	C
C-4 II	Female GU - Cervix	1.19	1.19	1.19	B
HeLa	Female GU - Cervix	3.75	3.75	3.71	C
HT-3	Female GU - Cervix	3.99	4.03	3.99	B
SiHa	Female GU - Cervix	5.60	5.60	5.53	B
Ca Ski	Female GU - Ovary	5.53	5.53	5.46	A
CaOV3	Female GU - Ovary	2.59	2.60	2.52	B
ME-180	Female GU - Ovary	3.22	3.22	3.20	B
MS751	Female GU - Ovary	2.65	2.65	2.63	B
OVCAR3	Female GU - Ovary	2.01	2.08	2.02	D
PA-1	Female GU - Ovary	4.73	4.73	4.73	B
SKOV3	Female GU - Ovary	1.73	1.73	1.72	B
AN3 CA	Female GU - Uterus	1.61	1.61	1.58	B
HEC-1-A	Female GU - Uterus	1.60	1.68	1.67	A
KLE	Female GU - Uterus	3.28	3.28	2.92	C
SW954	Female GU - Vulva	8.51	8.51	8.47	C
BV-173	Leukemia	2.17	2.17	2.17	B
CCRFCEM	Leukemia	3.85	3.85	3.82	A
CEM-C1	Leukemia	1.13	1.13	1.12	A
CML-T1	Leukemia	1.43	1.43	1.43	A
EM-2	Leukemia	2.58	2.58	2.56	A
HEL-92-1-7	Leukemia	5.29	5.29	5.25	A

J-RT3-T3-5	Leukemia	1.29	1.29	1.29	D
Jurkat	Leukemia	0.91	0.91	0.91	B
K562	Leukemia	3.75	3.75	3.75	A
KG-1	Leukemia	4.73	5.39	5.32	B
KU812	Leukemia	4.52	4.52	4.45	C
MEG01	Leukemia	4.55	4.55	4.55	A
MHH-PREB-1	Leukemia	3.82	3.82	3.82	C
MOLT-16	Leukemia	2.49	2.49	2.48	A
MOLT-3	Leukemia	1.42	1.42	1.42	C
MV-4-11	Leukemia	2.76	2.76	2.75	A
MX1	Leukemia	1.28	1.28	1.28	C
NALM-6	Leukemia	1.03	1.03	1.03	C
RS4;11	Leukemia	1.86	1.86	1.82	A
TF-1	Leukemia	4.55	4.55	4.45	C
Thp1	Leukemia	1.78	1.78	1.74	A
BC-1	Lymphoma	1.73	1.73	1.73	A
BCP-1	Lymphoma	3.26	3.26	3.23	A
CA46	Lymphoma	2.03	2.03	2.03	A
CRO-AP2	Lymphoma	3.99	3.99	3.99	A
Daudi	Lymphoma	1.33	1.33	1.33	A
DB	Lymphoma	1.09	1.10	1.10	B
DOHH-2	Lymphoma	1.01	1.01	1.01	A
DoTc2 4510	Lymphoma	1.38	1.38	1.36	A
EB2	Lymphoma	5.60	5.60	5.57	A
EB-3	Lymphoma	1.68	1.68	1.68	B
GA-10	Lymphoma	1.42	1.42	1.42	A
Hs 445	Lymphoma	1.46	1.46	1.44	C
Hs 611.T	Lymphoma	3.29	3.29	3.28	D
HT	Lymphoma	1.61	1.61	1.60	C
JeKo-1	Lymphoma	2.58	2.58	2.57	A
Jiyoye	Lymphoma	4.24	4.24	4.24	A
L-428	Lymphoma	1.24	1.24	1.24	A
MC116	Lymphoma	3.15	3.15	3.15	A
NAMALWA	Lymphoma	1.68	1.69	1.68	D
Raji	Lymphoma	3.92	3.92	3.92	A
Ramos (RA 1)	Lymphoma	2.33	2.33	2.33	C
RPMI 6666	Lymphoma	3.28	3.32	3.27	C
SR	Lymphoma	1.74	1.74	1.74	A
ST486	Lymphoma	1.08	1.08	1.08	A
SU-DHL-10	Lymphoma	4.17	4.17	4.17	A
SU-DHL-4	Lymphoma	1.82	1.82	1.82	C

SU-DHL-5	Lymphoma	1.02	1.02	1.02	B
SU-DHL-8	Lymphoma	1.74	1.74	1.74	A
SUP-T1	Lymphoma	3.75	3.75	3.75	A
TUR	Lymphoma	4.48	4.48	4.48	C
ARH-77	Myeloma	2.66	2.67	2.65	A
IM-9	Myeloma	0.68	0.68	0.68	B
RPMI 8226	Myeloma	0.99	1.00	0.99	C
SKO-007	Myeloma	0.99	1.00	0.99	B
U266B1	Myeloma	2.82	2.82	2.71	B
A-253	Head and Neck	8.23	8.23	8.23	B
A388	Head and Neck	1.92	1.94	1.93	B
A431	Head and Neck	3.29	3.30	3.30	A
Cal 27	Head and Neck	2.17	2.17	2.17	B
Detroit 562	Head and Neck	2.99	3.00	2.99	B
FaDu	Head and Neck	0.90	0.90	0.90	B
OE19	Head and Neck	2.97	2.98	2.96	C
OE21	Head and Neck	3.89	3.89	3.89	C
SCC-25	Head and Neck	5.99	5.99	5.95	C
SCC-4	Head and Neck	8.51	8.51	8.47	B
SCC-9	Head and Neck	7.35	7.42	7.39	B
769-P	Kidney	1.05	1.05	1.05	B
786-O	Kidney	2.81	2.81	2.81	B
A498	Kidney	1.80	1.80	1.79	B
A-704	Kidney	2.99	3.01	2.98	B
ACHN	Kidney	3.26	3.26	3.25	A
Caki-1	Kidney	4.66	4.66	4.59	C
Caki-2	Kidney	4.76	4.80	4.80	A
G-401	Kidney	4.13	4.13	4.13	B
SK-NEP-1	Kidney	3.99	3.99	3.99	D
HepG2	Liver	1.54	1.54	1.54	C
HLE	Liver	3.92	3.92	3.89	B
HLF	Liver	3.99	3.99	3.96	C
HuCCT1	Liver	3.64	3.64	3.64	B
HUH-6 Clone 5	Liver	1.70	1.70	1.69	B
OCUG-1	Liver	3.61	3.64	3.64	B
SNU-423	Liver	1.47	1.47	1.45	B
A427	Lung - NSCLC	4.13	4.13	4.10	A
A549	Lung - NSCLC	2.98	2.98	2.98	C
Calu1	Lung - NSCLC	2.72	2.72	2.69	A
Calu6	Lung - NSCLC	9.56	9.77	9.59	B
ChaGoK1	Lung - NSCLC	1.69	1.69	1.68	A

COR-L105	Lung - NSCLC	2.85	2.86	2.84	A
COR-L23	Lung - NSCLC	4.59	4.62	4.59	D
Hs 229.T	Lung - NSCLC	3.09	3.31	3.15	A
NCI-H292	Lung - NSCLC	3.50	3.50	3.49	A
NCIH441	Lung - NSCLC	>10.5	>10.5	>10.5	A
NCI-H460	Lung - NSCLC	2.99	2.99	2.99	A
NCI-H520	Lung - NSCLC	3.02	3.02	3.01	A
NCI-H596	Lung - NSCLC	8.89	8.93	8.86	A
NCI-H661	Lung - NSCLC	1.70	1.70	1.69	A
SKMES1	Lung - NSCLC	1.26	1.26	1.25	A
DMS114	Lung - SCLC	4.62	4.69	4.55	C
DMS53	Lung - SCLC	0.51	0.51	0.48	A
NCIH446	Lung - SCLC	3.75	3.75	3.75	B
NCI-H69	Lung - SCLC	5.01	5.01	4.73	A
SHP-77	Lung - SCLC	1.03	1.03	1.03	B
SW900	Lung - SCLC	3.64	3.68	3.61	C
AsPC-1	Pancreas	2.51	2.51	2.45	A
BxPC-3	Pancreas	4.48	4.48	4.48	A
Capan-1	Pancreas	>10.5	>10.5	>10.5	C
Capan-2	Pancreas	1.34	1.34	1.33	A
CFPAC-1	Pancreas	3.57	3.57	3.57	A
HPAF-II	Pancreas	2.30	2.31	2.29	C
Hs 766T	Pancreas	2.44	2.47	2.42	A
HuP-T4	Pancreas	>10.5	>10.5	>10.5	C
Mia PaCa-2	Pancreas	3.15	3.15	3.15	A
PANC-1	Pancreas	2.20	2.20	2.17	A
PSN-1	Pancreas	2.70	2.70	2.70	B
SU.86.86	Pancreas	>10.5	>10.5	>10.5	C
YAPC	Pancreas	3.37	3.37	3.34	A
BeWo	Placenta	10.05	>10.5	>10.5	B
JAR	Placenta	8.65	8.65	8.65	C
JEG-3	Placenta	4.38	4.38	4.34	B
22Rv1	Prostate	4.13	4.13	4.10	A
BM-1604	Prostate	3.89	3.89	3.85	C
BPH1	Prostate	4.10	8.82	7.98	A
DU145	Prostate	3.61	3.61	3.57	A
LNCaP	Prostate	3.17	3.17	2.62	C
PC-3	Prostate	4.06	4.06	4.03	A
A101D	Skin (Melanoma)	6.23	6.23	6.09	B
A375	Skin (Melanoma)	1.41	1.41	1.41	B
A7	Skin (Melanoma)	0.92	0.92	0.91	B

C32	Skin (Melanoma)	1.71	1.71	1.36	B
CHL-1	Skin (Melanoma)	1.59	1.59	1.59	D
COLO 829	Skin (Melanoma)	1.01	1.03	0.98	D
G-361	Skin (Melanoma)	2.70	2.70	2.69	B
HMCB	Skin (Melanoma)	1.46	1.47	1.46	C
Hs 294T	Skin (Melanoma)	1.73	1.73	1.67	B
Hs 688(A).T	Skin (Melanoma)	2.11	2.22	1.99	B
Hs 695T	Skin (Melanoma)	0.22	0.22	0.11	C
Hs 852.T	Skin (Melanoma)	3.64	3.64	3.50	B
Hs 934.T	Skin (Melanoma)	3.01	4.52	3.02	B
Hs 936.T(C1)	Skin (Melanoma)	2.26	2.26	2.22	B
MALME3M	Skin (Melanoma)	2.69	2.69	2.53	C
MeWo	Skin (Melanoma)	1.93	1.93	1.91	B
RPMI-7951	Skin (Melanoma)	0.74	0.74	0.73	C
SH-4	Skin (Melanoma)	2.60	2.60	2.58	B
SK-MEL-1	Skin (Melanoma)	3.96	4.27	4.13	B
SK-MEL-28	Skin (Melanoma)	2.38	2.39	2.37	A
SK-MEL-3	Skin (Melanoma)	5.25	5.25	5.15	C
WM-266-4	Skin (Melanoma)	1.19	1.19	1.18	B
G-292, clone A141B1	Soft Tissue - Osteosarcoma	2.26	2.26	2.16	B
HOS	Soft Tissue - Osteosarcoma	1.06	1.06	1.06	B
Hs 888.Sk	Soft Tissue - Osteosarcoma	3.09	3.19	3.10	B
KHOS-240S	Soft Tissue - Osteosarcoma	2.18	2.18	2.18	D
MG-63	Soft Tissue - Osteosarcoma	9.66	9.70	9.66	A
SaOS2	Soft Tissue - Osteosarcoma	3.36	3.43	3.33	B
SJSA1	Soft Tissue - Osteosarcoma	1.51	1.51	1.50	B
SW1353	Soft Tissue - Osteosarcoma	1.76	1.76	1.76	B
U2OS	Soft Tissue - Osteosarcoma	2.35	2.35	2.34	C
A204	Soft Tissue - Sarcoma	0.65	0.65	0.64	A
A-673	Soft Tissue - Sarcoma	1.15	1.15	1.15	B
Hs 729	Soft Tissue -	3.07	3.11	3.01	C

	Sarcoma				
Hs 821.T	Soft Tissue - Sarcoma	2.79	5.43	2.56	B
HT-1080	Soft Tissue - Sarcoma	0.59	0.59	0.59	A
MES-SA	Soft Tissue - Sarcoma	1.53	1.53	1.53	B
RD	Soft Tissue - Sarcoma	0.69	0.69	0.69	C
SJRH30	Soft Tissue - Sarcoma	1.46	1.46	1.46	A
SK-LMS-1	Soft Tissue - Sarcoma	2.23	2.23	2.21	C
SK-UT-1	Soft Tissue - Sarcoma	2.39	2.39	2.38	B
SW684	Soft Tissue - Sarcoma	9.14	9.14	7.95	C
SW872	Soft Tissue - Sarcoma	0.35	0.35	0.35	A
SW982	Soft Tissue - Sarcoma	1.20	1.20	1.19	B
TE 125.T	Soft Tissue - Sarcoma	2.05	6.34	1.31	B
TE 381.T	Soft Tissue - Sarcoma	1.56	1.56	1.55	A
VA-ES-BJ	Soft Tissue - Sarcoma	4.17	4.17	4.13	B
AGS	Stomach	0.85	0.85	0.85	B
HS 746T	Stomach	3.99	6.51	4.94	A
KATO III	Stomach	4.62	4.62	4.62	C
SK-PN-DW	Stomach	2.16	2.16	2.15	B
SNU-1	Stomach	1.51	1.51	1.51	C
SNU-16	Stomach	1.44	1.44	1.44	D
SNU-5	Stomach	4.80	4.80	4.73	D
NTERA-2 cl.D1	Testis	1.98	1.99	1.96	B

[A] 14 July 2016; [B] 22 August 2016; [C] 22 September 2016; [D] 5 October 2016

For compound **1**, a broad spectrum of activity was observed over the 280 cell types with very potent to strong (GI_{50} = 0.006 to 2.98 μM) activity towards 174 cell lines. Very potent activity was observed towards SK-NEP-1 kidney (GI_{50} = 0.00618 μM) and J-RT3-T3-5 leukemia (GI_{50} = 0.0101 μM) cell lines. Moderately potent activity was observed (GI_{50} = 0.11 μM) towards KG-1 leukemia cell line. Moderately potent activity (GI_{50} = 0.4 to 1.0 μM) was observed towards the following cell lines: 2 breast cell lines KPL-1, MDA-MB-453; 3 myeloma cell lines IM-9, RPMI8226, SKO-007; 3 melanoma cell lines A7, COLO829, RPMI-7951; 7 soft tissue cell lines HOS (osteosarcoma), KHOS-240S (osteosarcoma), SW1353 (osteosarcoma), A204 (sarcoma), HT-1080 (sarcoma), RD (sarcoma), SW 872 (sarcoma); 2 small cell lung carcinoma cell lines

DMS53, SHP-77; and also Colo 201 (colon); FaDu (head and neck), 769-P (kidney), HepG2 (liver), and AGS (stomach). Strong activity (GI_{50} = 1 to 2.98 μM) was shown towards 149 cell lines: 16 melanoma; 15 lymphoma; 9 female genitourinary; 14 soft tissue (sarcoma); 16 colon; 12 leukemia; 8 non-small cell lung carcinoma; 8 pancreas; 9 breast; 10 CNS; 8 bladder; 5 kidney; 4 head and neck, 4 endocrine, 1 myeloma, 3 liver, 2 small cell lung carcinoma, 2 prostrate, 2 stomach and 1 testis.

For compound **2**, a narrow spectrum of activity was observed over the 280 cell types with potent to strong (GI_{50} = 0.06 to 2.96 μM) activity towards 10 cell lines. Potent activity was observed towards SK-NEP-1 kidney (GI_{50} = 0.0606 μM) Strong activity (GI_{50} = 1 to 2.96 μM) was observed towards the following cell lines: 5 leukemia cell lines J-RT3-T3-5, Jurkat, MOLT-3, NALM-6, TF-1; 2 myeloma cell lines RPMI8226, SKO-007; 1 soft tissue cell line RD (sarcoma). For compound **2** activities towards Jurkat, MOLT-3, NALM-6, TF-1 (leukemia) and SKO-007 (myeloma) were similar in magnitude to compound **1**.

For compound **4**, a narrow spectrum of activity was observed over the 280 cell types with moderately potent to strong (GI_{50} = 0.68 to 2.92 μM) activity towards 12 cell lines. One strong activity (GI_{50} = 0.684 μM) was observed towards A204 (soft tissue sarcoma) similar in magnitude to that observed for compound **1**. Strong activity (GI_{50} = 1.23 to 2.92 μM) for compound **4** was observed towards the following cell lines: 5 lymphoma (Daudi, DOHH-2, GA-10, L-428, ST486); 2 leukemia (MX1, NALM-6); also for T47D (breast), CEM-C1 (leukemia), A-673 (soft tissue sarcoma). The activity towards these cell lines is comparable in magnitude to compound **1**, however, compound **4** show strong activity towards the J-RT3-T3-5 leukemia cell line (GI_{50} = 2.71 μM) approximately 270 times less activity than the very potent activity observed for compound **1** (GI_{50} = 0.0101 μM) towards this cell line.

The plant resin extract showed strong activity (GI_{50} = 0.11 to 1.03 μg/mL) towards 24 cell lines: 4 soft tissue sarcoma (A204, HT-1080, RD, SW 872); 4 melanoma (A7, COLO829, Hs695T, RPMI-7951); 3 myeloma (IM-9, RPMI8226, SKO-007); 2 breast (KPL-1, MDA-MB-453); 2 lymphoma (DOHH-2, SU-DHL-5); 2 small cell carcinoma (DMS53, SHP-77); 2 leukemia (Jurkat, NALM-6) and also bladder (UM-UC-3); colon (SW480); thyroid (CGTH-W-1); head and neck (FaDu); and stomach (AGS). For the

Hs695T melanoma cell line, calculated on a weight-weight basis, the plant resin extract (GI_{50} = 0.11 µg/mL) was approximately 3 times more active than compound **1** (GI_{50} = 0.37 µg/mL) towards this particular cell line. From weight comparison for all other cell lines the plant extract was less active than compound **1**.

Overall, compound **1** provides a broad spectrum of anticancer activity towards a wide range of cell lines. Compound **2** shows specificity for the LNCaP prostrate cell line, also specific activity towards SK-NEP-1 (kidney), Jurkat, MOLT-3, NALM-6, TF-1 (leukemia) and SKO-007, RPMI8226 (myeloma) similar in magnitude to compound **1**. Compound **4** showed moderately potent to strong activity (GI_{50} = 0.68 to 2.92 µM) towards a narrow range of cell lines (12 out of 280) compared with compound **1** (174 out of 280).

Table 30. Number of cancer cell types for levels of growth inhibitory activity for Compounds **1**, **2** and **4**

		Number of cell types		
GI Activity	**GI_{50} range (µM)**	**Comp 1**	**Comp 2**	**Comp 4**
very potent	0.001 - 0.029	2	0	0
potent	0.03 - 0.099	0	1	0
moderately potent	0.1 - 0.99	23	1	1
strong	1 - 2.99	149	8	11
moderately strong	3 - 9.99	99	110	125
weak	10 - 30.00	6	118	130
very weak	> 30	1	42	13
TOTAL		280	280	280

Table 31. Number of cancer cell types for levels of growth inhibitory activity for *M. insulare* extract

		Number of cell types
GI Activity	**GI_{50} range (µg/mL)**	***M. insulare* extract**
very potent	0.00035 - 0.0104	0
potent	0.0105 - 0.034	0
moderately potent	0.035 - 0.34	1
strong	0.35 - 1.04	23
moderately strong	1.05 - 3.49	165
weak	3.5 - 10.49	83
very weak	> 10.5	8
TOTAL		280

Inhibition of Toll-like receptor 4 (TLR4) activation on human peripheral blood mononuclear cells (PBMC's).

Study Objective

To evaluate compound capability to inhibit Toll-like receptor 4 (TLR4) activation on human peripheral blood mononuclear cells (PBMC's).

Experimental Protocol

Compound **1** was evaluated for ability to inhibit TLR4 in human PBMC's, as measured by release of specific cytokines. Evaluation was conducted by Eurofins Panlabs Inc., St Charles, Missouri, USA.

TLR4 Inhibition Assay Protocol

a) Cryopreserved human PBMC's were drip-thawed.

b) Cells were diluted to the appropriate density (1x105 per well) and seeded into 96-well polypropylene plates with 150 µL per well of culture medium (RPMI 1640, 10% heat-inactivated FBS, 1% penicillin/streptomycin, 2 mM L-glutamine).

c) Cells were incubated at 37°C, 5% CO_2 for 1 hour prior to the addition of test compounds or controls.

d) Test compounds were solubilized in DMSO to make stock solutions, and then diluted further with cell culture medium. The positive control, LPS (from *S. Minnesota* R595), was resuspended in endotoxin-free water at 0.5 mg/mL to make working stock solutions. Dexamethasone was used as a reference control compound.

e) Compounds and controls, including appropriate vehicle controls, were added to the PBMC's in volumes of 10 µL and incubated for 1 hour at 37°C, 5% CO_2. Compounds were tested in duplicate at final assay concentrations of 10, 3, 1, 0.3, 0.1, and 0.03 µM. Vehicle control wells simply received 10 µL of the appropriate vehicle.

f) After a 1-hour incubation, 40 µL of diluted working stock LPS were added to the test compound and control wells to give final assay volumes of 200 µL. Plates were incubated for 24 hours at 37°C, 5% CO_2.

g) Plates were centrifuged at 200 x g for 10 minutes. Cell culture supernatants were collected and stored at -80°C until needed for analysis.

h) Cytokine levels in each sample were determined using Luminex methodology, per the manufacturer's protocol.

PBMC Donor: Human donor 1 (lot # 100)

Results and Discussion

Stimulation of human PBMC's with LPS for 24 hours elicited the measurable release of appropriate cytokines within expected ranges. Conversely, dexamethasone inhibited the LPS-stimulated release of cytokines from human PBMC's, also within expected ranges. Compound 1 elicited measurable inhibition of the LPS-induced release of specific cytokines from human PBMC's, following a 24-hour stimulation.

As seen from the results shown in **Table 32**, compound **1** elicited a moderate to strong inhibition of the secretion of all cytokines at the top test concentration, giving measured IC_{50} values of 4.3 µM, 6.6 µM, 8.8 µM, and 8.9 µM for IL-10, IL-1β, IL-6, and TNFα, respectively. (IC_{50} values could not be measured for IL-8 and MIP-1α.)

Table 32. Compound 1 activity against certain LPS-induced cytokines

	Compound **1**
	LPS-induced cytokine
Assay	**IC_{50} (µM)**
I-1β	6.6
IL-6	8.8
IL-8	NA
IL-10	4.3

MIP-1α	NA
TNF-α	8.9

Bioprint Assays

The Bioprint assay (conducted by Eurofins Cerep, France) provides a profile that is designed with the dual purpose of assessing safety at targets with known safety liabilities as well as providing a rich enough profile to search for compounds with similar profiles.

Methodology

Compound **1** was tested at 10 μM. For compound **1** at 10 μM, the agonist radioligand assays for control specific inhibition of interest for biological activity or safety are as follows:-

GPCR Family:- adenosine A3 (h), 92%; adrenergic alpha 2C (h), 92%; cannabinoid CB2 (h), 71 %; cholecystokinin CCK1 (CCKA) (h), 81%; dopamine D1 (h), 67%; dopamine D3 (h), 85%; histamine H1 (h), 64%; melatonin MT1 (ML1A) (h), 91%.

Transporters:- norepinephrine transporter (h), 76%.

Non-steroid Nuclear Receptors:- PPARgamma (h), 91%.

For compound **1** at 10 μM, the enzyme assays for control specific inhibition of interest for biological activity or safety are as follows:-

AA Metabolism:- COX1 (h), 81%; COX2 (h), 74%.

Compound binding was calculated as a % inhibition of the binding of a radioactively labeled ligand specific for each target. Compound enzyme inhibition effect was calculated as a % inhibition of control enzyme activity. Results showing an inhibition or stimulation higher than 50% are considered to represent significant effects of the test compounds.

Results

Compound **1** results for inhibition of control specific binding to receptors are shown in **Table 33** whilst results for inhibition of control specific binding inhibition of enzymes in enzyme and cell-based assays are shown in **Table 34**.

Table 33. Bioprint results for Compound **1** tested at 10 µM for inhibition of control specific binding to receptors.

		Compound 1	Reference	
Family	Binding Assay	% Inhibition of Control Specific Binding	Compound	IC_{50} (µM)
GPCR				
ADENOSINE	A1 (h) (agonist radioligand)	10	CPA	0.0021
ADENOSINE	A2A (h) (agonist radioligand)	18	NECA	0.036
ADENOSINE	A2B (h) (antagonist radioligand)	8	NECA	0.59
ADENOSINE	A3 (h) (agonist radioligand)	92	IB-MECA	4.5E-04
ADRENERGIC	alpha 1A (h) (antagonist radioligand)	17	WB 4101	2.7E-04
ADRENERGIC	alpha 1B (h) (antagonist radioligand)	41	prazosin	1.7E-04
ADRENERGIC	alpha 2A (h) (antagonist radioligand)	35	yohimbine	0.0065
ADRENERGIC	alpha 2B (h) (antagonist radioligand)	7	yohimbine	0.0065
ADRENERGIC	alpha 2C (h) (antagonist radioligand)	92	yohimbine	0.004
ADRENERGIC	beta 1 (h) (agonist radioligand)	19	atenolol	0.34
ADRENERGIC	beta 2 (h) (agonist radioligand)	2	ICI 118551	7.8E-04
ADRENERGIC	Adrenergic beta3	33	Alprenolol	0.25
ANGIOTENSIN II	AT1 (h) (antagonist radioligand)	60	saralasin	0.0019
ANGIOTENSIN II	AT2 (h) (agonist radioligand)	54	angiotensin-II	1.4E-04
APELIN	APJ (apelin) (h) (agonist radioligand)	24	apelin-13,TFA	3.4E-04
BOMBESIN	BB3 (h) (agonist radioligand)	26	Bn(6-14)	0.0048
BRADYKININ	B2 (h) (agonist radioligand)	-37	NPC 567	0.038

CANNABINOID	CB1 (h) (agonist radioligand)	46	CP 55940	0.001
CANNABINOID	CB2 (h) (agonist radioligand)	71	WIN 55212-2	0.0022
CYTOKINES	TNF-alpha (h) (agonist radioligand)	-23	TNF-alpha	1.6E-04
CHOLECYSTOKININ	CCK1 (CCKA) (h) (agonist radioligand)	81	CCK-8s	1.5E-04
CHOLECYSTOKININ	CCK2 (CCKB) (h) (agonist radioligand)	6	CCK-8s	1.7E-04
CORTICOTROPIN RELEASING FACTOR	CRF1 (h) (agonist radioligand)	34	sauvagine	2.5E-04
DOPAMINE	D1 (h) (antagonist radioligand)	67	SCH 23390	3.9E-04
DOPAMINE	D2S (h) (agonist radioligand)	59	7-OH-DPAT	0.0033
DOPAMINE	D3 (h) (antagonist radioligand)	85	(+)butaclamol	0.0024
ENDOTHELIN	ETA (h) (agonist radioligand)	6	endothelin-1	4.9E-05
ENDOTHELIN	ETB (h) (agonist radioligand)	40	endothelin-3	1.7E-05
GABA	GABAB(1b) (h) (antagonist radioligand)	-17	CGP 54626	0.0022
GLUCAGON	glucagon (h) (agonist radioligand)	-20	glucagon	0.001
CHEMOKINES	CCR2 (h) (agonist radioligand)	48	MCP-1	8.7E-05
HISTAMINE	H1 (h) (antagonist radioligand)	64	pyrilamine	0.0023
HISTAMINE	H2 (h) (antagonist radioligand)	37	cimetidine	0.66
HISTAMINE	H3 (h) (agonist radioligand)	10	(R)alpha -Me-histamine	0.0016
HISTAMINE	H4 (h) (agonist radioligand)	23	imetit	0.0047
LEUKOTRIENES	BLT1 (LTB4) (h) (agonist radioligand)	27	LTB4	3.7E-04
LEUKOTRIENES	CysLT1 (LTD4) (h) (agonist radioligand)	10	LTD4	6.3E-04
MELANIN-CONCENTRATING-HORMONE	MCH1 (h) (agonist radioligand)	-5	human MCH	7.8E-05
MELANOCORTIN	MC1 (agonist radioligand)	11	NDP-alpha -MSH	1.2E-04
MELANOCORTIN	MC3 (h) (agonist radioligand)	60	NDP-alpha -MSH	2.7E-04
MELANOCORTIN	MC4 (h) (agonist radioligand)	37	NDP-alpha -MSH	4.0E-04
MELATONIN	MT1 (ML1A) (h) (agonist radioligand)	91	melatonin	2.8E-04
MOTOLIN	motilin (h) (agonist radioligand)	-12	[Nleu13]-motilin	8.9E-04

MUSCARINIC	M1 (h) (antagonist radioligand)	8	pirenzepine	0.031
MUSCARINIC	M2 (h) (antagonist radioligand)	1	methoctramine	0.032
MUSCARINIC	M3 (h) (antagonist radioligand)	-3	4-DAMP	0.001
MUSCARINIC	M4 (h) (antagonist radioligand)	19	4-DAMP	9.2E-04
NEUROKININ	NK1 (h) (agonist radioligand)	62	[Sar9,Met(O2)11]-SP	3.7E-04
NEUROKININ	NK2 (h) (agonist radioligand)	52	[Nleu10]-NKA (4-10)	0.0029
NEUROPEPTIDE Y	Y1 (h) (agonist radioligand)	29	NPY	1.6E-04
OPIOD & OPIOID-LIKE	delta (DOP) (h) (agonist radioligand)	62	DPDPE	0.002
OPIOD & OPIOID-LIKE	kappa (KOP) (agonist radioligand)	39	U 50488	0.0012
OPIOD & OPIOID-LIKE	mu (MOP) (h) (agonist radioligand)	43	DAMGO	5.3E-04
OPIOD & OPIOID-LIKE	NOP (ORL1) (h) (agonist radioligand)	-4	nociceptin	8.4E-04
PLATELET ACTIVATED FACTOR	PAF (h) (agonist radioligand)	39	C16-PAF	0.0034
PROSTANOID	EP2 (h) (agonist radioligand)	53	PGE2	0.0027
PROSTANOID	FP (h) (agonist radioligand)	54	PGF2alpha	0.003
PROSTANOID	IP (PGI2) (h) (agonist radioligand)	16	iloprost	0.017
SEROTONIN	5-HT1A (h) (agonist radioligand)	-18	8-OH-DPAT	8.3E-04
SEROTONIN	5-HT1B (antagonist radioligand)	42	serotonin	0.013
SEROTONIN	5-HT1D (agonist radioligand)	18	serotonin	0.0026
SEROTONIN	5-HT2A (h) (agonist radioligand)	9	(±)DOI	4.7E-04
SEROTONIN	5-HT2B (h) (agonist radioligand)	70	(±)DOI	0.0067
SEROTONIN	5-HT2C (h) (agonist radioligand)	32	(±)DOI	2.4E-04
SEROTONIN	5-HT4e (h) (antagonist radioligand)	2	serotonin	0.19
SEROTONIN	5-HT6 (h) (agonist radioligand)	42	serotonin	0.18
SEROTONIN	5-HT7 (h) (agonist radioligand)	14	serotonin	4.4E-04
SOMASTATIN	sst1 (h) (agonist radioligand)	18	somatostatin-28	5.5E-04
SOMASTATIN	sst4 (h) (agonist radioligand)	40	somatostatin-14	0.0042
UROTENSIN-II	UT (h) (agonist radioligand)	46	urotensin-II	9.5E-04

VASOACTIVE INTESTINAL PEPTIDE	VPAC1 (VIP1) (h) (agonist radioligand)	-9	VIP	2.7E-04
VASOPRESSIN	V1a (h) (agonist radioligand)	12	[d(CH2)51,Tyr(Me)2]-AVP	0.0015
VASOPRESSIN	V2 (h) (agonist radioligand)	11	AVP	0.0013
TRANSPORTERS				
CHOLINE	choline transporter (CHT1) (h) (antagonist radioligand)	-41	hemicholinium-3	0.0046
DOPAMINE	dopamine transporter (h) (antagonist radioligand)	63	BTCP	0.012
GABA	GABA transporter (antagonist radioligand)	-10	nipecotic acid	2.3
NOREPINEPHRINE	norepinephrine transporter (h) (antagonist radioligand)	76	protriptyline	0.0039
SEROTONIN	5-HT transporter (h) (antagonist radioligand)	56	imipramine	0.0044
ION-CHANNELS				
GABA	GABAA1 (h) (alpha 1,beta 2,gamma 2) (agonist radioligand)	-36	muscimol	0.053
GABA CHANNELS	BZD (central) (agonist radioligand)	-31	diazepam	0.0094
GABA CHANNELS	Cl- channel (GABA-gated) (antagonist radioligand)	42	picrotoxinin	0.33
GLUTAMATE CHANNELS	PCP (antagonist radioligand)	-11	MK 801	0.0096
GLUTAMATE CHANNELS	AMPA (agonist radioligand)	4	L-glutamate	0.37
GLUTAMATE CHANNELS	kainate (agonist radioligand)	15	kainic acid	0.023
GLUTAMATE CHANNELS	NMDA (antagonist radioligand)	9	CGS 19755	0.35
GLYCINE CHANNELS	glycine (strychnine-insensitive) (antagonist radioligand)	4	glycine	0.28
NICOTINIC CHANNELS	N neuronal alpha 4beta 2 (h) (agonist radioligand)	-3	nicotine	0.0046
NICOTINIC CHANNELS	N muscle-type (h) (antagonist radioligand)	1	alpha -bungarotoxin	0.0019
SEROTONIN CHANNELS	5-HT3 (h) (antagonist radioligand)	-2	MDL 72222	0.0086
Ca^{2+} CHANNELS	Ca2+ channel (L, dihydropyridine site) (antagonist radioligand)	55	nitrendipine	1.3E-04
Ca^{2+} CHANNELS	Ca2+ channel (L, diltiazem site) (benzothiazepines) (antagonist radioligand)	-30	diltiazem	0.057
Ca^{2+} CHANNELS	Ca2+ channel (L, verapamil site)	-4	D 600	0.027

	(phenylalkylamine) (antagonist radioligand)			
Ca^{2+} CHANNELS	Ca2+ channel (N) (antagonist radioligand)	5	omega -conotoxin GVIA	1.7E-06
K^+ CHANNELS	SKCa channel (antagonist radioligand)	14	apamin	9.7E-06
Na^+ CHANNELS	Na+ channel (site 2) (antagonist radioligand)	48	veratridine	5.9
NUCLEAR RECEPTORS				
NON-STEROID NUCLEAR RECEPTORS	PPARgamma (h) (agonist radioligand)	91	rosiglitazone	0.015
STEROID NUCLEAR RECEPTORS	AR (h) (agonist radioligand)	-9	mibolerone	0.0021
STEROID NUCLEAR RECEPTORS	Estrogen ER alpha (h) (agonist radioligand)	40	Diethylstilbestrol	4.5E-04
STEROID NUCLEAR RECEPTORS	GR (h) (agonist radioligand)	47	dexamethasone	0.0035
OTHER RECEPTORS				
SIGMA	sigma (non-selective) (h) (agonist radioligand)	11	haloperidol	0.045
THYROID HORMONE	Thyroid Hormone	9	Triiodothyronine	3.9E-05

Table 34. Bioprint results for Compound **1** tested at 10 µM for inhibition of control specific binding inhibition of enzymes in enzyme and cell-based assays.

		Compound **1**	Reference	
Family	Enzyme and Cell-based Assays	% Inhibition of Control Values	Compound	IC_{50} (µM)
KINASES				
RTK	FLT-1 kinase (h) (VEGFR1)	36	staurosporine	0.0098
RTK	IRK (h) (InsR)	-15	staurosporine	0.052
CTK	Abl kinase (h)	14	staurosporine	0.11
CTK	Fyn kinase (h)	6	PP1	0.11
CTK	Lyn A kinase (h)	9	staurosporine	0.012
CTK	ZAP70 kinase (h)	33	staurosporine	0.021
CMGC	CDK2 (h) (cycA)	12	staurosporine	0.011
CMGC	ERK2 (h) (P42mapk)	6	staurosporine	1
CMGC	p38alpha kinase (h)	4	SB202190	0.033
CAMK	CaMK2alpha (h)	2	AIP	0.092
OTHER NON-KINASE ENZYMES				
AA METABOLISM	COX1(h)	81	Diclofenac	0.0078

AA METABOLISM	COX2(h)	74	NS398	0.19
ATPASE	ATPase (Na+/K+)	22	ouabain	0.25
MONOAMINE & NEUROTRANSMITTER	acetylcholinesterase (h)	32	galanthamine	0.57
MONOAMINE & NEUROTRANSMITTER	COMT (catechol- O-methyl transferase)	-6	Ro 41-0960	0.061
MONOAMINE & NEUROTRANSMITTER	MAO-A (antagonist radioligand)	15	clorgyline	0.0012
NO SYNTHASES	inducible NOS	-1	1400W	0.029
PHOSPHODIESTERASES	PDE2A1 (h)	43	EHNA	1.2
PHOSPHODIESTERASES	PDE3B (h)	-3	milrinone	1.2
PHOSPHODIESTERASES	PDE4D2 (h)	55	Ro 20-1724	0.15
PHOSPHODIESTERASES	PDE5 (h) (non-selective)	11	dipyridamole	0.84
PHOSPHODIESTERASES	PDE6 (non-selective)	4	zaprinast	0.16
SERINE PROTEASES	caspase-3 (h)	-3	Ac-DEVD-CHO	0.0029
ASPARTIC PROTEASES	BACE-1 (h) (beta - secretase)	0	OM 99-2	0.081
ASPARTIC PROTEASES	HIV-1 protease	9	pepstatin A	2.4
METALLOPROTEASES	ACE (h)	14	captopril	5.8E-04
METALLOPROTEASES	ACE-2 (h)	-3	Ac-GG-26-NH2	0.2
METALLOPROTEASES	MMP-1 (h)	-2	GM6001	0.0054
METALLOPROTEASES	MMP-2 (h)	0	GM6001	7.9E-04
METALLOPROTEASES	MMP-9 (h)	1	GM6001	3.6E-04
MISCELLANEOUS ENZYMES	MT3 (ML2) (agonist radioligand)	31	melatonin	0.16
MISCELLANEOUS ENZYMES	xanthine oxidase/ superoxide O2- scavenging	-140	allopurinol	7.8

In vitro toxicity: Normal Cell Panel Toxicity Assay

The OncoPanel (Eurofins Panlabs Inc., St Charles, Missouri, USA) normal cell proliferation assay measures the proliferation response of normal cells to drug treatments through high-content fluorescence imaging.

Methodology

Normal cells (see description in **Table 35**) were grown in special medium for each cell type. Cells were seeded into 384-well plates and incubated in a humidified atmosphere of 5% CO_2 at 37°C. Compounds (information in **Table 36**) were added the day following cell seeding. At the same time, a time zero untreated cell plate was generated. After a 3-day incubation period, cells were fixed and stained to allow fluorescence imaging of nuclei.

Table 35. Description of cells used in normal cell panel toxicity assay

Normal cell name	Cell type	Source	Catalog number
CCD 841 CoN	Colon epithelial	ATCC	CRL-1790
HMEC	Mammary epithelial	ATCC	PCS-600-010
HREC	Renal mixed epithelial	ATCC	PCS-400-012
Wi38	Lung fibroblast	ATCC	CCL-75

Table 36. Information for compounds used in normal cell panel toxicity assay

Compound ID	F.W.	Amount received (mg)	Stock conc. (mM)	Stock volume (microL)	Max final test conc. (microM)
Carbonyl cyanide 3-chlorophenylhydrazone	204.62	5.70	10.00	2786	10.00
Compound **1**	318.00	4.80	30.00	500	30.00
Cycloheximide	281.35	5.40	10.00	1919	10.00
Paclitaxel	853.91	N/A	0.30	1000	0.30
Staurosporine	466.50	1.00	1.00	2144	1.00

Compounds were serially diluted in half-log steps from the highest test concentration specified in the above table, and assayed over 10 concentrations with a maximum assay concentration of 0.1% DMSO.

The experimental procedure and calculations are similar to the Oncopanel 10-day incubation cell proliferation assay described previously.

Results

Compound **1** activity (EC_{50} IC_{50} and GI_{50} (μM)) is shown against the reference compound paclitaxel in **Table 37**. Data on other reference compounds for comparison purposes is shown in **Table 38**.

Table 37. Compound **1** activity (EC_{50} IC_{50} and GI_{50} (μM)) against paclitaxel

		Compound **1**			Paclitaxel		
Cell Line	normal human primary cells	Cell Count EC_{50} (μM)	Cell Count IC_{50} (μM)	Cell Count GI_{50} (μM)	Cell Count EC_{50} (μM)	Cell Count IC_{50} (μM)	Cell Count GI_{50} (μM)
CCD 841 CoN	colon epithelial	4.86	14.3	5.27	0.0119	N/A	0.0221
HMEC	mammary epithelial	30	30	6.39	>30	>30	>30
HREC	renal mixed epithelial	6.45	7.98	4.3	0.00172	0.0484	0.0016
Wi38	lung fibroblast	5.45	10.4	5.92	0.0039	0.00941	0.0036

Table 38. Further reference compound activity

	Cycloheximide			Carbonyl cyanide 3-chlorophenylhydrazone			Staurosporine		
Cell Line	Cell Count EC_{50} (μM)	Cell Count IC_{50} (μM)	Cell Count GI_{50} (μM)	Cell Count EC_{50} (μM)	Cell Count IC_{50} (μM)	Cell Count GI_{50} (μM)	Cell Count EC_{50} (μM)	Cell Count IC_{50} (μM)	Cell Count GI_{50} (μM)
CCD 841 CoN	0.505	2.77	0.588	10	10	6.21	0.00024	0.00057	0.00019
HMEC	3.65	10	0.306	> 10	> 10	0.175	0.00229	> 1	0.00091
HREC	0.117	0.593	0.0369	0.553	1.52	0.308	0.00055	0.0027	0.0005
Wi38	0.285	0.871	0.369	8.84	8.84	6.15	0.00049	0.00074	0.00033

Table 39 shows representative data for the response when the cell line HREC is treated with compound **1** in an OncoPanel Normal Cell Proliferation Assay.

Table 39. Compound **1** against HREC

Concentration (microM)	Relative cell count (%)	
	Mean	StdDev
9.55E-04	98.5	8.8
3.02E-03	94.0	7.4
9.53E-03	93.3	6.6
3.01E-02	96.0	8.3
9.52E-02	95.8	4.5
3.01E-01	96.7	8.7
9.51E-01	89.3	4.7
3.00E+00	85.1	14.4
9.49E+00	40.4	3.3
3.00E+01	20.9	5.7

The data displayed in **Table 39** is graphed in Figure **19**.

Discussion

Compound **1** and reference compounds, paclitaxel, cycloheximide, carbonyl cyanide m-chlorophenylhydrazone (CCCP) and staurosporine, were tested on 4 normal cell types, CCD 841 CoN, HMEC, HREC and Wi38. In summary, compound **1** showed relatively low toxicity towards all 4 cell lines. Paclitaxel showed low toxicity towards the HMEC cell line and high toxicity towards the other three cell lines. Based on average GI_{50} for the 4 normal cell lines, the order of toxicity is staurosporine > paclitaxel > cycloheximide > CCCP > compound **1**.

In vitro toxicity: ADME-Toxicity Study

ADME-Toxicity study of compounds **1**, **2** and **4** was conducted by Eurofins Panlabs Inc, St Charles, MO, USA using a CYP panel.

Methodology

Cytochrome P450 Inhibition was monitored through HPLC-UV/VIS and HPLC-MS/MS detection. Peak areas corresponding to the metabolite of each substrate were recorded. The percent of control activity was then calculated by comparing the peak area obtained in the presence of the test compound to that obtained in the absence of the test compound. Subsequently, the percent inhibition was calculated by subtracting the percent control activity from 100 for each compound. IC_{50} values (concentration causing a half-maximal inhibition of control values) were determined by non-linear regression analysis of the concentration-response curve using Hill equation curve fitting [Dierks, E. A. *et al.* (2001)].

Results

Table 40. Inhibition of CYPs by compounds **1**, **2** and **4** against reference compounds

	% Inhibition of Control Values							
Human liver microsomes	Compound **1**		Compound **2**		Compound **4**		Reference	
In Vitro Metabolism	1 µM	10 µM	1 µM	10 µM	1 µM	10 µM	Compound	IC_{50} µM
CYP1A (phenacetin sub.)	28	92	38	63	14	85	Furafylline	16
CYP2B6 (bupropion sub.)	13	55	15	38	16	49	Clopidogrel	0.39
CYP2C8 (paclitaxel sub.)	14	76	12	52	24	61	Montelukast	0.57
CYP2C9 (diclofenac sub.)	5	77	20	72	31	91	Sulfaphenazole	0.28
CYP2C19 (omeprazole sub.)	37	90	34	73	25	78	Oxybutynin	6.7
CYP2D6 (dextromethorphan sub.)	13	45	18	44	21	45	Quinidine	0.12
CYP3A (midazolam sub.)	16	65	15	37	15	50	Ketoconazole	0.18
CYP3A (testosterone sub.)	7	77	17	57	20	48	Ketoconazole	0.18

Summary of Results

Enzyme - Substrates

CYP1A (phenacetin substrate)

Compounds **1**, **2** and **4** are strong inhibitors at 10 µM (63-92%). With IC_{50} values estimated to be < 10, Compounds **1**, **2** and **4** are stronger inhibitors the reference

standard furafylline (IC_{50}16 μM). Compounds **1** and **2** showed moderate inhibition at 1 μM (28% and 38% respectively).

CYP2B6 (bupropion substrate)

Compounds **1**, **2** and **4** are relatively weak inhibitors (13-16% at 1 μM) compared with the reference compound clopidogrel (IC_{50} 0.39 μM).

CYP2C8 (paclitaxel substrate)

Compounds **1**, **2** and **4** are relatively weak inhibitors (12-24% at 1 μM) compared with the reference compound montelukast (IC_{50} 0.57 μM).

CYP2C9 (diclofenac substrate)

Compounds **1** was a very weak at 1 μM (5%) and Compounds **2** and **4** relatively weak inhibitors (20 and 31%) compared with the reference compound sulfaphenazole (IC_{50} 0.28 μM).

CYP2C19 (omeprazole substrate)

Compounds **1**, **2** and **4** are moderately strong inhibitors (25-37% at 1 μM) with activity comparable with oxybutynin (IC_{50} 6.7 μM).

CYP2D6 (dextromethorphan substrate)

Compounds **1**, **2** and **4** are relatively weak inhibitors (12-21% at 1 μM) compared with the reference compound quinidine (IC_{50} 0.12 μM).

CYP3A (midazolam substrate)

Compounds **1**, **2** and **4** are relatively weak inhibitors (15-16% at 1 μM) compared with the reference compound ketoconazole (IC_{50} 0.18 μM).

CYP3A (testosterone substrate)

Compounds **1**, **2** and **4** are relatively weak inhibitors (7-20% at 1 μM) compared with the reference compound ketoconazole (IC_{50} 0.18 μM).

In vivo toxicity: Compound **1** Maximum Tolerated Dose for Mice

Two studies were conducted by Eurofins Panlabs Taiwan, Ltd. The purpose of Study 1 was to assess the possible adverse effects of compound **1** alone or in combination with

carboplatin in Maximum Tolerated Dose (MTD) assay. The purpose of Study 2 is a follow-up study performed at escalating doses.

The vehicle information and dosing volume used in the studies are shown in **Table 41**. **Table 42** and **Table 43** show results for Study 1 in terms of mortality and body weight observations. In regard to Study 2, **Table 44** and **Table 45** show results for mortality and body weight observations and behavioral, symptomatic i.e. neurological and autonomic signs for compound **1**, alone and in combination with carboplatin, are shown in **Table 46** and **Table 47**. Corresponding signs for the vehicles are shown in **Table 48** and **Table 49.**

Table 41. Vehicle information and dosing volume for MTD assay studies

Study	Test article	Vehicle	Concentration (mg/mL)	Dosing volume (mL/kg)	Dosage (mg/kg)
1	Compound **1**	10% Tween 20/ 90% PBS	10	10	100
2	Compound **1**	20% Tween 20/ 80% PBS	20	10	200

Test Substance and Dosing Pattern

Compound **1** was dissolved in 10% Tween 20/ 90% PBS or 20% Tween 20/ 80% PBS for IP injections. Compound **1** was administrated alone or in combination with carboplatin at a dosing volume of 10 or 20 mL/kg for each substance.

Study 1

For mortality, test substance (Compound **1**; 100 mg/kg) alone or in combination with carboplatin (8.75, 17.5, or 35 mg/kg; given on the same day) was administered to mice by IP injection to evaluate the possible adverse effects in MTD assay. The mice were a group of 3 female NOD/SCID mice at 6 - 7 weeks of age. The mortality was observed at 30 min and again at 3, 24, 48 and 72 hours after compound administrations.

For bodyweight, test substance (Compound **1**; 100 mg/kg) alone or in combination with carboplatin (8.75 or 17.5 mg/kg; given on the same day) was administered to a group of 3 female NOD/SCID mice at 6 - 7 weeks of age. The body weight of each animal was measured and recorded daily for 3 days.

Compound **1** alone did not elicit significant adverse effects and were considered tolerated. All test animals survived over the 72-hour observation period (**Table 42**). However, Compound **1** in combination with carboplatin was associated with slight to moderate limb tone, and resulted in a 33% mortality after 72 hours of dosing, reflecting the dose level was not well-tolerated (**Table 42**).

Compound **1**, in combination with the lower doses of carboplatin (8.75 and 17.5 mg/kg), was further investigated in the MTD study. Compound **1**, injected with two doses of carboplatin on the same day, was associated with slight to moderate abdominal tone during the first 30 minutes of administrations (**Table 44** and **Table 45**). However, no mortality and body weight losses were observed in test animals over the experimental period, signifying the dose levels were tolerated (**Table 44** and **Table 45**).

Table 42. MTD in mice (Study 1, Round 1 & 2)

Compound	Route	Dose (mg/kg)	Response (death / test)				
			30 min	3 hrs	Day 1	Day 2	Day 3
Vehicle[a]	IP	10 mL/kg	0/3	0/3	0/3	0/3	0/3
Vehicle[a]+Vehicle[b]	IP	10 mL/kg + 10 mL/kg	0/3	0/3	0/3	0/3	0/3
Compound **1**	IP	100 mg/kg	0/3	0/3	0/3	0/3	0/3
Carboplatin	IP	35 mg/kg	0/3	0/3	0/3	0/3	0/3
Compound **1** + carboplatin	IP	100 mg/kg + 35 mg/kg	0/3	0/3	0/3	0/3	1/3

Vehicle[a]+Vehicle[b]	IP	10 mL/kg + 10 mL/kg	0/3	0/3	0/3	0/3	0/3
Compound **1** + carboplatin	IP	100 mg/kg + 17.5 mg/kg	0/3	0/3	0/3	0/3	0/3
Compound **1** + carboplatin	IP	100 mg/kg + 8.75 mg/kg	0/3	0/3	0/3	0/3	0/3

Legend:
[a] 10% Tween 20/ 90% PBS
[b] 0.9% NaCl

Table 43. MTD in mice (Study 1; Round 2)

Compound	Route	Dose (mg/kg)	No.	Body Weight (g)			
				Day 0	Day 1	Day 2	Day 3
Vehicle[a]+Vehicle[b]	IP	10 mL/kg + 10 mL/kg	1	20	20	19	19
			2	20	20	20	19
			3	22	21	21	21
Compound **1** + carboplatin	IP	100 mg/kg + 17.5 mg/kg	1	22	21	21	20
			2	22	22	22	21
			3	21	21	21	21
Compound **1** + carboplatin	IP	100 mg/kg + 8.75 mg/kg	1	22	20	20	20
			2	21	21	22	21
			3	21	21	21	20

Legend:
[a] 10% Tween 20/ 90% PBS
[b] 0.9% NaCl

Study 2

A follow-up MTD study was performed to evaluate for the adverse effects of the test substance (Compound **1**) at escalating doses alone or in combination with carboplatin (17.5 mg/kg) via IP in a group of 3 female NOD/SCID mice at 6 - 7 weeks of age.

For mortality, treatment with compound **1** at escalating doses (200 mg/kg) alone and in combination with carboplatin (17.5 mg/kg; given on the same day) were administered by IP injection to a group of 3 female NOD/SCID mice at 6 - 7 weeks of age. The mortality was monitored at 30 min and again at 3, 24, 48 and 72 hours after compound administrations.

For body weight, test substance (Compound **1**) at escalating doses (200 mg/kg) alone or in combination with carboplatin (17.5 mg/kg; given on the same day) were administered by IP injection to a group of 3 female NOD/SCID mice at 6 - 7 weeks of age. The body weight of each animal was measured and recorded daily for 3 days.

On treatment with compound **1** (200 mg/kg) alone and in combination with carboplatin (17.5 mg/kg) exhibited a 33 – 100% mortality, but no marked weight loss during the study period (**Table 30** and **Table 31**).

Table 44. MTD in mice (Study 2)

Compound	Route	Dose (mg/kg)	Response (death / test)				
			30 min	3 hrs	Day 1	Day 2	Day 3
Vehicle[a]	IP	10 mL/kg	0/3	0/3	0/3	0/3	0/3
Vehicle[a]+Vehicle[b]	IP	10 mL/kg + 10 mL/kg	0/3	0/3	0/3	0/3	0/3
PT# 1206425 (UOS-70) (Compound **1**)	IP	200 mg/kg	0/3	0/3	1/3	3/3	3/3
PT# 1206425 (UOS-70) (Compound **1**) + carboplatin	IP	200 mg/kg + 17.5 mg/kg	0/3	0/3	0/3	1/3	1/3
Vehicle[a] (20% Tween20/80% PBS)	IP	20 mL/kg	0/3	0/3	1/3	2/3	2/3

Legend:

[a] 20% Tween 20/ 80% PBS
[b] 0.9% NaCl

Table 45. MTD in mice (Study 2; Round 1 & 2)

Compound	Route	Dose (mg/kg)	No.	Body Weight (g)			
				Day 0	Day 1	Day 2	Day 3
Vehicle[a] (20% Tween20/80% PBS)	IP	10 mL/kg	1	23	22	23	23
			2	24	23	23	23
			3	23	22	22	22
Vehicle[a]+Vehicle[b]	IP	10 mL/kg + 10 mL/kg	1	22	21	20	19
			2	22	22	21	19
			3	22	20	20	20
Compound **1**	IP	200 mg/kg	1	22	21	NA	NA
			2	21	NA	NA	NA
			3	21	21	NA	NA
Compound **1** + carboplatin	IP	200 mg/kg + 17.5 mg/kg	1	21	20	20	21
			2	22	22	NA	NA
			3	21	20	19	20
Vehicle[a]	IP	20 mL/kg	1	23	NA	NA	NA
			2	22	22	NA	NA
			3	23	22	22	21

Legend:
[a] 20% Tween 20/ 80% PBS
[b] 0.9% NaCl

For behavioral, symptomatic i.e. neurological and autonomic signs, test substance (compound **1**; 200 mg/kg) alone or in combination with carboplatin (17.5 mg/kg; given on the same day) were administered by IP injection to a group of 3 female NOD/SCID mice at 6 - 7 weeks of age. The animals were then observed for presences of acute toxic symptoms and autonomic effects for 30 min after the first dose.

Pronounced behavioral effects such as decreased startle, touch response, pinna and placing were observed on compound **1** treatment, alone and in combination with

carboplatin (see **Table 46**). Decreased neurologic signs, such as spontaneous activity, righting, ataxia and low limb post were observed on compound **1** treatment (**Table 46**). Hypothermia (decreased body temperature) was observed as an autonomic sign (**Table 47**).

Table 46. Behavioral and neurologic signs in mice for compound **1** (Study 2; Round 1)

Treatment	Compound 1			Compound 1+ carboplatin		
Route	IP			IP		
Dosage	200 mg/kg			200 mg/kg + 17.5 mg/kg		
BEHAVIORAL	No. 1	No. 2	No. 3	No. 1	No. 2	No. 3
B.W. (g)	22	21	21	21	22	21
Irritability	-	-	-	-	-	-
Hyperactivity	-	-	-	-	-	-
Inc. Startle	-	-	-	-	-	-
Inc. Touch	-	-	-	-	-	-
Dec. Startle Response	+	+	+	+	+	+
Dec. Touch Response	+	+	+	+	+	+
Inc. Exploration	-	-	-	-	-	-
Dec. Exploration	+	+	+	+	+	+
Pinna	+	+	+	+	+	+
Placing	±	±	±	±	+	±
NEUROLOGIC						
Tremor	-	-	-	+	-	+
Dec. Spont. Activity	+	+	+	+	+	+
Straub Tail	-	-	-	-	-	-
Reactivity	-	+	+	+	±	+
Righting	+	+	±	±	+	+
Ataxia	+	+	±	±	+	+
Convulsion C.T.C-T	-	-	-	-	-	-
Low Limb Post	+	+	+	+	+	+
Abdominal Tone	+	+	+	+	+	+
Limb Tone	+	+	+	+	+	+
Grip Strength	-	±	+	-	+	±

Table 47. Autonomic signs in mice for compound **1** (Study 2; Round 1)

Treatment	Compound 1			Compound 1 + carboplatin		
Route	IP			IP		
Dosage	200 mg/kg			200 mg/kg + 17.5 mg/kg		
AUTONOMIC	No. 1	No. 2	No. 3	No. 1	No. 2	No. 3
Skin Color	-	-	-	-	-	-
Respiration	D±	D+	D+	D+	D+	D+
Salivation F.V.	-	-	-	-	-	-
Lacrimation	-	-	-	-	-	-
Diarrhea	-	-	-	-	-	-
Body Temperature	↓+	↓+	↓+	↓+	↓+	↓+
Piloerection	-	-	-	-	-	-
Inc. Palpebral Size	-	-	-	-	-	-
Dec. Palpebral Size	-	-	-	-	±	-
Others	-	-	-	-	-	-
Death	-	-	-	-	-	-

Table 48. Behavioral and neurologic signs in mice for vehicles (Study 2; Round 1)

Treatment	Vehicle[a]			Vehicle[a]+Vehicle[b]		
Route	IP			IP		
Dosage	10 mL/kg			10 mL/kg + 10 mL/kg		
BEHAVIORAL	No. 1	No. 2	No. 3	No. 1	No. 2	No. 3
B.W. (g)	23	24	23	22	22	22
Irritability	-	-	-	-	-	-
Hyperactivity	-	-	-	-	-	-
Inc. Startle	-	-	-	-	-	-
Inc. Touch	-	-	-	-	-	-
Dec. Startle Response	-	-	-	-	-	-
Dec. Touch Response	-	-	-	-	-	-
Inc. Exploration	-	-	-	-	-	-

Dec. Exploration	-	-	-	-	-	-
Pinna	-	-	-	-	-	-
Placing	-	-	-	-	-	-
NEUROLOGIC						
Tremor	-	-	-	-	-	-
Dec. Spont. Activity	-	-	-	-	-	-
Straub Tail	-	-	-	-	-	-
Reactivity	-	-	-	-	-	-
Righting	-	-	-	-	-	-
Ataxia	-	-	-	-	-	-
Convulsion C.T.C-T	-	-	-	-	-	-
Low Limb Post	-	-	-	-	-	-
Abdominal Tone	-	-	±	±	±	±
Limb Tone	-	-	-	-	-	-
Grip Strength	-	-	-	-	-	-

Table 49. Autonomic signs in mice for vehicles (Study 2; Round 1)

Treatment	Vehicle[a]			Vehicle[a]+Vehicle[b]		
Route	IP			IP		
Dosage	10 mL/kg			10 mL/kg + 10 mL/kg		
AUTONOMIC	No. 1	No. 2	No. 3	No. 1	No. 2	No. 3
Skin Color	-	-	-	-	-	-
Respiration	-	-	-	-	-	-
Salivation F.V.	-	-	-	-	-	-
Lacrimation	-	-	-	-	-	-
Diarrhea	-	-	-	-	-	-
Body Temperature	-	-	-	-	-	-
Piloerection	-	-	-	-	-	-
Inc. Palpebral Size	-	-	-	-	-	-
Dec. Palpebral Size	-	-	-	-	-	-
Others	-	-	-	-	-	-
Death	-	-	-	-	-	-

Legend for **Tables 46** to **49**

[a] 20% Tween 20/ 80% PBS
[b] 0.9% NaCl
- : no effects
±: Slight to moderate effects
+: Severe effects
Inc.: Increased
Dec.: Decreased
Spont.: Spontaneous
C.: Chronic
T.: Tonic
C-T: Chronic-Tonic
↓: Low
D: Deep

In vivo anti-cancer activity: Compound 1 and gemcitabine

An *in vivo* study indicates that compound **1** is effective in combination with gemcitabine. The study design is detailed below and in **Table 50**. There is evidence for synergy from the study results results which are shown in **Table 51** and **Table 52**. Monotherapy and combinations were well tolerated.

Table 50. Tumor, Xenograft, Pancreas, MIA PaCa-2 in female nu/nu mice study design

	Test		**Conc.**	**Dosage**		**Mice[a]**
Group	Article	Route	mg/mL	mL/kg	mg/kg	(female)
1[#]	Vehicle[b]	IP	NA	10	NA qwk x 3[c]	8
2	Gemcitabine	IP	8	10	80 q4d x 4[d]	8
4	Compound **1**	IP	10	10	100 qwk x 3[c]	8
6	Compound **1** + Gemcitabine	IP + IP	10 + 8	10	100, qwk x 3[c] + 80, q4d x 4[d]	8

[#] Negative control group

[a] Female nu/nu mice aged 7-8 weeks are implanted with 1 x 10^7 MIA PaCa-2 cells (0.2 mL/mouse), and dosing is initiated when group mean tumor volumes reach ~80-150 mm^3.

[b] Test substance vehicle (10% Tween20 / 90% Saline)

[c] Doses are administered once weekly for 3 weeks.

[d] Doses are administered once every four days (four total administrations).

Body weight and tumor volumes are recorded twice weekly beginning on Day 1 and continuing until study completion.

Tumor growth inhibition (%TGI) is determined twice weekly during the dosing period by the formula: %TGI = (1 −[(T −T0)/(C −C0)]) × 100 where T = mean tumor volume of treated group, T0 = mean tumor volume of treated group at study start, C = mean tumor volume of control group and C0 = mean tumor volume of control group at study start.

Study is designed to continue for 28 days, or until the mean tumor volume within negative control group reaches 2000 mm^3, whichever comes first.

After TGI is determined, study may be converted to determine Tumor Growth Delay (TGD).

Animals are to be sacrificed if/when:
1. Body weight loss > 25%
2. Severe tumor ulceration

ESTIMATED TIMELINE

Animal Arrival: Within one month receiving test compounds

Tumor cells implantation: Within two weeks after animals are obtained

Dosing: Approximately 1-2 weeks after tumor cell implantation

SAMPLE REQUIREMENTS

Compound **1** 150 mg; Gemcitabine 256 mg.

PROTOCOL

Tumor, Xenograft, Pancreas, MIA PaCa-2

Procedure: Groups of (8) female nu/nu mice (7-8 weeks old), bred in an animal isolator (IVC racks) under specific pathogens free (SPF) condition at 22 plus or minus 2 °C are used. Viable human pancreatic carcinoma MIA PaCa-2 (ATCC CRL-1420) cells (1.0 x 107 in 0.2 mL) are injected subcutaneously into the right flank of experimental mice. When tumor volumes reach ~80-150 mm^3 (about 8-10 days post implant), the animals are randomly assigned into groups of eight, and test compounds and/or vehicle dose administrations are initiated (denoted as Day 1). Test compounds are administered as detailed in the "Study Design" section (**Table 50**). Tumor volumes and body weights are measured and recorded twice weekly over the course of the study period. Animals are monitored as a group. The endpoint of the experiment is a mean tumor volume in the negative control group of 2000 mm^3 or 28 days, whichever comes first.

Tumor volume (mm^3) is estimated according to the formula for a prolate ellipsoid: length (mm) x [width (mm)]2 x 0.5. Tumor growth inhibition (%TGI) will be determined twice weekly during the dosing period by the formula: %TGI = (1 −[(T −T0)/(C −C0)]) x 100 where T = mean tumor volume of treated group, T0 = mean tumor volume of treated group at study start, C = mean tumor volume of control group and C0 = mean tumor volume of control group at study start [Mohammed *et al.* 1998].

All aspects of this work including housing, experimentation, and animal disposal are performed in general accordance with the "Guide for the Care and Use of Laboratory Animals: Eighth Edition" (2011) in an AAALAC-accredited laboratory animal facility.

Table 51. Tumor volume change in a pancreas MIA PaCa-2 tumor xenograft model in response to treatment with compound **1** alone or in combination with Gemcitabine.

Assay Tumor Xenograft, Pancreas, MIA PaCa-2

WO#1060729 (AB67928) **Female nu/nu mice**

Gr.	Treatment	Dose (mg/kg) (Route)	No.	Tumor Volume (mm3)				
				Day1	Day4	Day8	Day11	Day15
1	Vehicle	NA (mg/kg) QWK x 3 IP	1	64	125	186	326	574
			2	74	65	87	128	151
			3	103	97	175	238	476
			4	122	111	142	179	422
			5	76	63	135	160	258
			6	90	79	81	96	171
			7	90	84	73	140	326
			8	103	125	180	315	629
			Mean	90	94	132	198	376
			SEM	7	9	17	31	63
2	Gemcitabine	80 mg/kg Q4D x 4 IP	1	65	65	114	165	213
			2	74	82	104	97	160
			3	104	128	151	215	419
			4	115	123	162	228	335
			5	76	73	75	103	130
			6	88	100	70	85	128
			7	91	58	70	94	115
			8	101	119	113	127	156
			Mean	89	94	107	139	207

			SEM	6	10	13	20	39
			% T/C	99	100	81	70	55
			% TGI	1	0	19	30	45
4	Compound 1	100 mg/kg QWK x 3 IP	1	67	56	126	368	600
			2	72	59	95	110	244
			3	104	105	125	192	276
			4	115	103	107	121	197
			5	81	129	187	266	414
			6	87	70	111	188	309
			7	93	92	177	251	409
			8	100	107	138	188	312
			Mean	90	90	133	211	345
			SEM	6	9	12	30	45
			% T/C	100	96	101	107	92
			% TGI	0	4	-1	-7	8
6	Compound 1 + Gemcitabine	100 mg/kg QWK x 3 IP + 80 mg/kg Q4D x 4 IP	1	69	46	48	57	80
			2	70	111	94	104	116
			3	108	86	101	97	103
			4	111	132	124	157	265
			5	84	68	71	35	95
			6	86	67	77	105	123
			7	96	55	28	25	23
			8	98	94	98	127	210
			Mean	90	82	80	88	127
			SEM	6	10	11	16	27
			% T/C	100	87	61	44	34
			% TGI	0	13	39	56	66

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Table 52. Body weight change in a pancreas MIA PaCa-2 tumor xenograft model in response to treatment with Compound 1 alone or in combination with Gemcitabine.

Assay # 581500 Tumor Xenograft, Pancreas, MIA PaCa-2

WO#1060729 (AB67928) **Female nu/nu mice**

Gr.	Treatment	Dose (mg/kg) (Route)	No.	Body Weight (g)				
				Day1	Day4	Day8	Day11	Day15
1	Vehicle	NA (mg/kg) QWK x 3 IP	1	28	27	27	27	26
			2	27	26	27	27	27
			3	25	24	25	26	27
			4	24	24	24	24	24
			5	26	25	25	25	25
			6	25	25	25	26	26
			7	25	23	23	24	24
			8	25	25	24	25	26
			Mean	25.6	24.9	25.0	25.5	25.6
			SEM	0.5	0.4	0.5	0.4	0.4
2	Gemcitabine	80 mg/kg Q4D x 4 IP	1	24	23	25	25	26
			2	30	28	30	31	31
			3	25	22	25	26	27
			4	26	25	27	27	27
			5	24	24	25	25	25
			6	25	24	25	25	25
			7	25	24	24	25	25
			8	26	25	25	25	25
			Mean	25.6	24.4	25.8	26.1	26.4
			SEM	0.7	0.6	0.7	0.7	0.7
4	Compound 1	100 mg/kg QWK x 3 IP	1	29	27	29	29	29
			2	26	24	26	25	25
			3	25	24	26	25	26
			4	25	23	25	25	24
			5	25	25	25	27	26
			6	23	23	23	25	23
			7	25	25	25	27	26
			8	26	26	26	27	26
			Mean	25.5	24.6	25.6	26.3	25.6
			SEM	0.6	0.5	0.6	0.5	0.6
6			1	25	24	24	24	24

			2	24	23	23	24	24
	Compound 1	100 mg/kg	3	27	27	26	26	26
		QWK x 3	4	27	25	26	26	26
	+	IP	5	23	22	23	23	23
	Gemcitabine	+	6	26	25	25	25	24
		80 mg/kg	7	27	26	26	26	26
		Q4D x 4	8	25	24	24	23	23
		IP	Mean	25.5	24.5	24.6	24.6	24.5
			SEM	0.5	0.6	0.5	0.5	0.5

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

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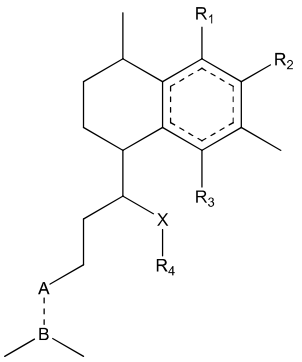
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Claims

1. A compound of Formula (**I**),



(**I**)

a geometric isomer, stereoisomer, pharmaceutically acceptable salt or solvate thereof, or a combination thereof,

wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC_{4\text{-}5}$alkadienyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl, $OC(O)C_{4\text{-}5}$alkadienyl or =O;

R_2 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC_{4\text{-}5}$alkadienyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl, $OC(O)C_{4\text{-}5}$alkadienyl or =O;

R_3 is independently H, OH, $OC_{1\text{-}5}$alkyl or $OC(O)C_{1\text{-}5}$alkyl or =O;

and no more than one of R_1, R_2 and R_3 is H;

where R_4 is OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC_{4\text{-}5}$alkadienyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl or $OC(O)C_{4\text{-}5}$alkadienyl; and

A---B is CH=C or CH_2-CH,

provided that where R_2 is H, X is not CH_2.

2. The compound according to claim 1, wherein:

X is CH_2, CHOH or C(O);

R_1 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl or =O;

R_2 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph, $OC(O)C_{2\text{-}5}$alkenyl or =O;

R_3 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
and no more than one of R_1, R_2 and R_3 is H;
where R_4 is OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC_{2\text{-}5}$alkenyl, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph or $OC(O)C_{2\text{-}5}$alkenyl; and
A---B is CH=C or CH_2-CH.

3. The compound according to claim 1, wherein:
X is CH_2, CHOH or C(O);
R_1 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph or =O;
R_2 is independently H, OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC(O)C_{1\text{-}5}$alkyl, OC(O)Ph or =O;
R_3 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
and no more than one of R_1, R_2 and R_3 is H;
where R_4 is OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC(O)C_{1\text{-}5}$alkyl or OC(O)Ph; and
A---B is CH=C or CH_2-CH.

4. The compound according to claim 1, wherein:
X is CH_2, CHOH or C(O);
R_1 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
R_2 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
R_3 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
and no more than one of R_1, R_2 and R_3 is H;
where R_4 is OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC(O)C_{1\text{-}5}$alkyl or OC(O)Ph; and
A---B is CH=C or CH_2-CH.

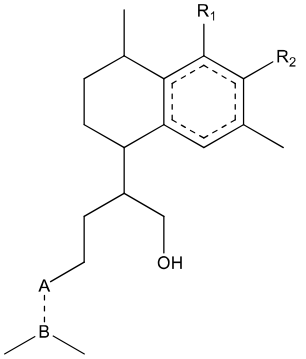
5. The compound according to claim 1, wherein:
X is CH_2;
R_1 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
R_2 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
R_3 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
and no more than one of R_1, R_2 and R_3 is H;
R_4 is OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC(O)C_{1\text{-}5}$alkyl or OC(O)Ph; and

A---B is CH=C or CH_2-CH.

6. The compound according to claim 1, wherein:
X is CHOH;
R_1 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
R_2 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
R_3 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
and no more than one of R_1, R_2 and R_3 is H;
R_4 is OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC(O)C_{1\text{-}5}$alkyl or OC(O)Ph; and
A---B is CH=C or CH_2-CH.

7. The compound according to claim 1, wherein:
X is C(O);
R_1 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
R_2 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
R_3 is independently H, OH, $OC_{1\text{-}5}$alkyl, $OC(O)C_{1\text{-}5}$alkyl or =O;
and no more than one of R_1, R_2 and R_3 is H;
R_4 is OH, $OC_{1\text{-}5}$alkyl, OCH_2Ph, $OC(O)C_{1\text{-}5}$alkyl or OC(O)Ph; and
A---B is CH=C or CH_2-CH.

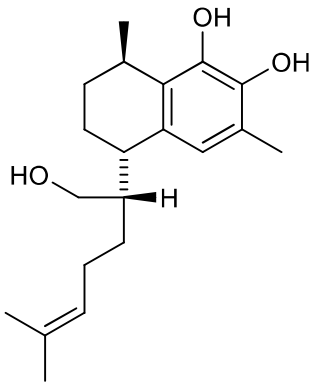
8. The compound according to claim 1, wherein the compound is a compound of Formula (**Ic**):



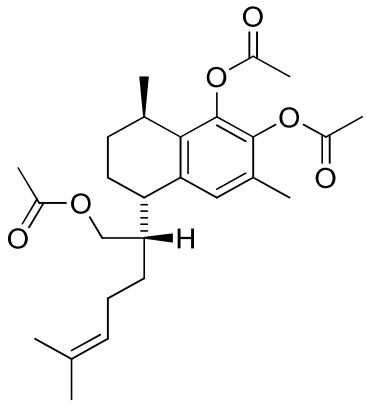
(**Ic**).

9. The compound according to claim 1, wherein A---B is CH=C.

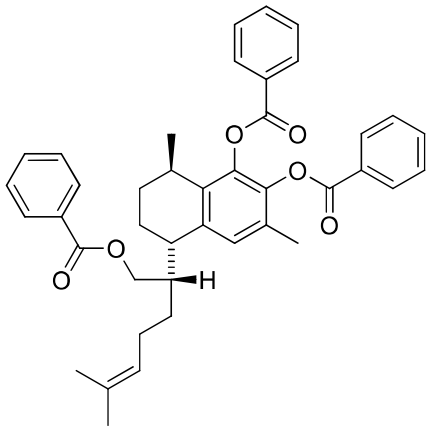
10. The compound according to claim 1, wherein the compound is selected from the group consisting of:



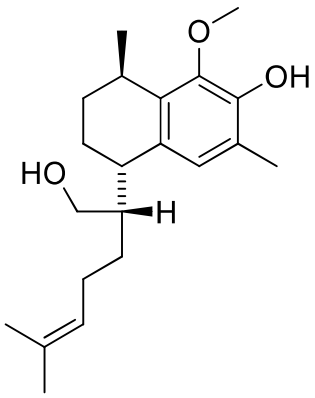
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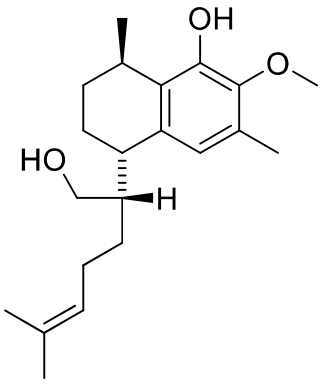
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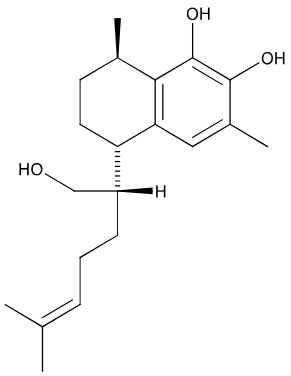


, and



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11 The compound according to claim 1, wherein the compound is:



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12. A pharmaceutical composition comprising the compound, geometric isomer, stereoisomer, pharmaceutically acceptable salt thereof, or a mixture thereof according to claim 1 and a pharmaceutically acceptable excipient.