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CORSO DI DOTTORATO IN SCIENZE FARMACEUTICHE, ALIMENTARI E COSMETOLOGICHE (XXXII ciclo)

Isolation, structural elucidation and evaluation of bioactivity of secondary metabolites from aromatic plants

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List of contents

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Aim of the thesis

Objective of my research project is to identify and isolate new bioactive terpenoids from aromatic plants grown in Liguria (Italy). The main line of research in our laboratories is the study of the antimicrobial activity of extracts and compounds isolated from *Salvia* species. The aim is to isolate and identify possible promising compounds for future biological applications. The research activity was mainly carried out at the Department of Pharmacy, University of Genoa, Laboratory of Phytochemistry.

This thesis reports the work during my three - years of doctorate. The surface extract of the aerial parts, the methanolic extract of the roots of *S. tingitana* and the methanolic extract of the roots of *Salvia corrugata* were investigated. Further purification of fractions will be carried out as well as structural elucidation of the isolated compounds.

Summary

Plants have always been in existence for thousands of years because they formed the basis of sophisticated traditional medicine systems and continue to provide mankind with new remedies [1]. Some, may not comprehend the scientific reason behind the medicines but personal experience has shown them the highly effective use of plant in therapeutic doses. Countries like China and India together with other traditional medicine systems have also been documented; and continued to do so as estimated by the World Health Organization [2]. In the past, natural products were used as therapeutic products and for long time were the main source of drugs. Infact there is a growing interesting in alternative therapies and the therapeutic use of the products. There are many examples of these natural plants and their therapeutic resources demonstrated by Rates in 2001, Rios in 2005 and others [3]; [4]. In my thesis I have mainly dealt with plants coming from the genus *Salvia.* Sage ora *Salvia* is widely appreciated for its great beauty in horticultural trade; its 900 species of variations found in different parts of the world and the noitable translation from Latin which means "to save", still confirms its essential use both in traditional medicine and in culinary purposes. While our laboratory was investigating the methanolic extract of roots of *Salvia corrugata* for the first time, we isolated some quinone diterpenes. In order to gather complete information about the distribution of these compounds within *Salvia* species, we performed a literature investigation. We also included a classification of how sage changed in time beginning with morphology parameters followed by geographic distribution as far as the most recent molecular phylogenetic studies.

Regarding the phytochemistry of *Salvia*, plants produce an array of primary and secondary metabolites [5]. In the past the latter were seen as waste products as a results of "errous" of primary metabolism but it has became clear that many secondary products are the essential key components of active and potent defence mechanisms [6]. The three main categories of plants secondary metabolites are: terpenes/terpenoids, alkaloids and phenolic acids [7]. The most aboundant and structurally diverse groups of plants secondary metabolites are terpenoids [8]. Terpenoids contain an whole number of 5 carbon units (isoprene) forming the sequential combination of these basic 5C units, from which we can obtain the categories of: C_{10} (mono-), C_{15} (sesqui-), C_{20} (di-), C_{25} (sester-), C_{30} (tri-), C_{40} (tetra-terpenoids). Throughout history the use of terpenoids as treatment for various kinds of diseases can be seen because different terpenoid molecules have various health benefitial properties [9]. Note that *Salvia* species produce terpenoids such as triterpenes, diterpenes and monoterpenes.

The two species considered in my thesis are: *Salvia tingitana* Etl. and *Salvia corrugata* Vahl. *Salvia tingitana* Etl. is an aromatic multi-stemmed perennial shrub, till 100 cm, with eglandular and glandular indumentum, with white flowers showing a cream-yellow lower lip [10]; [11]. The species has a long and enigmatic history. The chemical separation of the extract of the aerial parts of *S. tingitana* afforded one nor-sesterterpene (**1**), eight new sesterterpenes (**2**-**9**) and five known sesterterpenes, together with other known compounds that include five labdane and one abietane diterpene, one sesquiterpene and four flavonoids. The new compounds were identified by NMR spectroscopy, including TOCSY, COSY, HSQC, HMBC and ROESY experiments, HRESIMS, and ECD and VCD analysis. The antimicrobial activity of compounds was evaluated against thirty human pathogens. The

compounds were also tested for the inhibition of the ATP production in the purified mammalian rod outer segments. Molecular docking was also performed. Finally, the ATP production in the presence and absence of manool (**17**) by *Enterococcus faecalis* MB1 (VRE) and *E. faecium* MB 152 (VRE) was assessed in whole-cell assay.

The methanolic extract of the roots of *S. tingitana*, was also investigated. The methanolic extract was tested for the antimicrobial activity against different Gram positive clinical isolates which include multiresistant strains of *Staphylococcus aureus*, *S. epidermidis*, *E. faecium*, *E. faecalis* and *Micrococcus luteus* showed MIC values ranging from 8 to 32 μg/mL. The methanolic extract was subsequently purified by silica gel column chromatography, giving 11 semi purified fractions, that were tested against different other Gram positive multi-resistant clinical bacterial strains, also of marine origin. All fractions were active against the tested strains showing MIC values ranging from 2 to 64 μg/mL, with the exception of fraction 1 and fraction 11. Fraction IIIc was the most active, which displayed MIC values ranging from 2 to 8 μg/mL against both Staphylococci and Enterococci. Fraction IIIc was then purified, by semi-preparative RP-HPLC, giving compounds Hypargenin C, Royleanone and 7-*O*-Methylhorminone, identified by IR, 1D and 2D NMR, ESI-MS and HR-MS analysis. Hypargenin C, which was isolated in suitable amounts, exhibited MIC values ranging from 2 to 8 μg/mL against the same Gram positive isolates.

Salvia corrugata Vahl. is an American species and it is grown near the Mediterranean coastal area as an ornamental plant. The methanolic extract of the roots and the twelve semi-purified fractions purified by silica gel column chromatography were tested against different multidrug resistant clinical strains also of marine origin, showing MIC values which go from 4 to >128 μg/mL. 7-*O*-methylhorminone, Horminone and 7-*O*-acetylhorminone were isolated. Horminone and 7-*O*-acetylhorminone, obtained in adaptable quantities, displayed MIC values ranging from 4 to 64 μg/mL against the same bacterial strains.

1 Use of herb since antiquity to date

Plants are an essential source of medicine which play a key role in our World Health. Medicinal herbs or plants have been known to be a very potential source of therapeutics or curative fields. The use of medicinal plants has attained a decisive role in the health system all over the world. [1]. Domestic medicine consisted largely in the use of vegetable products, or herbs which are still used today. Herbal remedies cured common colds and constipation. However, grave and disabling diseases, were put into different categories because they derived from supernatural origin. Magic and religion played an important role in the medicine of early human study. An example of such an irrational conception is the *Doctrine of Signatures*, elements of which are found in various healing cultures of the world. The *Doctrine of Signatures* is based on the assumption that the appearance of plants could give clues to their medicinal properties—it is seen as God's signature on the plant. [1]. Some, may not comprehend the scientific reason behind the medicines but they know from personal experience that some medicinal plants can be highly effective, if used at therapeutic doses [1].

The first traces of the use of Medicinal plants date back to 4000 B.C. Since then Western civilisation already knew about the use of curative plants also known today as opium, thyme and liquorice, senna, coriander, saffron, cinnamon and garlic [12] have been documented as far back as Babylon in old engravings in rocks. The Egyptian culture has given us a great number of documents of their knowledge for medicinal purposes. The best known, dating back to 3000 B.C, Ebers Papyrus takes its name from the German Egyptologist Georg Ebers. The documents showed at least 800 recipes and approximately 700 medicinal plants, both local and foreign origin. Among the examples mentioned are also aloe, absinth, peppermint, colocynth, cannabis and others [12].

Vegetable drugs from indigenous plants like cardamom, cinnamon that appeared in Western Pharmacopoeias come from India, while the Chinese Materia medica has always been extensive and also consists of famous herbs from ancient times. Among the drugs taken over by western medicine from the Chinese are Rhubarb, castor oil, kaolin, aconise and cannabis sativa. *Ephedra Vulgaris* has been utilized in China for at least 4000 years and the isolation of its alkaloid ephedrine has very much helped the Western cure of asma and other close states. Ginseng has shown its diuretic properties, while reserpine, which is the active principle of the Chinese plant *Rauwolfia*, has been used in the treatment of hypertension. There again, the Greek Roman period in Europe, has also left scripts dealing with medicinal plants used for treatment of illnesses. Hippocrates is often called "*The Father of the medicinal art*" [12] because of the many references which described the plants he used. His successors like Theophrastus wrote "*Historia plantarum*" again describing their use as medicinal plants, followed by Plinius the elder, who wrote "*Historia naturalis*". This document was used as a reference source for several centuries dealing with medicine, plants and their products. The best known medical period from the Roman period was Pedanius Dioscorides who wrote "*De Materia Medica*" describing 600 medicinal plants. This document called Pharmacopeias was considered to be the precursor of later documents on medicinal plants (see Indian medicine). Dioscorides used extracts from mandragora to induce anesthesia [12] under surgery. Persons were not left unconscious but had a feeling of not being present. Claudius Aelius Galenus theories dominated Western medical science for well over a millenum. The Roman physician and philosopher was one of the early ones to prepare medicines in dosage forms and explained the process of coating on pills. Once again his

documentations on 130 medicinal plants and recipes led the way into Pharmaceutical sciences of today known as Galenical pharmacy.
During the Middle Ages medicine passed from the Christian church and Arab Scholars. The most important contribution of Arabian medicine was in chemistry and in the acquisition of knowledge in the preparation of medicine. At that time the chemists were alchemists but during their experiments, various substances were named and identified and some were found to have great medicinal use. Arab pharmacies spread and were government supervised. They also developed a system of dosage for medications using mathematics. Avicenna, a famous philosopher and physician, is best known for his report "*Canon Avicenna*" (*Canon of medicine*) which carefully described the understanding of medicine and pharmacology of that time. Pharmacies were created where remedies like camphor, mastix, rhubarb, saffron and aloe were also sold. Description of the production of juices, tintures, extracts of herbs, pills with coatings and distillation of alcohol are also found in the *Canon of medicine*. Avecenna also recognized other factors like proper diet, climate changes and environment on our health.
The Monastery period was very important for the health care system. The Salernoschool wrote about the importance of sanitary sanitation in documents like "*Regime sanitates Salernitanum*". Most plants were used for health benefits and the Monastery gardens that spread all over Europe were introduced by Ansegis, requested by "Charles the great". Ansegis was the origin of the text "*Capitulare de villis*" which included rules on how to live and grow medicinal plants in the monasteries. His work was such a great success that he was canonized as Saint Ansegisus. Later the great reformer Paracelsus Phillipus Aurelius Theophrastus Paracelsus Bombastus von Hohenheim, better known as Paracelsus [12] was the very first to carry out clinical trials in order to test the effect of the products, which he used as a doctor before actually applying them on his patients. He was the founder of clinical studies and his definition of what could be a poison is still valid: "*Everything is poison; it is just the concentration that will decide if something is nontoxic*."
The invention of the letter press by Johanes Gutenberg led to a resurrection of the Greek-Roman knowledge in the 15th and 16th century, and also to the compilation of several herbal books that were distributed widely in Europe, thus contributing to a spread of knowledge. Two influential examples are the "*Mainz Herbal*" Herbarius Moguntius (1484) and the "*Germen Herbal*" (1485).
The "Scientific period" started after Paracelsus. Modern science started around 1600 till present. One of the names to be remembered forever is Carl von Linnè who underlined the importance of giving a specific identification and systematization to all living species. He introduced plant systematics that contained rules on the determination of characteristics of the plant and later utilized these characteristics to categorized plants into a system which simplified their identification. "*The system of Linnè*" still carry his name. Today, gene classification is used.
Another Swedish scientist and pharmacist, Carl Wilhelm Scheele is best known for the discovery of oxygen and nitrogen which became an important basis for modern chemistry. Two important German chemists are: Friedrich Wohler who is best known for being the first to synthetize urea and to isolate several chemical elements; Paul Ehrlich who worked on hermatology in autoimmunity that he called "horror autotoxicus".
In 1923 Sir Alexander Fleming, a Scottish biologist, first discovered the enzyme lysozyme, but he is best known for the re- discovery of penicillin from the fungus *Penicillinum notatum in* 1928, for which he received the Nobel Price [12]. The result led to a radical change in the

treatment of diseases, caused by bacteria and has saved a large number of deaths worldwide.

In my thesis I have mainly dealt with plants coming from the genus *Salvia*.

2 Genus *Salvia*

For a long time *Salvia*, or Sage, has been used in traditional medicine as well as for culinary purposes. The ethymology of the word Sage derives from the Latin verb "salvare" (to heal/to save), and the Latin proverb "*Cur moriatur homo, cui Salvia crescit in horto*?" (*Why should a man die who has sage in his garden*?) has confirms its use for centuries [13]. In English there is a corresponding proverb: "*He that would live for aye, Must eat Sage in May*". The word was popularly altered by the French to Sauja and Sauge coming from Old English, "Sawge", which is used in the present day name of Sage [14]. In the middle of the 7th century, Linneo, a Swedish biologist and naturalist, gave the specific epithet *officinalis* to this plant. In the 11th and 12th centuries, the Salerno Medical School, considered Sage as the best miraculous herb and therefore named it *Salvia salvatrix*.
In traditional medicine, *Salvia* species have been adopted to treat colds, bronchitis, tuberculosis, haemorrhage and menstrual disorders [15]. The plants are typically 30-150 cm tall, herbaceous or suffruticose, and perennial, seldom biennial, or annual, with flowers in different shades of colors [16].

2.1 Taxonomy history

Various attempts to classify *Salvia* were carried out in the19th century introducing different subgenera and sections [17].
In 1777 Etlinger published the first botanical monograph of *Salvia* recognizing 48 species. Later, Bentham formed the first infrageneric grouping on *Salvia* in the *Labiatarum* (1832-1836) [18], which was based on calyx, corolla and stamen morphology [19], and gave the last world-wide revision of the genus, and put the then known 266 species into [19] 14 sections. The genus is characterized by modified lever-like stamens which play the main role in the process of pollen transfer. Because of this unusual structure, the genus as a whole has long been thought as monophyletic. In the second study (De Candolle's *Prodromus* 1848), Bentham [20] classified 406 *Salvia* species into 12 sections [19]. In a third study (1876), he added *Salvia* into the tribe *Monardeae*, along with *Perovskia* Karel, *Dorystaechas* Boiss et. Heldr., *Meriandra* Benth., *Salviastrum* Scheele, *Audibertia*, *Rosmarinus* L., *Monarda* L., *Blephilia* Raf., and *Ziziphora* L. In order to further classify the 12 sections, he established four subgenera, *Salvia*, *Sclarea*, *Calosphace* and *Leonia*, based on the geographical distribution and morphology of the calyx, corolla and stamens. This classification is still used today [17]. Modifications on Bentham's 1876 subgeneric arrangement have been modified by Briquet, (1895-1897), Stibal (1934) and Pobedimova, (1954). The latter assigned *Salvia* spp. which was distributed in the former USSR to seven subgenera and eight sections [21]. In 1873 Bunge revised the sections accepted by Bentham in 1848, in particular the Southwest Asian ones [17]. In the *Flora Orientalis* (Boissier, 1875), the Turkish *Salvia* species were placed into 7 sections, all of which were previously recognized by Bentham (1833), that is the sections *Salvia* (syn. *Eusphace*), *Hymenosphace*, *Horminum*, *Aethiopis*, *Drymosphace*, *Plethiosphace*, and *Hemisphace*. In 1972 Hedge changed sect. *Eusphace* to sect. *Salvia* [22]. However in 1895 Briquet in the *Pflanzenfamilien* did give a more recent review without a monographic treatment [11]. Approximately 500 *Salvia* species in 17 sections and eight subgenera were arranged by him and *Salviastrum*, *Polakia* Stapf and *Ramona* Greene (=*Audibertia* Benth. *sensu* Boissier, 1879) were considered as genera distinct from, but associated to *Salvi*a. These genera were put into in the tribe *Salvieae* [17]. Epling (1938-1939) updated subgenus *Calosphace* and recognized about 470 species, all of which are found in the New World,

mainly in Central and South America. Stibal also updated the Chinese (1934) and Indian (1936) species. Hruby´ (1962) proposed the upgrading of some subsections to the genus level which was also proposed by Rafinesque (1837) more than one century earlier [17].
Hedge starts talking about "species-groups", so he revised the Europan and African species and prepared the Turkish and Iranian *Salvia* accounts [23]. When treating SW Asian *Salvia* Hedge concentrated on N African/SW Asian disjunctions and talked about their relationships [17]. Hedge (1974) believed that previous classifications were insufficient and therefore he suggested a worldwide research to clarify the subgeneric and sectional delimitation in the genus. The first revision of *Salvia* L in Turkey was revised by Hedge in *Flora of Turkey* in 1982 [24]. 'Species groups' were not explicitly named but rather indicated by horizontal dots [17]. The results of the studies carried out by Hedge's view of 'species groups' gave a better understanding of relation in Old World *Salvia*, as well as providing a more up-to-date infrageneric classification for the corresponding local floras [17].

2.2 Molecular phylogenetic studies

Recent phylogenetic studies confirm that *Salvia* is polyphyletic with four distinct clades (Clade I-IV), of which five added genera (*Dorystaechas, Meriandra, Perovskia, Rosmarinus e Zhumeria*). There are two phylogenetic and taxonomical valid proposals on how to treat the paraphyly: one is either by including the five above mention genera in the *Salvia* genera, in the broad sense and dealing with the five genera as subgenera itself; or by subdividing the species in six genera. Several coding and non-coding regions have been proposed for use as DNA barcodes in plants. These include rbcL, matK, psbA-trnH, and ribosomal intergenic spacer regions (ITS) [25]. According to the results of molecular studies presented by Walker et al. 2004, based on chloroplast rbcL and trnL-F sequences, three clades were identified (Clade I-III): *Salvia* clade I— largely Old World but with one New World lineage; *Salvia* clade II—New World lineage comprising subg. *Calosphace* and sect. *Audibertia*; and *Salvia* clade III—an independent Asian lineage. Following up, Walker et al. 2007, thanks to a slight increase of samples, individualized the genera *Zhumeria* in a different position and so renamed *Salvia* "Clade III". However, in 2014 according to Will and Claßen-Bockhoff *Salvia* "Clade III" was indicated as two independent clades: Clade III (specie *Salvia* asiatica SW e *Zhumeria*) and Clade IV (E Asian *Salvia*) [26].
Regarding relative studies on the *Salvia* origin from China: Takano and Okada in 2011 did phylogenical analysis on 11 species of Japanese *Salvia* stating that they are monophyletic and they discovered that the species were distributed into three subclasses: 1) *S. plebeia* (subg. *Sclarea*), (2) subg. *Salvia* and (3) subg. *Allagospadonopsis* [27]. In the phylogenetic analysis carried out by Li et al. 2013, the Chinese and Japanese species of *Salvia* (except *S. deserta*) clearly formed a separate clade. The classification suggested by Li et al. 2013 foresaw three subclades in the Chinese clade: (i) subg. *Allagospadonopsis* and sect. *Drymosphace*; (ii) sect. *Notiosphace* and the sister species *S. trijuga* (sect. *Drymosphace*) and *S. pauciflora* (sect. E*urysphace*); and (iii) sect. *Eurysphace*. The first subclade contained two principal groups: (i) sect. *Drymosphace* and (ii) subg. *Allagospadonopsis* plus several individuals from sect. *Drymosphace*, and *S. yunnanensis* (sect. *Drymosphace*) were its sister group. Moreover, all species introduced from America were in Clade II, and all species from Europe were in Clade I [28]. Samples of representative taxa of 73 sections of *Calosphaceae* were used to investigate and identify the phylogenetic relationships and principal lineages using chloroplast (intergenic spacer psbA-trnH) and nuclear ribosomal DNA (internal transcribed spacer). Phylogenetic analysis of the combined data sets determined monophyly

of seven sections (*Blakea, Corrugatae, Erythrostachys, Hastatae, Incarnatae, Microsphace, and Sigmoideae*) and four principal lineages (*S. axillaris, ''Hastatae* clade'', ''*Uliginosae* clade'', and ''*core Calosphace*'') [29]. Moreover, Jenks and collegues claimed that Epling's infra-subgeneric sections were not supported as monophyletic in their results because many of Epling's sections were distinct being made up of species from multiple centers of diversity. In most cases sections along regional/geographical lines were polyphyletic when sampled, comprising eleven disjunct sections. In their results *Tomentellae* and *Ulginosae* were paraphyletic. Will et al. (2015) maintained that the five genera (*Dorystaechas, Meriandra, Perovskia, Rosmarinus e Zhumeria*) incorporated in *Salvia* should be kept as distinct genera and that *Salvia* should be subdivided into smaller and easier to handle groups. This course of action would leave only the clade (ca. 250 species; Walker & Sytsma, 2007) containing the type of *Salvia* (*Salvia officinalis* L.) as the taxa bearing the *Salvia* name (assuming no new genera are proposed within the "*Salvia officinalis*" clade) [26]. Will e Claßen-Bockhoff (2017) then proposed dividing *Salvia* into 6 genera: *Salvia* sensu stricto (*s.s*.). *Lasemia, Ramona, Glutinaria, Pleudia e Polakia*, based on ITS data (internal transcribed spacer), from 220 *Salvia* species. 86 of these were sequenced for the first time. The sequences were combined with the accessions available from GenBank [17]. The 4 main clades identified by Will and Claßen-Bockhoff (2017) thanks to ITS data were (Clade I–IV): (1) Clade I (*Salvia s.s.*), (2) Clade II (most NW *Salvia* + *Dorystaechas* + *Meriandra*), (3) Clade III (SW Asian *Salvia* with *Zhumeria*) and IV (E Asian *Salvia*). Within Clade I, four principal lineages were identified: (1) subclade I-B, (2) subclade I-A, (3) *S. taraxacifolia*, the *S. verticillata* group, subclade I-C, and *S. leriifolia* as one weakly supported clade, and (4) subclade I-D [17]. The taxonomical treatment suggested by Will e Claßen-Bockhoff (2017) had meant that approximately 750 species of *Salvia* would have been transferred to the resuscitated genera *Glutinaria, Lasemia, Ramona, Pleudia* and *Polakia,* which would lead to ongoing taxonomic confusion because the boundaries between the genera are not morphologically distinct. Moreover, it was found that some ITS sequences utilized in Will and Claßen-Bockhoff (2017) were debatable, which could have come from species misindentified and/or GenBank uploading mistakes [19].

Broadly speaking about the concept of *Salvia*, Drew et al. 2017 considered the five genera to be as subgenera as *Salvia* embedded itself, according to phylogenetic, practical and taxonomical considerations. From recent classification by Hu et al. 2018 it would be better to keep a broad definition of *Salvia* as suggested by Drew et al. 2107. In 2018, Hu supported the idea of a broader definition of *Salvia* and he treats EA *Salvia* as subgenera, *Glutinaria*, identifying eight sections found inside the subgenera. All of these eight sections should all have the same taxonomic weight. Supporting the philosophy of Will and Claßen-Bockhoff (2017), EA *Salvia* should be handled as either eight genera or eight sections of a single genus. Considering EA *Salvia* as eight separate genera would be confusing; moreover, it seems unsustainable to consider EA *Salvia* as a single genus because Hu et al. were unable to discover any individual morphological feature that distinguishes EA *Salvia* from *Salvia* in the other centres of diversity [19]. So Hu et al. considered *Salvia* clade as a subgenus, including eight sections reported here below (**Fig. 1**):

Fig. 1 [19]

Salvia							
Subgenus : **Glutinaria**							
Section: **Sonchifoliae** (G1)	Section: **Notiosphace** (G2)	Section: **Substoloniferae** (G3)	Section: **Glutinaria** (G4)	Section: **Annuae** (G5)	Section: **Eurysphace** (G6)	Section: **Drymosphace** (G7)	Section: **Sobiso** (G8)

2.3 Name of plants and their importance – Do they really matter?

The initial idea of our work was to study the quinone *ortho* and *para* diterpenes from a chemical point of view because of their phytochemical and pharmacological properties. However, during the study we realized that different classification of sage weren't exactly as they should have been. Consequentely, this led to a correction of nomenclatural names and taxonomical classifications. In order to gather complete information about the distribution of these compounds within *Salvia* species, we performed a literature investigation, and we recently published the results as a review.
The species considered in our review, according to the findings of the phylogenetic studies [30], [31]; [32], [17], [26] and regarding taxonomic treatment suggested by Drew and colleagues in 2017 and Hu and colleagues in 2018, belonged to subgenera *Calosphace* (Benth.) Benth., *Audibertia* J.B.Walker, B.T.Drew, & K.J.Sytsma, *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew and to two other lineages tentatively named as "*Salvia officinalis clade*" "*Salvia aegyptiaca clade*" (**Table 1** Appendix) [33].

2.4 Geografical distribution

The genus *Salvia* is largely distributed in different countries including those where temperatures are milder and warmer like the Mediterranean, Central Asia, the Pacific Islands, tropical Africa, and America. The genus *Salvia* has a subcosmopolitan distribution, which is widely absent in the North and the majority of the low-lying tropical areas of the world for example the Amazon basin and central and west Africa. About 90 *Salvia* species are present in Turkey and half of them are endemic. Sixty species in Iran out of which 17 are endemic. Africa grows the largest amount of species, found in the northwest and the southern parts. Whereas there is no genus has been reported for western and central tropical Africa [34]. In Mexico, there are approximately 300 species of *Salvia*, of which 85–88% are endemic [35]. The plants are typically 30-150 cm tall, herbaceous or suffruticose, and perennial, seldom biennial, or annual, with flowers of different colors [16].
The 130 species of *Salvia* considered in our work have distributed extensively in three regions of the world: 65 species come from central Asia/Mediterranean, 41 from eastern Asia, but only 24 from Central and South America. The division of the species displayed overlapping phytogeographic ranges reflecting the principal areas of the biodiversity of the genus [33].

3 Phytochemistry of *Salvia* L.: secondary metabolites (SM)

Salvia L. species produced an array of secondary metabolites [36]. Unlike the past, secondary metabolites are considered to be a key components of active and potent defence mechanism [6] and are essential and necessary for the plant to ward off pathogens [37].
We can classify plant natural products into three main groups, on the basis of their biosynthetic origins: the terpenoids, the alkaloids, and the phenylpropanoids and allied phenolic compounds [38]. The largest group of natural compounds are Terpenoids, also known as terpenes [39]. All terpenoids can be built using the C_5 isoprene unit, even though structurally they have a very large diversity [40]. Terpenoids are classified into hemiterpenoids (C_5), monoterpenoids (C_{10}), sesquiterpenoids (C_{15}), diterpenoids (C_{20}), sesterterpenoids (C_{25}), triterpenoids (C_{30}), tetraterpenoids (C_{40}, carotenoids), and polyterpenoids (C_{5n}) based on the number of carbon atoms [41].
The main secondary metabolites of *Salvia* species are flavonoids and terpenoids. The aerial parts of *Salvia* species usually produce flavonoids and triterpenoids, whereas in the roots, the principal compounds are diterpenoids. Both sesquiterpenoids and sesterterpenoids are quite rare in *Salvia* species [42].

4 Biological activities considered in this thesis

4.1 The impact of antimicrobial resistance

The discovery of antibiotics is one of the key achievements of modern medicine [43]. The formal discovery of antibiotics occurred in 1928 [44], when Fleming discovered penicillin. He observed that some bacteria were inherently sensitive and others inherently resistant. There were already early warning signs of what was to come. In 1942, René Dubos foresaw bacterial resistance. "*Rather than counter bacterial resistance with even more potent weapons*", he concluded that we should, "*seek instead more peaceful coexistence with pathogens*" [45]. The Nobel Prize was awarded to Fleming in 1945. He observed that initially sensitive bacteria could develop resistance, especially if exposed to low doses, and warned that if penicillin were to become cheap and easily available, 'negligent' use, might encourage resistance and failure of therapy [46]. In the early 1950s resistance to penicillin emerged not long after its introduction and therefore, related to patient deaths [44]. Antibiotics do not target human biochemical processes but those of another life form: bacteria. Bacteria can evolve and adadapt to their environment, thus developing several protective mechanisms so as to reduce their susceptibility to antibiotics ('antibiotic resistance') [43]. The antibiotic resistance becomes more serious when microorganisms, develop resistance not only to a single antimicrobial agent, but also to several antimicrobials or chemical classes available in the market. These microorganisms are often referred as multidrug-resistant (MDR) [47]. The important spread of antibiotic resistance determinants among commensal, environmental and pathogenic bacteria has attained global dimensions [48]. Bacteria evolve not only by mutation, but also by allowing for horizontal gene transfer (HGT) within and between species [43]. Intrinsic and acquired bacterial mechanisms of resistance are both characterized by an irreversible phenotype. Note that these mechanisms are not influenced neither by antibiotics nor environment; certainly, the response of bacteria to signs such as the presence of antibiotics, especially at sub-inhibitory concentrations, or environmental conditions like

pH, anaerobiosis, cation level, is the the formation of biofilm [49]. Biofilms are structured microbial communities of surface-attached cells embedded in a self-produced matrix of extracellular polymeric substances (EPS) composed of proteins, lipids, nucleic acids, polysaccharides, and other components [47]. While bacteria are in the biofilm state, they are definitely more resistant to external attack, including antibiotics [50]. Bacteria embedded in biofilms experiment numerous changes in gene regulation that lead biofilm cells to become phenotypically and metabolically different from their planktonic counterparts [47]. Numerous nosocomial infections like those concerning the use of central venous catheters, urinary ones, prosthetic heart valves, and orthopaedic devices are notely associated with biofilms that adhere to the biomaterial surface [51]. Biofilm formation is present in 5 distinct stages for most species. Their definition is a combination of genetic and phenotype change. All species of bacteria have specific sets of environmental indication which will initiate biofilm [50]. The resistance problem is proved by the increase in the growing MIC values of the isolated microorganisms. At present, MIC values in patients can be of 16 g/mL and MICs of >128 g/mL, sporadically occur [49]. An attempt of traditional means to locally control or slow down the progress of antibiotic resistance in patients, based on a better antibiotic prescribing policies, are not up to global standards [48]. As a result, more recent pathogens with multidrug-resistance profiles like *Acinetobacter baumannii* have become apparent, such as “old” pathogens as *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae* which presently are now resistant to frontline antibiotics [52]. Transmission of antibiotic-resistant bacteria in hospitals (and more generally in society) is facilitated by overcrowding and poor hygiene. Hospitals and other healthcare facilities are usually associated with antibiotic resistance [43]. Hospital pathogens tend to be the most resistant. This tends to favour firstly the emergence within hospitals of free-living opportunistic pathogens that are relatively antibiotic resistant, probably because of their exposure to natural antibiotics in the environment. Secondly, inherently sensitive organisms begin to acquire new, usually highlevel, resistance mechanisms [46]. The principal mechanisms of bacterial resistance to antimicrobials include drug inactivation, target modification, alteration in the accessibility to the target through drug efflux and decreased uptake, as well as over-expression of the drug target. The requirement of the new genetic programming by the cell in response to the presence of antibiotics is needed by all of these mechanisms [52]. The majority of the existing antibacterial leads have been derived from natural sources, which continue to be important for new lead discovery [53]. Therefore, it is possible to say that the antibiotic resistance is a phenomenon that has always existed, even before their use as treatment of infective diseases and agriculture or livestock. As of matter of fact, antibiotics are present everywhere in nature, for example micro-organisms and plants produce antimicrobials as secondary metabolites [49]. The plant kingdom is considered to be a source of new chemical compounds, which could be essential owing to their potentiality in medicine for the development of novel therapeutic agents. Several plant compounds have been considered as antibacterials and may be compared to antibiotics [52]. Unlike synthetic molecules, phytochemical products display an unmatched structural diversity with complex and novel multilayer mechanisms of action [47]. Phytochemicals are structurally distinct from micro-organism, derived from antibiotics and have different modes of action. Concerning the plant chemical ecology, plants produce antibacterial secondary

metabolites as part of their chemical defense strategy to preserve themselves against microbes in their environment. The accumulation of low-molecular-weight compounds that work as phytoalexins is a well known defence mechanism [54]. Various species of *Salvia* have been described as interesting sources of such bioactive compounds [54]; [55]. Useful phytochemicals with antimicrobial activity can be divided into several classes that include: phenolics and polyphenolics, terpenoids, alkaloids, lectins and peptides, and polyacetylenes. The principal subclasses are: simple phenols and phenolic acids, quinones, flavonoids, coumarins, tannins, terpenoids, alkaloids, lectins and polyketides, isothiocyanates, polyamines, sulfides, thiosulfinates, glycosides, phenanthrenes and stilbenes, and many others [47]. It is possible to categorize antimicrobial agents based on their main mechanisms of action. These mechanisms comprise: interference with cell wall synthesis (e.g., β-lactams and glycopeptide agents), inhibition of protein synthesis (macrolides and tetracyclines), interference with nucleic acid synthesis (fluoroquinolones and rifampin), inhibition of a metabolic pathway (trimethoprim-sulfamethoxazole), and disruption of bacterial membrane structure (polymyxins and daptomycin) [56]. Moreover, antibiotics have been classified on the basis of their chemical structure and how they kill bacteria or inhibit their growth [49].
Urgent strategies are necessary to confront the processes influencing antibiotic resistance pollution in the microbiosphere [48].

4.2 Effect on ectopic oxidative phosphorylation in rod outer segments of bovine retina

Oxidative stress is a primary risk factor for inflammatory and degenerative retinopathies. Most of the energy needed by human cells is provided by mitochondria in the form of ATP [57]. The majority of ATP is synthesized during oxidative phosphorylation or photophosphorylation by the proton-translocating ATP synthase (F_oF_1-ATPase) [58]. The mitochondrial ATP synthase (F_1F_o-ATPase) is a multisubunit, membrane-bound assembly central to biological energy conversion. F_1 is a water-soluble catalytic complex composed of five subunits ($\alpha_3\beta_3\gamma\delta\varepsilon$), with the catalytic site placed on the β subunit. F_0 is made up of different membrane proteins (a, b, c, d, e, F6, A6L) and oligomycin sensitivity-conferring protein (OSCP), which helps the stalk region between F_0 and F_1. Moreover, a native peptide is also bound to the F_1 under de-energized conditions which serves to inhibit the ATPase activity of the enzyme (called F_1 inhibitor protein, IF_1) [59]. The retinal rod outer segment (OS) is defined as a stack of disks surrounded by the plasma membrane, which contains proteins related to phototransduction, and also mitochondrial proteins involved in oxidative phosphorylation [60].
Bacterial energy metabolic pathways are mainly unexplored as drug targets both, for the resistant Gram-positive and Gram-negative bacteria. The production of ATP by bacteria, using the respiratory chain and ATP synthase, can be obtained either by substrate-level phosphorylation of fermentable carbon sources or by oxidative phosphorylation [61]. Diarylquinoline compounds have shown antimicrobial activity by blocking ATP synthase. Recent blocking of the ATP synthase enzyme by TMC207, has shown an effective strategy in the treatment of drug-resistant *Mycobacterium tuberculosis*. Furthermore, mycobacteria are very different from other Gram-positive or Gram-negative bacteria regarding their susceptibility for currently used antibacterials [61]. Diarylquinolines have shown activity against key Gram-positive pathogens (*Staphylococcus aureus*) [62]. Drug-resistant mutations were mapped to the ATP synthase enzyme, and biochemical analysis as well as drug-target

interaction studies reveal ATP synthase as a target for these compounds. The reduction of the ATP synthase expression plays a key role suppressing *S. aureus* growth and metabolism. Some polyphenolic phytochemicals are natural compounds showing a potent antioxidant activity. Furthermore, they act as ATP synthase inhibitors. For example resveratrol, a natural stilbene phytoalexin inhibitor of ATP synthase, targets the F_1 component. It affects both ATPase and ATP synthase activity by binding between α and β subunits [63]. Polyphenols are known to have an inhibitory activity on ATP synthase both in mitochondria and in rod Outer Segments (OS).

Taking into account that overall structure and energy transduction mechanism of the ATP synthase are conserved, from bacteria to human, and that exudates of *Salvia* spp are rich in terpenoids and in flavonoid aglycones, we performed a bioguided purification of the total extract on the basis of both the antimicrobial and ATP synthase inhibition activities, in order to investigate the possible molecular target of antimicrobial effect of *Salvia tingitana*. We used purified rod outer segments (OS) as a subcellular system.

5 Salvia species *considered in this thesis*

5.1 Salvia corrugata

Subgenus: *Calosphace* [64]

Sectio: *Corrugatae* [64]

In: Proceedings of the American Academy of Arts and Sciences 35(25): 538-539 1900.

Distribution: Central or South America. Mountains, secondary scrubs. Alt. 2500-3000 m. [64]

Synonyms: *Sphacele gaudichaudii* Briq. (in: Annuaire du Conservatoire et Jardin Botaniques de Genève 2:182, 1898); *Alguelagum gaudichaudii* Briq. (nomen, in: Annuaire Conserv. Jard. Bot. Geneve 2:182, 1898) [65]

Description:

It is a frutex of the Andean Region (Azuay, Bolívar, Cañar, Chimborazo, Cotopaxi, Guayas, Loja, Tungurahua), Peru (Amazonas, Huancavelica, Lambayeque, Piura), frequent between 1000-1500 m and 2500-4000 m [66]. It is widely cultivated as an ornamental plant and it is grown near the Mediterranean coastal area [67]. *S. corrugata* exhibits woody stems of white-rust colour, owing to the presence of a dense pubescence. The internodes of the main branches are 5-10 cm long, while those of lateral ones from 0.5 to 1 cm. The leaves are 6-12 cm long and 1.5-3 cm wide. They are oblong-lanceolate, acute or blunt, with a rounded-truncated base. The petioles are 0.5-1 cm long and the inflorescences are organized in verticillasters with 5-10 mm bracts. Flowers show blue-purple corollas 2 cm long. The upper lip of the corolla is 7-8 mm while the lower one is 6-9 mm [64].

5.2 Salvia tingitana Etl.

Subgenus: Lamiaceae

Distribution: S. Spain, NW. Africa [65]

Synonyms: *Sclarea tingitana* (Etl.) Raf., Fl. Tellur. 3: 94 (1837) [65]

Description*:*
The species is an aromatic, woody-based, multi-stemmed perennial shrub, till 100 cm; with erect stems, rigid, with sparse, eglandular and glandular hairs. Basal leaves with short petioles, ovate to oblong, 7 cm long, subcordate, obtuse, crenate to undulate, distinctly rugose, with frequent, tapering, eglandular hairs intermixed with sessile glands; cauline leaves few, smaller, sessile. Inflorescence is a broad, branched panicle; verticillasters 6-10, approximating above, 3-6-flowered; bracts broadly ovate, 1-2 × 0.7-1.5 cm, with an acuminate apex. Calyx green, broad, 15-20 mm, not noticeably accrescent in fruit, strongly ridged, with diverging lips with spinulose apices, with long, eglandular multicellular hairs intermixed with short, sessile glands. Corolla white with a cream-yellow lower lip, 25-30 mm, c. 10 mm straight or gradually widening towards throat, esquamulate; upper lip. Nutlets 3 × 2.2 mm, prominently mucilaginous on wetting [10].

5.2.1 History

Salvia tingitana has been cultivated since the end of the 17th century but its origin has for long been uncertain and confused. We believed that it was grown in Northen Africa as the word itself “tingitana” refers to the town now called Tangiers. In 2008 case studies by Foley, Hedge and Moller have given a more complete botanical and horticultural description of the plant. Comparisons and herbarum species and drawings were made so as to understand the plant confusing story. Some of the earliest specimens were taken from De Tannefort collection in the 1690’s, Alpini’s illustrations, entitled *De Plantis Exoticis Libri Duo*, in the 1600’s. Arduino’s studies descriptions (Padua Botanical gardens) and Rivinus published drawing of a plant named *Horminum tingitanum*. However it was Etlinger in 1777 who described it scientifically and named the plant as *S. tingitana*. Today the only certain known locality is in Soudi Arabia but its long history has been associated with nearby countries like Egypt (see illustration Alpini- Syria, Aleppo, Tunis and Tangi). Over the centuries *S. tingitana* was mostly mentioned in the 18th and 19th century when it was also cultivated as an ornamental shrubs in Paris (Palais des Roi); for its aromatic properties in botanic gardens in Padua, Turin and Berlin. There were many published records of *S. tingitana* being cultivated in different parts of Europe like Britain, whereas fewer references were given in the 20th century. In recent times and today, however throughout the world there has been a new interest in growing *S. tingitana* in warmer parts of the world like California, South Africa, Australia and the Mediterranean with small differences in color. There are still some obscure

origins of *S. tingitana*. We believed that it was used and cultivated as a medicinal plant, being a strongly aromatic plant as far back as the Arabian Empire and then expanded to the North countries mentioned before. We also know that *S. tingitana* is a distinct species. This aromatic herb has been used in the past for ots health benefits (medical uses) and healing qualities. It also has anti-inflammatory and antioxidant properties, not to mention its strong aromatic flavor which is used in aromatic oils, the perfum industry as well as in working.

5.2.2 Taxonomy

S. tingitana was described over 230 years ago. However, an unexpected number of species have been considered to be closed allies of *S. tingitana*, or have been confused with it [10]. It has been confused especially with *Salvia sclarea*, but also with *Salvia disermans*, *Salvia argentea*, *Salvia praecox*, *Salvia coarctata*, *Salvia spinosa* and *Salvia desoleana*. Recently (1980s and 1990s), some botanists [68] debatabled that *S. tingitana* is only a cultivated form of *S. sclarea* and could be considered a synonym of it [10]. Recent chromosome analysis of *Salvia* species displays that *S. tingitana* is a distinct species. *S. tingitana* displays a chromosome count of 2n=42, which is unusual for the *Salvia* genus. More common are 2n=14, 16, 20, and 22. Only *S. merjamie*, has been conclusively shown to have a chromosome count of 2n=42 so far. *S. sclarea*, on the contrary, has a count of 2n=22 chromosomes. Mucilage testing were used to compare *S. tingitana* with other possible related species. Those tests defined *S. tingitana* to be a unique species [10] **Fig. 2**.

Fig. 2 [10]

Table 1. Some differential characters of *Salvia tingitana, S. sclarea* and *S. desoleana.*

Salvia tingitana	*S. sclarea*	*S. desoleana*
Perennial shrub	Biennial/perennial herb	Perennial herb
Bracts shorter than calyx, green	Bracts clearly longer than calyx, pink-mauve	Bracts as long as calyx, green-violet
Corolla white/yellow	Corolla lilac/white	Corolla lilac/white
Corolla tube ± straight, esquamulate	Corolla tube strongly ventricose, squamulate	Corolla tube strongly ventricose, squamulate
Nutlets 3 × 2.2 mm	Nutlets 2 × 1.5 mm	Nutlets c. 3 × 2.5 mm
$2n = 42$	$2n = 22$	$2n = 44$

Among the numerous classes of terpenoids, I have decided to focus on the two main classes of compounds for my doctoral: Diterpene, paying more attention on Diterpene *orto* and *para* quinone, and Sesterterpene class.

6 Diterpenes

Diterpenes constitute a large group of C_{20} compounds [1] and they are the most diverse class of secondary metabolites with more than 10,000 different structures. The diterpenoids identified in the Lamiaceae family show around 50 different skeletons [33]. There are two different pathways in which diterpenes may be synthetized: the mevalonate pathway, via mevalonic acid (MVA), and the mevalonate-independent pathway, via deoxyxylulose phosphate (DXP). Diterpenoids biosynthesis is initiated in plastids, in which the common diterpenoids precursor geranylgeranyl diphosphate (GGPP) is synthesized *de novo* from isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP) *via* the action of geranylgeranyl diphosphate synthase (GGPPS), which is a type of the short-chain prenyltransferases (SC-PTSs) [69]. Diterpenes are constitued by head (isopropylidene end) to tail (alcohol end) of four isoprene (C_5H_8) building blocks [70]. These compounds are isolated in insects, marine organisms, fungi, and higher plants, precisely many of them have been isolated from Asteraceae and Lamiaceae [71]. The interest in the isolation of diterpenes is growing because of their biological activity, ecological function, use as templates for synthesis and taxonomic function [72].
Based on the ring number, diterpenoids can be classified as follows: acyclic, bicyclic, tricyclic, tetracyclic, macrocyclic, and miscellaneous. *Salvia* is a genus known for the isolation of these compounds [73], many of which endowed with interesting biological activity. Antibacterial, cytotoxic, and cardiovascular activities have been extensively reported [74], [75]. We could divide *Salvia* diterpenoids in 2 categories. The first one concerns monocyclic and bicyclic diterpenoids containing labdanes, clerodanes, neoclerodanes, *seco*-clerodanes and other rearranged clerodanes. The second one includes tricyclic and tetracyclic diterpenes represented by pimaranes and abietanes including quinone abietanes, *nor*-abietanes, rearranged *nor*-abietanes, dinor-abietanes, *seco*-abietanes, tanshinones and other particular rearranged abietanes (e.g. Icetexane) [76].

6.1 Focus on Diterpenes Quinones isolated from Salvia species

Diterpenoid quinones have been systematized till 1994 considering their distribution, structure, chemistry and total synthesis. Moreover, the chemical and biological potentials of the diterpenoid quinone methides have been reconsidered [73]. Aromatic abietanes are characterized by an aromatic quinonoid C ring and a different degree of oxygenation at several positions [77]. Oxygenated abietane type diterpenes with a common *ortho*- or *para*-quinone chromophore are found principally in roots of *Salvia* species [33]. Many of these diterpene quinone could present aromaticity and a highly oxidation pattern bearing hydroxyl and carbonyl functionalities principally on C-20, C-11, C-7- and C-6 [73].
Recently, many new members of natural abietane-type diterpenoids with an aromatic C ring have been isolated and described in several specific reviews on naturally occurring diterpenoids by Professor Hanson [77] and present about 50 different skeletons. Abietanes isolated from *Salvia* species are often characterized by *para*-quinone abietanes presenting a 11,14-*p*-benzoquinone on the C-ring, like horminone, acetylhorminone, royleanone, tanshinone etc. For example, royleanone was isolated from the aerial parts of *S. ballotiflora*

Benth. and *S. regla* Cav. [78]; [79] and the roots of *S. aethiopis* L. [80]. Various royleanone derivatives which showed hydroxy, methoxy and ethoxy group at C-7 and/or C-12, were identified from several *Salvia* species [33]. In few cases, also *o*-quinone C ring can be present in abietane structures isolated from *Salvia* species [74] like the 11,12-dioxo-abieta-8,13-dien which is isolated from *S. napifolia* [81]. A common rearrangement of abietanes is the icetexane skeleton that has been found in Chinese *Salvia* species [82]. The icetexane skeleton takes the formal name 9(10/20)-*abeo*abietane, indicating that it is believed to arise in Nature from a rearrangement of the abietane skeleton. Icetexanes can be classified into various subclasses based on the presence or absence of oxygenation at the C3, C11, C14 and C19 positions [83]. Fruticuline A and demethylfruticuline A, which are two important icetexane diterpenes quinones, were isolated from the aerial parts of *S. fruticulosa* Benth and *S. corrugata* Vahl. *S. milthiorrhiza* Bunge afforded several norabietane type diterpenes called tanshinones with a 1,2-quinone in the C ring.

To sum up 4 main groups of diterpene quinones can be classified in *Salvia* species: 11,12-*ortho*-quinone abietane, 11,14-*para*-quinone abietane, *seco*-abietane quinones and *abeo*-abietanes quinones. **Table 2** (Appendix) shows all the isolated diterpene quinones from 1962 to January 2019 [33].

6.2 Chemical investigation of roots of S. corrugata

The methanolic extract of the roots of *S. corrugata* was fractionated by Si gel MPLC eluting with *n*-hexane/$CHCl_3$/CH_3OH at concentrations varying from 100:0:0 to 0:0:100 to obtain 12 fractions (I–XII). Fraction **IV** (280.6 mg) (eluted with $CHCl_3$, from 0.45 to 0.51 L) was purified by semi-preparative RP HPLC (eluents A: H_2O, B: CH_3OH, gradient: B 5% at time 0 min, B 100% at time 61 min, B 100% at time 70 min) to obtain **1'** (3.8 mg). Fraction **VI** (93.5mg) (eluted with $CHCl_3$, from 0.78 to 0.96 L) was purified by semi-preparative RP HPLC (eluents A: H_2O, B: CH_3OH, gradient: B 5% at time 0 min, B 100% at time 61 min, B 100% at time 70 min) to obtain **2'** (1.5mg) and **3'** (1.7mg). **Fig. 3**.

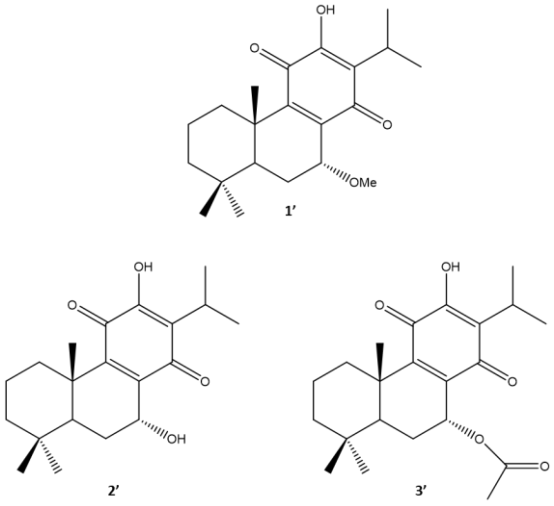

Fig 3. Compounds isolated from the roots of *S. corrugata: 7-O-methylhorminone* (**1'**), *Horminone* (**2'**) and *7-O-acetylhorminone* (**3'**)

6.2.1 Antimicrobial activity

The antimicrobial activity of the methanolic extract of the roots of the 12 semi-purified fractions and of horminone (**2'**) and 7-*O*-acetylhorminone (**3'**) was assessed by determining Minimal Inhibitory Concentration (MIC) (µg/mL) values on several staphylococcal and enterococcal clinical strains, previously isolated from different clinical specimens and identified following the standard procedures [84]. MICs were obtained in line with the microdilution procedure detailed by the Clinical and Laboratory Standards Institute [85].

Tables 3 and 4

Strains	Methanolic extract	IV	VI	VII	VIII	2'	3'
S.aureus MB18*	>128	8	16	64	64	8	16
*S.epidermidis MB 22**	>128	16	32	64	32	16	8
S.capitis MB71*	>128	32	16	16	>128	8	8
S.haemolyticus MB115*	>128	16	64	32	128	16	4
S.hominis MB124*	>128	32	16	16	64	16	4
S.lugdunensis MB96	>128	4	64	16	16	8	8
S.saprophyticus MB41	>128	8	8	16	>128	4	4
S.simulans MB94	>128	4	32	32	32	4	16
S.warneri MB74*	>128	8	32	32	64	16	4

All MICs were obtained in triplicate.

MIC values (µg/mL) of the methanolic extract of the roots, of the 4 active semi-purified fractions and of horminone and 7-*O*-acetylhorminone obtained on 9 staphylococcal clinical isolates. Fractions **I**, **II**, **III, V**, **IX**, **X**, **XI** and **XII** displayed MIC values >128 µg/mL.

Strains	Methanolic extract	III	IV	VIII	2'	3'
E.faecalis MB 1°	128	>128	8	16	64	32
E.faecalis MB 76°	128	>128	8	16	32	64
E.faecium MB 2°	64	32	8	16	64	>128
E.faecium MB 116°	128	64	4	16	64	>128
E.gallinarum MB141	64	>128	16	8	32	64
E.durans MB 113	128	>128	32	16	32	32
E.avium MB119	64	>128	8	16	16	32

*=resistant to Methicillin; **°=**resistant to Vancomycin

MIC values (µg/mL) of the methanolic extract of the roots, of the 3 active semi-purified fractions and of horminone and 7-*O*-acetylhorminone obtained on 7 enterococcal clinical isolates. Fractions **I**, **II**, **V**, **VI**, **VII**, **IX**, **X**, **XI** and **XII** displayed MIC values >128 µg/mL.

6.3 Chemical investigation of roots of S. tingitana

Dryed roots (21.89 g) of *S. tingitana* were extracted with methanol. The methanolic extract (2.47 g) was fractionated by Si gel MPLC eluting with *n*-hexane/$CHCl_3$/CH_3OH at concentrations varying from 100:0:0 to 0:0:100 to obtain 11 fractions (**I_c–XI_c**). Fraction **III_c** was subsequently purified by CC on silica gel (MPLC; monitoring by TLC) with a n-hexane/ $CHCl_3$ (8:2, 0.42 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.57 L; 95:5, 0.45 L; 0:1, 0.06 L) into 14 fractions (**I_{ci}-XIV_{ci}**). Fraction **III_{ci}** (70.1 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.42 to 0.45 L) was purified by semi-preparative HPLC to obtain **1''** (1.2 mg) and **2''** (1.4 mg). Fraction **V_{ci}** (153.8 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.51 to 0.60 L) was purified by semi-preparative HPLC to obtain **3''** (2.3 mg). **Fig. 4**.

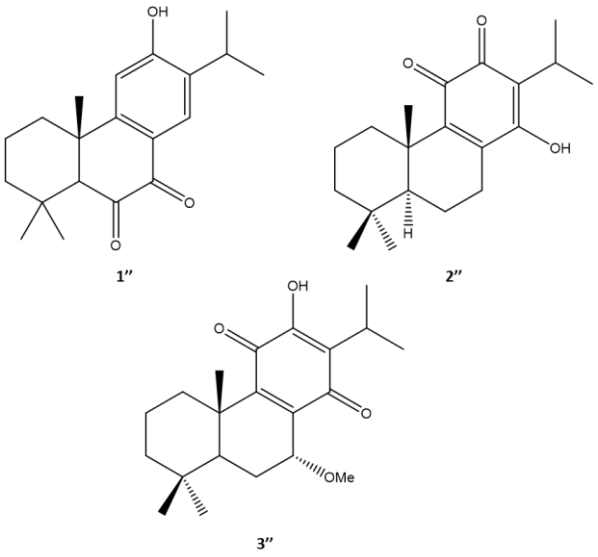

Fig 4. Compounds isolated from the roots of *S. tingitana*: *Hypargenin C* (**1''**), *Royleanone* (**2''**) and *7-O-Methylhorminone* (**3''**)

6.3.1 Antimicrobial activity

The methanolic extract (2.47 g) and the semi-purified fractions were evaluated for the antimicrobial activity.

Table 5

STRAINS	Methanolic extract	I_c	II_c	III_c	IV_c	V_c	VI_c	VII_c	$VIII_c$	IX_c	X_c	XI_c
E.faecalis MB 1°	>128	>128	32	4	16	16	16	64	64	64	128	>128
E.faecalis MB 76°	>128	>128	32	8	16	16	32	128	64	64	>128	>128
E.faecium MB 2°	>128	>128	16	4	16	16	32	128	64	64	128	>128
E.faecium MB 116°	>128	>128	16	4	16	16	32	128	64	128	128	>128
E.gallinarum MB111°	>128	>128	32	8	16	16	32	64	64	64	128	>128
E.durans MB113	>128	>128	32	8	16	16	32	128	64	128	>128	>128
E.avium MB119	>128	>128	16	4	8	16	16	64	64	64	>128	>128
E.gallolyticus MB141	>128	>128	32	8	16	16	32	128	64	64	>128	>128
E.aureus MB18*	>128	>128	16	4	8	8	8	16	8	16	16	>128
E.epidermidis MB22*	>128	>128	16	4	8	8	8	8	8	16	8	>128
E.saprophyticus MB41	>128	>128	16	4	8	8	16	8	8	16	16	>128
E.capitis MB71*	>128	>128	32	4	4	4	8	16	8	16	16	>128
E.warneri MB74*	>128	>128	16	4	8	8	16	16	16	32	16	>128
E.simulkans MB94	>128	>128	8	2	8	8	16	16	16	32	16	>128
E.lugdunensis MB96	>128	>128	8	2	4	8	8	8	16	16	16	>128
E.haemolyticus MB115*	>128	>128	16	4	4	4	16	16	8	32	16	>128
E.hominis MB124*	>128	>128	8	4	8	8	8	16	16	16	16	>128

*°= resistant to Vancomycin; *= resistant to Methicillin*

Tables 6 and 7

Strain	Methanolic extract	Hypargenin C
S.aureus MB18*	16	4
S.aureus MB 6	8	2
*S.epidermidis MB 22**	16	4
S.epidermidis MB93	32	4
S.capitis MB192*	16	2
S.haemolyticus MB193*	32	4
S.hominis MB194*	16	2
S.lugdunensis MB129	8	2
S.warneri MB137*	4	2
S.simulans MB163*	16	4
S.saprophyticus MB41	32	2

Strain	Methanolic extract	Hypargenin C
E.faecalis MB 1**	16	2
E.faecalis MB 92	32	4
E.faecium MB 2	16	4
E.faecium MB 152**	16	2
E.durans MB113	32	4
E.gallinarum MB105**	16	4
E.avium MB119	16	4
E.casseliflavus MB159**	32	4
M luteus MB88	16	4

*Methicillin resistant strain; **Vancomycin resistant strain

The pure compound Hypargenin C which is isolated in sufficient quantities, displayed MIC values which go from 2 to 8 µg/mL against several Gram positive pathogens.

7 Sesterterpenes

To date, sesterterpenoids are a largely unexplored class of terpenes comprising about 1,000 members isolated from nature, which represent <2% of the reported terpene family members [86]. Sesterterpenoids come from geranylfarnesylpyrophosphate and are found mostly in fungi and marine organisms [87]. As other classes of terpenes, the structural diversity of sesterterpenes largely originates from the very first scaffold generating step, which in this case is catalyzed by sesterterpene synthases (STSs), a class of terpene synthase (TPS) [86]. Sesterterpenoids are terpenoids with C_{25} carbon frameworks derived from five isoprene units [88]. Norsesterterpenoids are compounds that contain C_{21}–C_{24} and they are also grouped into sesterterpenoids. Sesterterpenoids can be classified into 6 subgroups, on the basis of the carbocycle numbers included in their molecular structures: linear, monocarbocyclic, dicarbocyclic, tricarbocyclic, tetracarbocyclic, and Miscellaneous sesterterpenoids [89].

Linear Sesterterpenoids

The main source of linear sesterterpenoids is represented by marine organisms and particularly sponges. The terminal units often comprise either a furan, a *y*-lactone or a tetronic acid moiety [90]. Even if the structures of linear sesterterpenoids are very simple, many of them have important cytotoxic properties against human tumor cells, with an unknown mechanisms of action [89].

Monocarbocyclic Sesterterpenoids

Various monocarbocyclic sesterterpenoid compounds have been demonstrated to have important cytotoxicities. Unfortunately, little is known regarding their functional mechanisms [89].

Bicarbocyclic Sesterterpenoids

Sesterterpenoids with a dicarbocyclic skeleton often display structures reminiscent of the clerodane and labdane diterpenoids [89]. The studies on the Australian sponge, *Luflariella geometrica*, have revealed the presence of a large number of related dicarbocyclic sesterterpenoids. These possess the same dicarbocyclic unit and differ in the nature of the side chain [90]. Several sesterterpenes display cytotoxicities against a variety of cancer cell lines [89].

Tricarbocyclic Sesterterpenoids

Many of these sesterterpenoids have also been found to display cytotoxicities [89].

Tetracarbocyclic Sesterterpenoids

The majority of tetracarbocyclic sesterterpenoids belong to the scalarane series [90]. This class of sesterterpenes are emerging as a class of interesting compounds showing significant activities against cancer cells. Scalaranes have been reported to have broad and important cytotoxicities against tumor cells [89].

Miscellaneous sesterterpenoids

Different studies demonstrate that miscellaneous sesterterpenoids display significant cytotoxicities against tumor cells [89].

7.1 Sesterterpenes isolated from Lamiaceae family

Many sesterterpenes were isolated from the Lamiaceae family and have been involved in plant defense mechanisms [86]. Within this family the main species that produce sesterterpenoids are: *Leucosceptrum canum* Sm, *Colquhounia coccinea* var *mollis, Scutellaria violacea* var*. sikkimensis* Hook.f.

Leucosceptrum canum Sm is a species characterized by small, cream-white flowers arranged in dense, terminal spikes [91]. It is a small tree, locally known as Bhusure in Nepal, is distributed in the temperate Himalayans regions, Myanmar, and China [92]. The species is known as a honey plant, and in 1929 Cowan & Cowan remarked that, ''*a quantity of sweet juice exudes from the flowers, and this is sucked by Paharia herdsmen, and by many birds*''. The former are probably less efficient than the latter as pollinators, although, and it can therefore be assumed that the plant is ornithophilous. [91].
Colquhounia coccinea var. *mollis* (Schlechtendal) Prain is a large shrub 1/2 m high distributed mainly in the southwest of China, with vivid whorls of orange-scarlet flowers [93]. *Scutellaria* plants, belonging to the Lamiaceae family, include about 350 species, and are widely distributed in template zones and tropical zones of Europe, North America, and East Asia. They have been used as traditional medicines in many countries. *Scutellaria violacea* var. *sikkimensis* Hook.f is distributed in high altitude regions of Yunnan and Sichuan Provinces [94]. It was found that *Leucosceptrum canum* and *Colquhounia coccinea* var *mollis*, hold two exclusive classes of defensive sesterterpenoids, which are leucosceptroids and colquhounoids, respectively. They are closely related owing to their common 5/6/5 core structure but are distincted from each other on the basis of differences in stereochemistry at C-6 and C-7 and subsequently modifications [88]. Leucosesterterpenone and leucosterlactone are two tetracyclic sesterterpenoids isolated from *L. canum* [87]. Further investigation led to the isolation and identification of more than 100 defensive sesterterpenoids from the leaves and flowers of the above two plants. Moreover, Choudhary and collegues reported the isolation of different sesterterpenoids from *L. canum* of Nepalese origin. The skeletons of these sesterterpenoids are diverse from those discovered in the Chinese plant. Sesterterpenoids were also reported to be present in two important food crops, wheat (*Triticum aestivum*) and potato (*Solanum tuberosum*) [88].

7.2 Sesterterpenes isolated from Salvia species

The first sesterterpene lactone, salvisyriacolide, has been isolated from the aerial parts of *S. syriaca* by Rustaiyan and collegues in Iran [13]. Sesterterpenes have been also isolated from *S. hypoleuca*, *S. sahendica*, *S. mirzayanii*, S. *lachnocalyx*, *S. limbata*, *S. palaestina*, *S. yosgadensis*, *S. aethiopis* and *S. dominica*. Note that seven of these species belong to the flora of Iran and the first four are endemic. Sesterterpenes have been usually isolated from the aerial parts of *Salvia.* spp. Salvileucolide methyl ester, for example, was isolated as the major constituent from aerial parts of *S. hypoleuca* and *S. sahendica* [34]. Two new sesterterpenes lactones, yosgadensolide A (6α,14-dihydroxymanoyloxide-15,17- dien-16,19-olide) and yosgadensolide B (6α, 16-dihydroxymanoyloxide- 14,17-dien-16,19-olide) and their epimers with rare skeleton were isolated from the aerial parts of *S. yosgadensis* [13]. Furthermore, the chemical investigation of *S. yosgadensis* gave five 19,20-dinorsesterterpenes, yosgadensonol, 13-*epi*-yosgadensonol [34]. Five sesterterpene lactones were also isolated from *S. lachnocalyx* [96]. Three new sesterterpenes were isolated from the aerial parts of *S. palaestina* and two new unusual dinorsesterterpenes 6-dehydroxy-yosgadensonol and 6-dehydroxy-13-epiyosgadensonol were also found from the aerial parts of *S. limbata* [13]. 3-*epi*-salviaethiopisolide and salviaethiopisolide, two 19,20-dinorsesterterpenes, were isolated from *S. aethiopis* collected from Salamanca of Spain. The fractions of the aerial parts of *S. hypoleuca* gave six sesterterpene lactones, with a lactone ring between C-4 and C-6 [34]. Twenty-four tricyclic sesterterpenoids were isolated from the aerial parts of *S. dominica* and all of them contain a differentially functionalized decalin and

furan-2-one rings joined with a substituted pentane side chain. Furthermore, salvidominicolide A, salvidominicolide B, two new sesterterpenes, were isolated from this species by Hasan and collegues (2016). Five new manoyloxide-type sesterterpenoids from *S. mirzayanii* have been isolated [97] along with other two sesterterpenes [98]; [99].
In conclusion, the reported sesterterpenoids are bicyclic and mostly sesterterpene lactones. Many of them contain a differentially functionalized decalin and furan-2-one rings joined with a substituted pentane side chain [100].

7.3 Biological and pharmacological properties of sesterterpenes

Plant sesterterpenoids have been shown to exhibit a broad range of biological activities, such as antiinflammatory, anticancer, cytotoxic, and antimicrobial bioactivities, as well as phytotoxicity and plant defense [101], serving as insect antifeedant and antifungal agents, as cytostatic agents against human lung cancer cell, as inhibitors of tubulin tyrosine ligase, as prolylendopeptidase inhibitors, and as enhancers of interleukin-2 gene expression [88]. Nevertheless, the exact biological function and precise binding partners of these bioactive compounds are frequently unknown, thus they can be defined as “orphan” molecules [101]. Sesterterpenes show inhibitory activity against parasitic protozoa, suppression of the expression of cyclooxygenase-2 and inducible nitric oxide synthase. They are inhibitors of hypoxia-inducible factor-1 (HIF-1) [102]. Many sesterterpenes inhibit the activity of the human secreted type IIA phospholipase A2 (PLA2) which is involved in the pathogenesis of a variety of inflammatory diseases via the production of arachidonic acid. Thus, secreted PLA2 has been considered an important target for the development of anti-inflammatory drugs [102]. Moreover, some sesterterpenoids possess multifunctional activities. For example, manoalide showed both anti-inflammatory and antimicrobial activities. It is important to note that many sesterterpenoids can suppress the growth of tumor cells *in vitro* and so they can be seen as promising candidates for anticancer drugs. Unfortunatly, their functional mechanisms and molecular targets are not known so far [89].
The structural diversity and the relevant biological activities of sesterterpenoids have made them attractive targets for both biomedical and synthetic purposes [102].

7.4 Extraction of aerial parts of S. tingitana

For the isolation of surface constituents, fresh aerial parts (10.3 kg) of *S. tingitana* were immersed in CH_2Cl_2 for 20 s to afford 103.0 g of a mixture of secretion product and cuticular constituents (”exudate”). The exudate was partitioned with *n*-hexane affording two fractions, namely “fraction *n*-hexane - soluble” (85.8 g) and “fraction *n*-hexane - insoluble” (17.7 g).

The fraction “*n*-hexane - insoluble” was chromatographed in aliquots of 1.0 g on Sephadex LH-20 (53x2.5 cm; $CHCl_3$-CH_3OH 7:3 as eluent, 0.24 L; monitoring by TLC) to afford six fractions (I_a-VI_a): fraction I_a (0.2 g) (from 0.00 to 0.12 L) with waxy compounds, fraction II_a (1.4 g) (from 0.12 to 0.14 L), fraction III_a (8.6 g) (from 0.14 to 0.18 L), fraction IV_a (3.9 g) (from 0.18 to 0.20 L), fraction V_a (1.6 g) (from 0.20 to 0.22 L) and fraction VI_a (0.6 g) (from 0.22 to 0.24 L).

Fraction II_a was separated by CC on silica gel (MPLC; monitoring by TLC) with a mixture of *n*-hexane-$CHCl_3$ (8:2, 0.36 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.96 L; 9:1, 0.30 L; 1:1, 0.36 L; 0:1, 0.42 L) into 13 fractions (1ai-13ai). Fraction 9ai (139.0 mg) (eluted with $CHCl_3$-CH_3OH 1:1, from 1.14 to 1.70 L) was purified by semi-preparative HPLC to obtain **3** (1.6 mg) and **10** (4.7 mg).

Fraction III_a was separated by CC on silica gel (MPLC; monitoring by TLC) with a mixture of n-hexane-$CHCl_3$ (8:2, 0.42 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.24 L; 1:1, 0.48 L; 0:1, 0.42 L) into 25 fractions (1aii-25aii). Fraction 9aii (306.2 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.60 to 0.75 L) was purified by semi-preparative HPLC to obtain 2 (27.7 mg), 22 (4.5 mg), 23 (5.4 mg), and 24 (4.0 mg). Fraction 10aii (498.9 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.75 to 0.84 L) was purified by semi-preparative HPLC to obtain **2** (3.9 mg), **5** (4.7 mg), **1**1 (16.7 mg), and **24** (5.8 mg). Fraction 12aii (263.0 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 1.05 to 1.20 L) was purified by semi-preparative HPLC to obtain **5** (21.8 mg) and **11** (38.2 mg). Fraction 13aii (97.3 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 1.20 to 1.32 L) was purified by semi-preparative HPLC to obtain **5** (10.4 mg) and **11** (8.3 mg). Fraction 14aii (81.1 mg) (eluted with $CHCl_3$-CH_3OH 9:1, from 1.32 to 1.50 L) was purified by semi-preparative HPLC to obtain **5** (6.0 mg). Fraction 15aii (87.7 mg) (eluted with $CHCl_3$-CH_3OH 9:1, from 1.50 to 1.53 L) was purified by semi-preparative HPLC to obtain **5** (6.0 mg). Fraction 17aii (892.3 mg) (eluted with $CHCl_3$-CH_3OH 9.1, from 1.56 to 1.59 L) was purified by semi-preparative HPLC to obtain **3** (7.2 mg), **6** (35.2 mg), and **12** (3.5 mg). Fraction 18aii (675.0 mg) (eluted with $CHCl_3$-CH_3OH 9.1, from 1.59 to 1.62 L) was purified by semi-preparative HPLC to obtain **9** (4.6 mg) and **10** (6.6 mg). Fraction 19aii (1502.7 mg) (eluted with $CHCl_3$-CH_3OH 9.1, from 1.62 to 1.68 L) was purified by semi-preparative HPLC to obtain **1** (2.1 mg), **7** (16.4 mg), **10** (19.1 mg), **12** (9.8 mg), **13** (4.3 mg), and **14** (23.0 mg). Fraction 20aii (146.2 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 1.68 to 1.71 L) was purified by semi-preparative HPLC to obtain **14** (61.8 mg).

Fraction IV_a was separated by CC on silica gel (MPLC; monitoring by TLC) with a mixture of *n*-hexane-$CHCl_3$ (8:2, 0.39 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.78 L; 95:5, 0.33 L; 0:1, 0.21 L) into 15 fractions (1aiii-15aiii). Fraction 7aiii (33.3 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.87 to 0.96 L) was purified by semi-preparative HPLC to obtain **15** (1.9 mg). Fraction 8aiii (43.1 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.96 to 1.17 L) was purified by semi-

preparative HPLC to obtain **16** (4.2 mg). Fraction 9aiii (333.1 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 0.96 to 1.17 L) was purified by semi-preparative HPLC to obtain **15** (14.9 mg) and **16** (4.2 mg). Fraction 10aiii (141.4 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.17 to 1.23 L) was purified by semi-preparative HPLC to obtain **3** (2.6 mg), **16** (7.1 mg), and **25** (4.6 mg). Fraction 11aiii (55.6 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.23 to 1.26 L) was purified by semi-preparative HPLC to obtain **6** (3.2 mg) and **8** (2.1 mg). Fraction 13 aiii (92.1 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.29 to 1.38 L) was purified by semi-preparative HPLC to obtain **14** (1.0 mg) and **16** (1.0 mg). Fraction 14aiii (48.0 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.38 to 1.50 L) was purified by semi-preparative HPLC to obtain **14** (7.1 mg).

Fraction V_a was separated by CC on silica gel (MPLC; monitoring by TLC) with *n*-hexane (0.54 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.51 L; 95:5, 0.42 L; 0:1, 0.39 L) into 13 fractions (1aiv-13 aiv). Fraction 10aiv (174.1 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.35 to 1.41 L) was purified by semi-preparative HPLC to obtain **23** (13.3 mg).

The fraction "*n*-hexane - soluble" was chromatographed in aliquots of 1.0 g on Sephadex LH-20 (53x2.5 cm; $CHCl_3$-CH_3OH 7:3 as eluent, 0.26 L; monitoring by TLC) to afford seven fractions (I_b-VII_b): fraction I_b (3.1 g) (from 0.00 to 0.12 L) with waxy compounds, fraction II_b (5.6 g) (from 0.12 to 0.14 L), fraction III_b (14.7 g) (from 0.14 to 0.16 L), fraction IV_b (31.4 g) (from 0.16 to 0.18 L), fraction V_b (16.1 g) (from 0.18 to 0.20 L), fraction VI_b (3.2 g) (from 0.20 to 0.22 L), and fraction VII_b (0.8 g) (from 0.22 to 0.24 L).

Fraction II_b was separated by CC on silica gel (MPLC; monitoring by TLC) with mixtures of *n*-hexane-$CHCl_3$ (1:0, 1.23 L; 6:4, 0.27 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 1.17 L; 95:5, 0.15 L; 0:1, 0.42 L) into 23 fractions (1bi-23bi). Fraction 18bi (763.6 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 2.52 to 2.55 L) was separated by CC on silica gel (MPLC; monitoring by TLC) with *n*-hexane (0.48 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.68 L; 95:5, 0.33 L; 0:1, 0.15 L) into 10 fractions (1bii-10bii). Fraction 5bii (73.0 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.78 to 0.90 L) was purified by semi-preparative HPLC to obtain **2** (6.6 mg) and **11** (2.1 mg). Fraction 8bii (eluted with $CHCl_3$-CH_3OH 95:5, from 1.32 to 1.44 L) was purified by semi-preparative HPLC to obtain **3** (85.6 mg), **8** (2.8 mg), and **11** (89.3 mg). Fraction 19bi (1136.4 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 2.55 to 2.58 L) was separated by CC on silica gel (MPLC; monitoring by TLC) with *n*-hexane (0.42 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.78 L; 95:5, 0.42 L; 0:1, 0.09 L) into 10 fractions (1biii-10biii). Fraction 8biii (321.6 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 1.23 to 1.50 L) was purified by semi-preparative HPLC to obtain **3** (2.3 mg), **10** (15.5 mg), and **11** (12.7 mg).

Fraction III_b was separated by CC on silica gel (MPLC; monitoring by TLC) with a mixture of *n*-hexane-$CHCl_3$ (6:4, 0.63 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 1.14 L; 95:5, 0.15 L; 0:1, 0.66 L) into 24 fractions (1biv-24biv). Fraction 11biv (611.7 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.78 to 0.84 L) was separated by CC on silica gel (MPLC; monitoring by TLC) with *n*-hexane (0.39 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.63 L; 95:5, 0.60 L; 0:1, 0.09 L) into 14 fractions (1bv-14bv). Fraction 4bv (100.8 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.51 to 0.60 L) was purified by semi-preparative HPLC to obtain **26** (2.4 mg). Fraction 6bv (137.7 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.78 to 0.90 L) was purified by semi-preparative HPLC to obtain **4** (6.0 mg). Fraction 12biv (eluted with $CHCl_3$-CH_3OH 1:0, from 0.84 to 0.87 L) was

purified by semi-preparative HPLC to obtain **4** (9.1 mg). Fraction 14 biv (504.2 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.99 to 1.05 L) was purified by semi-preparative HPLC to obtain **23** (36.1 mg). Fraction 16 biv (484.4 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.99 to 1.05 L) was purified by semi-preparative HPLC to obtain **22** (1.6 mg) and **23** (3.8 mg). Fraction 17 biv (1502.6 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 1.17 to 1.32 L) was purified by semi-preparative HPLC to obtain **2** (27.4 mg). Fraction 20 biv (742.5 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 1.56 to 1.77 L) was purified by semi-preparative HPLC to obtain **15** (168.5 mg). Fraction 21 biv (135.3 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.77 to 1.83 L) was purified by semi-preparative HPLC to obtain **15** (32.8 mg).

Fraction IV_b was separated by CC on silica gel (MPLC; monitoring by TLC) with a mixture of *n*-hexane-$CHCl_3$ (6:4, 0.75 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 1.08 L; 95:5, 0.30 L; 0:1, 0.42 L) into 18 fractions (1bvi-18bvi). Fraction 3bvi (1.8 g) (eluted with *n*-hexane-$CHCl_3$ 6:4, from 0.15 to 0.18 L) was purified by semi-preparative HPLC to obtain **17** (5.6 mg) and **27** (33.4 mg). Fraction 4bvi (759.8 mg) (eluted with *n*-hexane-$CHCl_3$ 6:4, from 0.18 to 0.21 L) was purified by semi-preparative HPLC to obtain **27** (7.2 mg). Fraction 5bvi (10.53 g) (eluted with *n*-hexane-$CHCl_3$ 6:4, from 0.21 to 0.51 L) was separated by CC on silica gel (MPLC; monitoring by TLC) with *n*-hexane (0.45 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.84 L; 95:5, 0.36 L; 0:1, 0.06 L) into 6 fractions (1bvii-6bvii). Fraction 3 bvii (780.5 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.51 to 0.63 L) was purified by semi-preparative HPLC to obtain **15** (254.6 mg) and **23** (22.5 mg). Fraction 4 bvii (5.11 g) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.63 to 0.78 L) was separated by CC on silica gel (MPLC; monitoring by TLC) with *n*-hexane (0.45 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.84 L; 95:5, 0.36 L; 0:1, 0.06 L) into 23 fractions (1bviii-23bviii). Fraction 13bviii (318.4 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.96 to 1.05 L) was purified by semi-preparative HPLC to obtain **23** (6.8 mg). Fraction 14bviii (770.9 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.96 to 1.05 L) was purified by semi-preparative HPLC to obtain **15** (258.1 mg). Fraction 15bviii (741.4 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.05 to 1.17 L) was purified by semi-preparative HPLC to obtain **15** (292.3 mg). Fraction 17bviii (635.2 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.29 to 1.32 L) was purified by semi-preparative HPLC to obtain **15** (131.0 mg). Fraction 17bviii (635.2 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.29 to 1.32 L) was purified by semi-preparative HPLC to obtain **15** (67.0 mg). Fraction 6bvi (2.24 g) (eluted with *n*-hexane-$CHCl_3$ 6:4, from 0.51 to 0.75 L) was separated by CC on silica gel (MPLC; monitoring by TLC) with *n*-hexane (1.00 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 1.05 L; 95:5, 0.60 L; 0:1, 0.06 L) into 10 fractions (1bix-10bix). Fraction 5bix (270.4 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.26 to 1.29 L) was purified by semi-preparative HPLC to obtain **15** (233.5 mg). Fraction 7bvi (3.17 g) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.75 to 0.84 L) was separated by CC on silica gel (MPLC; monitoring by TLC) with *n*-hexane (0.42 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.54 L; 95:5, 0.75 L) into 18 fractions (1bx-18bx). Fraction 14 bx (188.7 mg) eluted with $CHCl_3$-CH_3OH 95:5, from 1.26 to 1.29 L) was purified by semi-preparative HPLC to obtain **15** (148.0 mg). Fraction 12bvi (1.31 g) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.83 to 1.86 L) was separated by CC on silica gel (MPLC; monitoring by TLC) with *n*-hexane (0.45 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.54 L; 95:5, 0.72 L) into 14 fractions (1bxi-14bxi). Fraction 11bxi (1.31 g) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.35 to 1.47 L) was purified by semi-preparative HPLC to obtain **8** (7.1 mg), **10** (3.3 mg), and **12** (1.4 mg). Fraction 13bvi (342.6 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.86 to 1.89 L) was purified by semi-preparative

HPLC to obtain **1** (1.7 mg), **8** (1.5 mg), **10** (2.6 mg), **12** (1.7 mg), **13** (6.0 mg), and **14** (10.8 mg). Fraction 14bvi (296.7 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.89 to 1.92 L) was purified by semi-preparative HPLC to obtain **11** (2.7 mg), **12** (81.5 mg) and **14** (18.3 mg). Fraction 17bvi (54.5 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 2.13 to 2.19 L) was purified by semi-preparative HPLC to obtain **11** (1.2 mg).

Fraction V_b was separated by CC on silica gel (MPLC; monitoring by TLC) with a *n*-hexane (0.39 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.84 L; 95:5, 0.39 L; 0:1, 0.06 L) into 16 fractions (1bxii-16bxii). Fraction 3bxii (2.5 g) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.39 to 0.54 L) was separated by CC on silica gel (MPLC; monitoring by TLC) with a *n*-hexane (0.39 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.54 L; 95:5, 0.72 L; 0:1, 0.06 L) into 14 fractions (1bxiii-14bxiii). Fraction 3bxiii (125.9 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.48 to 0.60 L) was purified by semi-preparative HPLC to obtain **27** (8.9 mg). Fraction 5bxiii (116.3 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.66 to 0.75 L) was purified by semi-preparative HPLC to obtain **15** (10.1 mg), **17** (17.3 mg) and **18** (4.9 mg). Fraction 6bxiii (177.9 mg) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.75 to 0.89 L) was purified by semi-preparative HPLC to obtain **17** (17.3 mg) and **19** (1.6 mg). Fraction 9bxiii (249.9 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 0.93 to 0.99 L) was purified by semi-preparative HPLC to obtain **21** (3.0 mg). Fraction 11bxii (355.1 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.32 to 1.35 L) was purified by semi-preparative HPLC to obtain **15** (10.0 mg). Fraction 13bxii (237.7 mg) (eluted with $CHCl_3$-CH_3OH 95:5, from 1.41 to 1.47 L) was purified by semi-preparative HPLC to obtain **13** (2.8 mg) and **16** (2.1 mg).

Fraction VI_b was separated by CC on silica gel (MPLC; monitoring by TLC) with a *n*-hexane (0.24 L) and mixtures of $CHCl_3$-CH_3OH (1:0, 0.93 L; 95:5, 0.45 L; 0:1, 0.07 L) into 20 fractions (1bxiv-20bxiv). Fraction 5 bxiv (312.7) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.39 to 0.45 L) was purified by semi-preparative HPLC to obtain **27** (47.7 mg). Fraction 6 bxiv (46.4) (eluted with $CHCl_3$-CH_3OH 1:0, from 0.45 to 0.51 L) was purified by semi-preparative HPLC to obtain **27** (10.4 mg). Fraction 13 bxiv (74.5) (eluted with $CHCl_3$-CH_3OH 1:0, from 1.02 to 1.17 L) was purified by semi-preparative HPLC to obtain **20** (2.7 mg). Fraction 17bxiv (87.1) (eluted with $CHCl_3$-CH_3OH 1:0, from 1.32 to 1.41 L) was purified by semi-preparative HPLC to obtain **13** (1.1 mg).

7.4.1 Results

Thus, the surface extract of the aerial parts of *S. tingitana* afforded one nor-sesterterpene (**1**), eight new sesterterpenes (**2**–**9**), and five known sesterterpenes, along with other known compounds including five labdane and one abietane diterpene, one sesquiterpene and four flavonoids.

The absolute configuration of compounds **1**– **9** were first studied by electronic circular dichroism (ECD). Vibrational circular dichroism (VCD) was used in the cases where sufficient material was available. VCD spectra of compounds **2**, **3**, **6** and **7** were recorded and compared to their calculated spectra at the B3LYP/6-31+G(d,p) level of theory (**Figures 8**, **S17**, **S26** and **S58**, Supporting Information). Similarity indices SimVA (Vibrational Absorption) and SimVCD were calculated with VCD SpecTech31 using scaling factors between 0.8 and 1.2 (**Figures 8**, **S17**, **S26** and **S58**, Supporting Information). The scaling factor corresponding to the maximal value of SimVA calculated for all configurations was used to plot the calculated spectra.

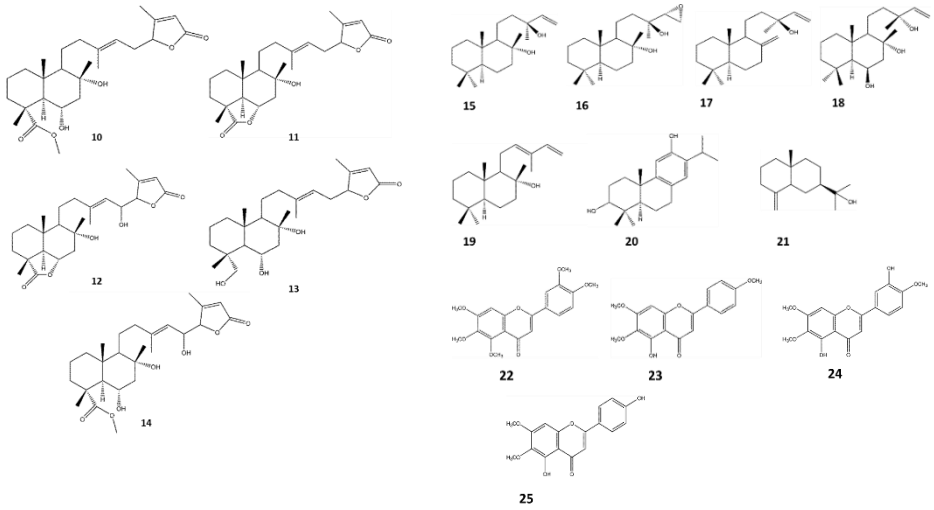

Fig. 5. Known compounds isolated from aerial parts of *S. tingitana*: *salvileucolide methylester* (**10**) [103], *salvileucolide-6,23-lactone* (**11**) [103], *8α,15(S)-dihydroxylabd-13(14),17-dien-23,6α-16(S),19-diolide* (**12**) [101] , *6α,8α,23-trihydroxy-labd-13(14),17-dien-16(R),19-olide* (**13**) [101], *6α,8α,15(S)-trihydroxy-23-carboxymethyllabd-13(14),17-dien-16(S),19-olide* (**14**) [101], *sclareol* (**15**) [104] , *14α-epoxysclareol* (**16**) [105], *manool* (**17**) [106], *6β-hydroxysclareol* (**18**) [105], *(8α,12Z)-12,14-labdadien-8-ol* (**19**) [107], *hinokiol* (**20**) [108], *β-eudesmol* (**21**) [109], *3',4',5,6,7-pentamethoxy-flavone* (**22**) [110], *salvigenin* (**23**) [111], *eupatorin* (**24**) [112], *cirsimaritin* (**25**) [113].

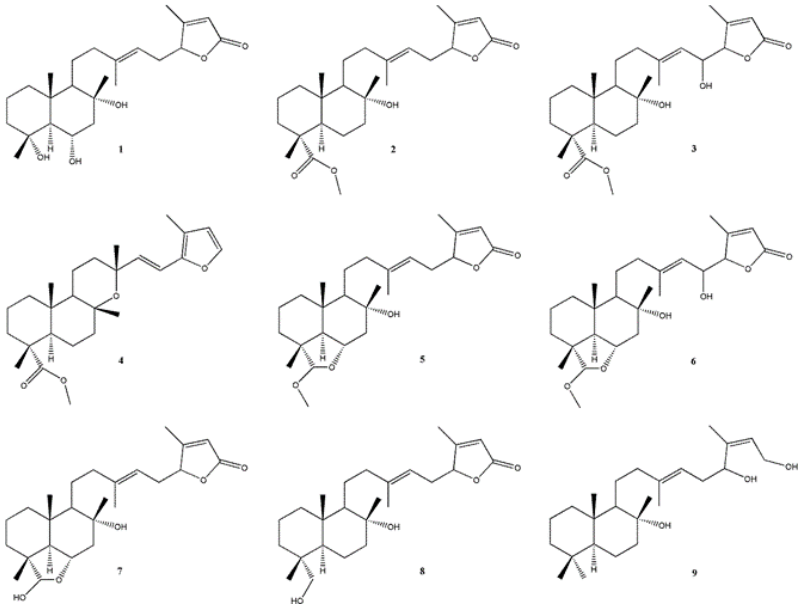

Fig. 6. New sesterterpenes isolated from *S. tingitana*

A molecular formula of $C_{24}H_{38}O_5$ for compound **1**, obtained as a colorless amorphous powder, was established from positive ion mode HRESIMS data ([M + Na]+, m/z 429.2559) indicating six indices of hydrogen deficiency. The IR spectrum showed absorption bands at 3369, 1738, and 1644 cm^{-1}, indicating the presence of hydroxy, carbonyl, and olefinic groups. The ^1H NMR spectrum (**Table 8**) exhibited signals corresponding to five methyls (δ_H 0.78, H3-25; δ_H 1.18, H3-22; δ_H 1.36, H3-24; δ_H 1.66, H3-21; δ_H 2.15, H3-20), two oxymethynes (δ_H 3.97, ddd, J = 11.0, 10.0, 4.8 Hz, H-6; δ_H 4.88, dd, J = 7.2, 5.1 Hz, H-16) and two trisubstituted olefinic protons (δ_H 5.06, H-14; δ_H 5.83, H-18). $^1H - {}^1H$ COSY and 1D TOCSY measurements allowed to establish the spin systems C-1 – C-3, C-5 – C-7, C-9 – C-12, C-14 – C-16. The NMR signals and the degree of insaturation suggested that the structure must be tricyclic. The downfield shift of C-4 (δ_C 74.3), C-3 (δ_C 42.0) and C-5 (δ_C 59.7) suggested the presence on an oxygenated group at position 4, confirmed by HMBC correlations H-2 / C-4, H-3 / C-4, H-5 / C-4 and H3-24 / C-4. This data and the comparison with related sesterterpenes led to establish that **1** was a C-23 nor-sesterterpene. The HMBC correlations H-5 / C-6, H-6 / C-5, H2-7 / C-6 confirmed the location of the other hydroxyl group at C-6. The presence of a α,β-unsaturated butenolide moiety [114], [100] at C-15 was inferred on the basis of the proton resonance of H-18, the carbonyl resonance at C-19 (δ_C 172.6), the HMBC correlations H_2-15 / C-17, H-16 / C-18, H-18 / C-16, H-18 / C-17 and H-18 / C-19, and H_3-20 / C-16 and H_3-20 / C-18, and the long range COSY coupling between CH_3-20 and H-18. NOESY experiment displayed correlations between H-6, H_3-22, H_3-24 and H_3-25, and correlation of H-5 with H-9, indicating a *trans* junction of the decalin system and the β-orientation of H-6 and of the CH_3-24. The E configuration of Δ13 double bond was established from the ^{13}C chemical shift of C-21 [114]. Compound **1** exhibited a strong negative CE at 209 nm and a shoulder at 245 nm (Figures **S7**, **S15**, **S42**, **S57** and **S66**, Supporting Information). ECD was not suited to establish the absolute configuration for this compound. Compound **1** was elucidated as *4ß,6α,8α-trihydroxy-labd-13(14),17-dien-16,19-olide*.

Compound **2,** a colorless amorphous powder, had a molecular formula of $C_{26}H_{40}O_5$. (HRESIMS m/z 455.3037 [M + Na]+, index of hydrogen deficiency = 7). The NMR data of **2** (**Table 8**) were very similar those of *salvileucolide methylester* [103], with the exception of the presence of a methylene group at C-6 (δ_H 1.35, 1.51; δ_C 23.7) instead of an hydroxymethine, confirmed by HMBC correlations H_2-6/C-5, H_2-6/C-7, H_2-6/C-8, H_2-6/C-10 and H_2-7/C-6. J values of H-5 (δ_H 1.77, dd, J = 12.0, 2.3 Hz) and NOESY experiment allowed to assign the same relative configuration of salvileucolide methylester [103]; [115]. Particularly, NOE correlations were observed between H-5 and H-9, and between H_3-22, H_3-24 and H_3-25, coherent with the β-orientation of H_3-22, H_3-24, H_3-25, and the A/B trans ring junction of the decaline system. Compound **2** showed a strong negative CE at 209 nm and a shoulder at 245 nm (Figures **S7**, **S15**, **S42**, **S57** and **S66**, Supporting Information). For compound **2**, the maximal SimVCD value of the calculated spectrum for the absolute configuration (*4R,5R,8R,9R,10S,16R*) was 0.379, compared to 0.281 for (*4R,5R,8R,9R,10S,16S*). This suggested a better fit of (*4R,5R,8R,9R,10S,16R*). Visual evaluation of the experimental and calculated VCD spectra showed a significantly better fit of the bands at 1644, 1106, 1065 and 1039 cm^{-1}. Compound **2** was assigned as (*4R,5R,8R,9R,10S,16R*). Thus, compound **2** was

identified as (*4R,5R,9R,10S)-(8R)-Hydroxy-23-carboxymethyl-labd-13(14),17-dien-16(R),19-olide.*

High-resolution mass spectrometry of **3** a colorless amorphous powder, produced a sodiated molecular ion at m/z 471.3029 [M + Na]+, consistent with a molecular formula of $C_{26}H_{40}O_6$ indicating seven degrees of unsaturation. On the basis of NMR spectroscopic data (**Table 8**), the gross structure of **3** appear similar to *6α,8α,(15S)-trihydroxy-23-carboxymethyl-labd-13(14),17-dien-(16S),19-olide,* [101] except for the presence of a methylene group at position C-6 (δ_H 1.37, 1.58; δ_C 23.1). The attribution was confirmed by the connectivity of H_2-6 in the COSY spectrum with H-5 (δ_H 1.79) and H_2-7 (δ_H 1.48 and 1.82), and in the HMBC spectrum with C-5, C-7, C-8 and C-10, as well as by the other HMBC correlations H-5/C-6 and H-7/C-6. The NOESY experiment, showing NOE correlations of H_3-22 with H_3-24 and H_3-25, and of H-5 with H-9, and the ^{13}C resonance of C-21 confirmed the relative stereochemistry of the bicyclic ring and the E geometry of the Δ13 double bond reported for the similar compound [101]; [114]. For compound **3**, two negative CEs at 209 nm and 244 nm, and a positive CE at 228 nm were observed (Figures **S24**, **S49**, Supporting Information). Since this compound possessed a hydroxy group at C-15, the positive CE at 228 nm was characteristic for the chirality of carbon 15. However, the calculated spectra did not sufficiently match with the experimental data. This lack of fit can be explained by the absence of major chromophores and the flexibility of the side chain. Thus, ECD was not suited to establish the absolute configuration for this compound. For these reasons, vibrational circular dichroism (VCD) was used. For compound **3**, similarity analysis gave no clear preference to either of the calculated spectra. By visual comparison of the major CEs in the experimental spectrum at 1497, 1346, 1299, 1249, 1198, 1171 and 1063 cm^{-1} to the calculated spectra, the absolute configuration was determined as (*4R,5R,8R,9R,10S,15R,16R*). Thus, compound **3** was identified as *(4R,5R,9R,10S)-(8R,15R)-Dihydroxy-23-carboxymethyl-labd-13(14),17-dien-(16R),19-olide.*

The HRESIMS (positive mode) of compound **4** displayed a pseudomolecular ion peak at m/z 437.3054 [M + Na]+ equating to eight degrees of unsaturation and corresponding to the molecular formula $C_{26}H_{38}O_4$. Compound **4** was isolated as a colorless amorphous powder. The IR spectrum exhibited absorption bands for carbonyl (1726 cm^{-1}), olefinic (1661 cm^{-1}) and conjugated ether groups (1246 cm^{-1}). The ^{13}C NMR data (**Table 9**) showed 26 carbon signals, consisting of six methyls, seven methylenes, four methines (two of them were sp^2 carbons), four quaternary carbons, one carboxylic carbon and resonances for one furan ring. The ^{1}H NMR spectrum (**Table 9**) exhibited resonances of four olefinic protons (δ_H 6.16, H-15; δ_H 6.22, H-18; δ_H 6.26, H-14; δ_H 7.24, H-19), and one methyl belonging to an methoxyl group (δ_H 3.66, H_3-OMe). Compound 4 has four rings, as four degrees of unsaturation accounted for the carbonyl group and the three double bonds. The NMR data suggested the presence of a manoyloxide scaffold [96]. The location of the carboxymethyl group (δ_C 179.3; δ_H 3.66, s) at C-23 was based on the chemical shift of C-4, C-23 and C-24, and HMBC correlations of H-3, H-5 and H_3-24 with C-23. The HMBC correlations H-14 / C-16, H-14 / C-17 and H-15 / C-16 confirmed the presence of a furan moiety (δ_C 116.8, C-16; δ_C 148.6, C-17; δ_C 114.7, C-18 and δ_H 6.22, d, J = 1.0 Hz, H-18; δ_C 140.9, C-19 and δ_H 7.24, d, J = 1.0 Hz, H-19) at C-15. NOESY

experiments showed cross-peaks between H_3-22, H_3-24 and H_3-25, and between H-5 and H-9, that confirm the relative stereochemistry of the manoyloxide scaffold [96]. The full relative stereochemistry, especially at position 13, could not be elucidated owing to the overlapping of the signals of H_3-21 and H_3-22. For compound **4**, two positive CEs at 221 nm and at 274 nm (stronger) were measured (Fig. **S34**, Supporting Information). By comparing the experimental with the calculated ECD spectra, the absolute configuration could be determined, in part, as (*4R,5R,8R,9R,10S*), whereas the configuration at C-13 could not be established. Compound **4** was identified as *(4R,5R,9R,10S)-Manoyloxide-14,16,18-trien-(14Z)-19,16-oxide-23-methoxy oic acid.*

High-resolution mass spectrometry of **5** a colorless amorphous powder, produced a sodiated molecular ion at m/z 455.2798 [M + Na]+, consistent with a molecular formula of $C_{26}H_{40}O_5$ On the basis of NMR spectroscopic data (Table 2), The ^{1}H and ^{13}C NMR spectra (**Table 9**) showed similarities with **2**, except for the presence of a 6,23-epoxide, supported by HMBC correlations of H-6 (δ_C 73.6, C-6 and δ_H 3.72, ddd, J = 11.4, 11.3, 4.4 Hz) with C-4 and C-23, and HMBC correlations of H-23 (δ_C 112.6, C-23 and δ_H 4.43, s) with C-6. The relative stereochemistry at C-4, C-5, C-6, C-9, and C-10 was established based on the coupling constants of H-5 (δ_H 1.49, d, J = 11.4), H-6 (δ_H 3.72, ddd, J = 11.4, 11.3, 4.4) and H-9 (δ_H 1.09, t, J = 5.2, 5.2) and the NOESY correlations of H-6 with H_3-22, H_3-24 and H_3-25, and of H-5 with H-9 and H_3-OMe/C-23. The E geometry of the Δ13 double bond was inferred from the ^{13}C chemical shift of C-21. Compound **5** exhibited a strong negative CE at 209 nm and a shoulder at 245 nm (Figures **S7**, **S15**, **S42**, **S57** and **S66**, Supporting Information). Compound **5** was identified as *8α-Hydroxy,23α-O-methyl-23,6α-epoxy-labd-13(14),17-dien-16,19-olide.*

The molecular formula of compound **6**, a colorless amorphous powder, was established to be $C_{26}H_{40}O_6$ on the basis of HRESIMS (m/z 471.2880 [M + Na]+), with seven degrees of unsaturation. The ^{1}H and ^{13}C NMR data of **6** (**Table 9**) were very similar to those of **5**. The only difference was in the hydroxylation of C-15 (δ_H 4.66, dd, J = 8.6, 3.5 Hz, H-6; δ_C 69.2). HMBC correlation of H-16 to C-15 confirmed the presence of the OH at this position (**Table 9**). The relative stereochemistry of compound **6** was established considering the NOESY interactions of H-6 with H_3-22, H-23, H_3-24 and H_3-25, and on the ^{13}C chemical shift of C-21, as for compound **5**. For compound **6**, two negative CEs at 209 nm and 244 nm, and a positive CE at 228 nm were observed (Figures **S24**, **S49**, Supporting Information). Since both compounds possessed a hydroxy group at C-15, the positive CE at 228 nm was characteristic for the chirality of carbon 15. However, the calculated spectra did not sufficiently match with the experimental data. This lack of fit can be explained by the absence of major chromophores and the flexibility of the side chain. Thus, ECD was not suited to establish the absolute configuration for this set of compounds. For these reasons, vibrational circular dichroism (VCD) was performed. The similarity analysis for compound **6** showed a clear preference for (*4R,5R,6S,8R,9R,10S,15R,16R,23S*) as the absolute configuration with a maximal SimVCD value of 0.483. A visual inspection of the major CEs 1454, 1221, 1204, 1170, 1077 and 1046 cm^{-1} confirmed this. Therefore, the absolute configuration of compound **6** was assigned as (*4R,5R,6S,8R,9R,10S,15R,16R,23S*). Thus, compound **6** was identified as

(4R,5R,6S,9R,10S,23S)-(8R,15R)-Dihydroxy,23α-O-methyl-23,6α-epoxy-labd-13(14),17-dien-(16R),19-olide.

Compound **7,** a colorless amorphous powder, had a molecular formula of $C_{25}H_{38}O_5$. (HRESIMS m/z 441.2611 [M + Na]+, index of hydrogen deficiency = 7). The NMR data of **7** (**Table 10**) strongly suggested the similarity of **7** with **5** with the exception for the presence of a hydroxy instead of the metoxy group at C-23 (δ_H 4.43, s, H-23; δ_C 111.1), confirmed by the HMBC correlation H_3 24 / C-23. ROESY correlations of H-6 with H_3-22, H_3-24 and H_3-25, of H 23 with H_3-24, as well as the ^{13}C chemical shift of C-21 corroborated the same relative configuration as for compound **5**. Compound **7** exhibited a strong negative CE at 209 nm and a shoulder at 245 nm (Figures **S7**, **S15**, **S42**, **S57** and **S66**, Supporting Information). For these reasons, vibrational circular dichroism (VCD) was used. For compound **7**, both calculated VCD spectra showed an excellent fit, with maximal SimVCD values of 0.468 for (*4R,5R,6S,8R,9R,10S,16S,23S*) and 0.369 for (*4R,5R,6S,8R,9R,10S,16R,23S*). Visual inspection of major CEs at 1642, 1393, 1341, 1283, 1222, and 1124 cm^{-1} and, in particular, a broad positive CE between 1100 and 1045 cm^{-1} indicated the absolute configuration of **7** as (*4R,5R,6S,8R,9R,10S,16R,23S*). Compound **7** was identified as *(4R,5R,6S,9R,10S,23S)-(8R,23α)-Dihydroxy-23,6α-epoxy-labd-13(14),17-dien-(16R),19-olide.*

Compound **8** had a molecular formula $C_{25}H_{40}O_4$ as deduced from HRESIMS (m/z 427.2868 [M + Na]+), indicating seven degrees of unsaturation The NMR data for **8** (**Table 10**) were very similar to those of **2**, with the exception of the presence of an hydroxymethyl group (δ_H 3.47, d, J = 11.0 and 3.06, d, J = 11.0, H2-23; δ_C 72.0) instead of the methoxycarbonyl, confirmed by HMBC correlations H-5 with C-23 and H_2-23 with C-3, C-4, C-5, C-24. The relative stereochemistry of **8** was identical to that of **2.** Compound **8** exhibited a strong negative CE at 209 nm and a shoulder at 245 nm (Figures **S7**, **S15**, **S42**, **S57** and **S66**, Supporting Information). ECD was not suited to establish the absolute configuration for this compound. Thus, compound **8** was identified as *8α,23-Trihydroxy-labd-13(14),17-dien-16,19-olide.*

Compound **9** was obtained as colorless amorphous powder. Its molecular formula was determined to be $C_{25}H_{44}O_3$ on the basis of the [M + Na]+ peak observed at m/z 415.3167in the positive-ion HRESIMS, indicating four degrees of unsaturation. The IR spectrum of **9** exhibited hydroxy group (3369 and 1022 cm^{-1}) and olefinic groups (1663 and 1647 cm^{-1}) absorption peaks. The ^{13}C NMR spectrum (**Table 10**) revealed a total of 25 carbon resonances for six methyl, eight methylenes, one hydroxymethylene (δ_C 58.4), four methines, one oxymethine (δ_C 70.5) and five quaternary carbons. Two of the four degrees of hydrogen deficiency could be accounted by the NMR data (two double bonds) (**Table 10**). Thus, it was apparent that only two rings were present in the structure. The observation was confirmed by the loss of the carbonyl signal at C-19 (δ_H 4.18, dd, J = 12.6, 6.8 and 4.04, dd J = 12.6, 6.9, H2-19; δ_C 72.0), compared to compound **1**, and by the chemical shifts of H-16 (δ_H 4.49, t, J = 6.9 and C-16; δ_C 70.5), indicating the absence of the α,β-unsaturated butenolide moiety. COSY and 1D TOCSY experiments provided evidence of the spin systems H-1 / H-3, H-5 / H-7, H-11 / H12, H-14 / H-16 and H-18 / H-19. The planar structure of **9** could be constructed, according to HMBC correlations (**Table 10**). Determination of the relative stereochemistry of

9 hinged upon the NOESY correlations involving H-5 with H-9 and H_3-22 with H_3-24 and H_3-25, and upon H-14 (δ_H 4.49, dd, J = 6.9, 6.9) and H-18 (δ_H 5.50, dd, J = 6.9, 6.8) coupling constants. For compound **9**, only one positive CE was observed at 201 nm (Figure **S74**, Supporting Information), and the calculated spectra did not match with the experimental data due to the absence of a lactone ring leading to increased conformational flexibility and the lack of a suitable chromophore. Compound **9** was identified as *Labd-13(14),17-dien-8(R),16,19-triol.*

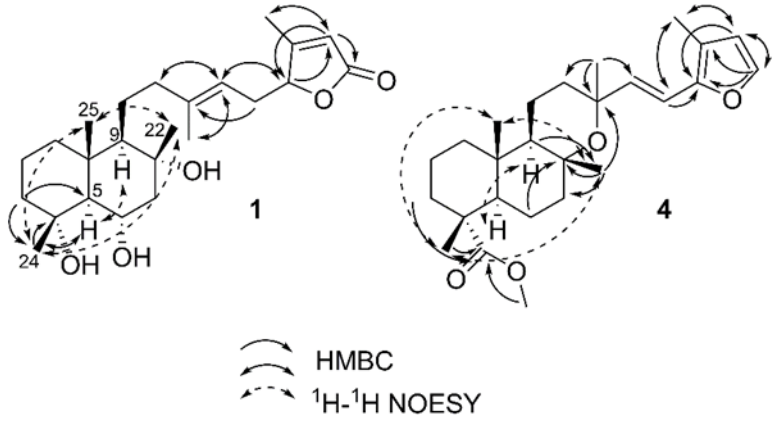

Fig. 7. Selected HMBC and ROESY correlations for compounds **1** and **4** isolated from *S. tingitana*.

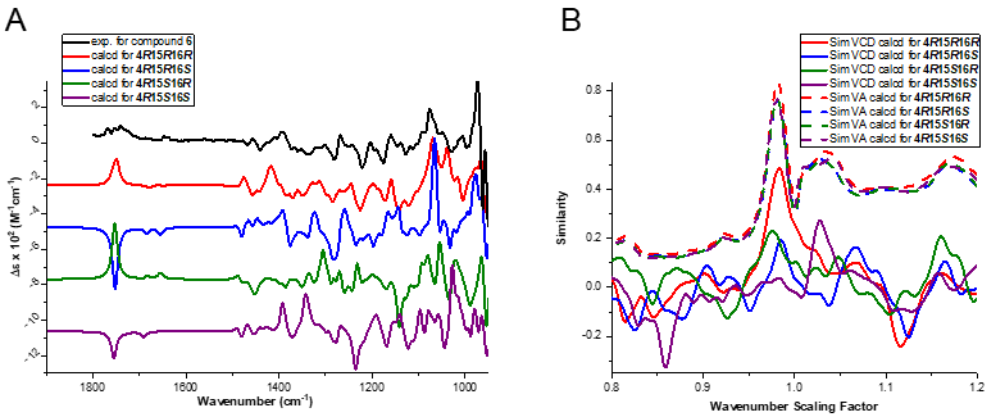

Fig. 8. Comparison of experimental and computed VCD in $CDCl_3$ spectra for compound **6** (A). Similarities (SimVA and SimVCD) between experimental and computed VA and VCD spectra of **6** were plotted as functions of wavenumber scale factor (B). 4R stands for *4R5R6S8R9R10S23S*. The wavenumber scale factor corresponding to the maximal SimVA value in B (0.9820) was used to scale the computed spectra in A.

7.4.2 Spectroscopic data

Compound **1**: colorless gum; $[\alpha]_D^{25}$ –8 (c 0.1, CH_3OH); UV (CH_3OH) λmax (log ε) 201 (4.52) nm; ECD (CH_3OH, c 0.4 mM, 0.1 cm); Δε –0.48 (209 nm), –0.03 (246 nm); IR (KBr) ν max 3369, 2928, 2858, 1756 sh, 1738, 1667, 1643, 1458, 1442, 1389, 1300, 1262, 1173 (sh), 1154, 1124, 1095, 1069, 1040, 1023, 983, 933, 888, 847, 736, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz), see **Table 8**; HRESIMS (positive-ion mode) m/z 429.2559 [M + Na]+ (calcd for $C_{24}H_{38}O_5$, 429.2617).

Compound **2**: colorless amorphous powder; $[\alpha]_D^{25}$ –4 (c 0.2, CH_3OH); UV (CH_3OH) λmax (log ε) 205 (4.37) nm; ECD (CH_3OH, c 0.4 mM, 0.1 cm); Δε –4.97 (209 nm), –0.76 (246 nm); IR (KBr) ν max 3444, 2929, 2868, 1754, 1726, 1645, 1452, 1446, 1388, 1299, 1248, 1170, 1151, 1136, 1081, 1065, 983, 935, 849, 805, 736, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz), see **Table 8**; HRESIMS (positive-ion mode) m/z 455.3037 [M + Na]+ (calcd for $C_{26}H_{40}O_5Na$, 455.2774).

Compound **3**: colorless amorphous powder; $[\alpha]_D^{25}$ +2 (c 0.1, CH_3OH); UV (CH_3OH) λmax (log ε) 208 (3.94) nm; ECD (CH_3OH, c 0.4 mM, 0.1 cm); Δε –0.94 (207 nm), +0.69 (223 nm), –0.58 (244 nm); IR (KBr) ν max 3401, 2923, 2852, 1759 (sh), 1728, 1645, 1456, 1388, 1297, 1249, 1170, 1151, 1115, 1064, 1037, 985, 850, 803, 735, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz), see **Table 8**; HRESIMS (positive-ion mode) m/z 471.3029 [M + Na]+ (calcd for $C_{26}H_{40}O_6Na$, 471.2723).

Compound **4**: colorless amorphous powder; $[\alpha]_D^{25}$ +27 (c 0.1, CH_3OH); UV (CH_3OH) λmax (log ε) 210 (3.37), 269 (3.48) nm; ECD (CH_3OH, c 0.4 mM, 0.1 cm); Δε +1.09 (221 nm), +1.46 (274 nm); IR (KBr) ν max 3400 (w), 2929, 2867, 2333, 1727, 1661, 1456, 1387, 1246, 1170, 1142, 1093, 1077, 1061, 968, 957, 890, 840, 734, 709 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz), see **Table 9**; HRESIMS (positive-ion mode) m/z 437.3054 [M + Na]+ (calcd for $C_{26}H_{38}O_4$, 437.2668).

Compound **5**: colorless amorphous powder; $[\alpha]_D^{25}$ –4 (c 0.2, CH_3OH); UV (CH_3OH) λmax (log ε) 205 (4.65) nm; ECD (CH_3OH, c 0.4 mM, 0.1 cm); Δε –10.86 (209 nm), –2.17 (242 nm); IR (KBr) ν max 3436, 2925, 2869, 2310, 1756, 1741, 1668, 1644, 1457, 1443, 1387, 1298, 1266, 1173, 1148, 1101, 1048, 983, 961, 929, 890, 845, 739, 707 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz), see **Table 9**; HRESIMS (positive-ion mode) m/z 455.2798 [M + Na]+ (calcd for $C_{26}H_{40}O_5Na$, 455.2773).

Compound **6**: colorless amorphous powder; $[\alpha]_D^{25}$ +46 (c 0.04, CH_3OH); UV (CH_3OH) λmax (log ε) 212 (4.06) nm; ECD (CH_3OH, c 0.4 mM, 0.1 cm); Δε –3.46 (209 nm), +1.00 (225 nm), –1.82 (244 nm); IR (KBr) ν max 3401, 2925, 2862, 2312, 1759, 1738, 1666, 1641, 1458, 1440, 1387, 1303, 1268, 1174, 1152, 1101, 1036, 988, 961, 928, 912, 890, 845, 736, 701, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz), see **Table 9**; HRESIMS (positive-ion mode) m/z 471.2880 [M + Na]+ (calcd for $C_{26}H_{40}O_6Na$, 471.2723).

Compound **7**: colorless amorphous powder; $[\alpha]_D^{25}$ +14 (c 0.4, CH_3OH); UV (CH_3OH) λmax (log ε) 209 (4.04) nm; ECD (CH_3OH, c 0.4 mM, 0.1 cm); Δε –8.06 (210 nm), –1.39 (244 nm); IR (KBr) ν max 3430, 3058, 2930, 2869, 2715, 1756 (sh), 1732, 1644, 1455, 1445, 1387, 1301, 1262, 1171, 1151, 1072, 1053, 982, 962, 937, 892, 867, 847, 736, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 600

MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz), see **Table 10**; HRESIMS (positive-ion mode) m/z 441.2611 [M + Na]+ (calcd for $C_{25}H_{38}O_5Na$, 441.2253).

Compound **8**: colorless amorphous powder; $[\alpha]_D^{25}$ –10 (c 0.2, CH_3OH); UV (CH_3OH) λmax (log ε) 201 (4.45) nm; ECD (CH_3OH, c 0.4 mM, 0.1 cm); Δε –7.63 (209 nm), –1.20 (244 nm); IR (KBr) ν max 3411, 2927, 2970, 1756 (sh), 1739, 1666, 1644, 1510, 1456, 1442, 1386, 1300, 1264, 1173, 1152, 1122, 1100, 1066, 1047, 983, 938, 885, 848, 737, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz), see **Table 10**; HRESIMS (positive-ion mode) m/z 427.2868 [M + Na]+ (calcd for $C_{25}H_{40}O_4Na$, 427.2824).

Compound **9**: colorless amorphous powder; $[\alpha]_D^{25}$ +10 (c 0.06, CH_3OH); UV(CH_3OH) λmax (log ε) 201 (4.47) nm; ECD (CH_3OH, c 0.4 mM, 0.1 cm); Δε +7.75 (201 nm); IR (CH_2Cl_2) ν max 3369, 2925, 2854, 1723 (w), 1663, 1647, 1455, 1387, 1263, 1158, 1125, 1083, 1065, 1046, 1022, 937, 907, 846, 738, 607 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150MHz), see **Table 10**; ESIMS2 m/z (rel. int.) 397 [(M-H_2O) + Na]+ (100), 385 [(M-CH_2O) + Na]+ (18), 369 [(M-HCOOH) + Na]+(12); HRESIMS (positive-ion mode) m/z 415.3167 [M + Na]+ (calcd for $C_{25}H_{44}O_3Na$, 415.3188).

Table 8. ^{1}H and ^{13}C NMR Spectroscopic Data of Compounds **1**, **2** and **3** ($CDCl_3$, 600 MHz)

	1			**2**			**3**		
position	δ_C, type	δ_H	HMBC	δ_C, type	δ_H	HMBC	δ_C, type	δ_H	HMBC
1	38.9, CH_2	1.60[b]	2, 3, 5, 9, 10	38.7, CH_2	1.67[b]	2, 3, 5, 10, 25	39.6, CH_2	1.68[b]	2, 10, 24, 25
		1.05[b]			1.04, ddd (13.0, 12.5, 3.8)			1.07[b]	
2	18.6, CH_2	1.62[b]	1, 3	17.6, CH_2	1.61[b]	1, 3, 4	17.8, CH_2	1.62[b]	1, 3, 4
		1.53[b]			1.54[b]			1.55[b]	
3	42.0, CH_2	1.76[b]	1, 2, 4, 5, 24	37.0, CH_2	1.73, m	1, 2, 4, 5, 24	37.2, CH_2	1.73, m	2, 4, 5, 23, 24
		1.44[b]			1.53[b]			1.56[b]	
4	73.4, C	-	-	47.7, C	-	-	47.8, C	-	-
5	59.7, CH	1.43[b]	1, 4, 6, 7, 9, 10, 24, 25	50.6, CH	1.77, dd (12.0, 2.3)	1, 4, 6, 7, 9, 10, 23, 24, 25	50.7, CH	1.79[b]	4, 5, 6, 7, 9, 10, 23, 24, 25
6	67.9, CH	3.97, ddd (11.0, 10.0, 4.8)	5	23.7, CH_2	1.51[b]	5, 7, 8, 10	23.1, CH_2	1.58[b]	5, 7, 8, 10
					1.35[b]			1.37[b]	
7	53.2, CH_2	2.19, d (12.0, 4.8)	5, 6, 8, 9, 22	44.2, CH_2	1.82, ddd (12.1, 3.2, 3.1)	5, 6, 8, 9	44.6, CH_2	1.82[b]	5, 6, 8, 9
		1.63[b]			1.47, m			1.48[b]	
8	72.8, C	-	-	74.1, C	-	-	74.4, C	-	-
9	59.2, CH	1.15, dd (4.1, 4.1)	8, 10, 11, 12, 25	61.3, CH	1.09[b]	1, 8, 10, 11, 12	61.5, CH	1.12[b]	1, 5, 7, 8, 10, 11
10	38.6, C	-	-	39.1, C	-	-	37.1, C	-	-
11	22.9, CH_2	1.59[b]	8, 9, 10, 12	23.4, CH_2	1.52[b]	8, 9, 10, 12, 13	23.8, CH_2	1.59[b]	8, 9, 12, 13
		1.37[b]			1.34[b]			1.38[b]	
12	42.1, CH_2	2.11[b]	9, 11, 13, 14, 21	43.2, CH_2	2.11[b]	9, 11, 13, 14, 21	43.2, CH_2	2.19[b]	9, 11, 13, 14
		2.08[b]			2.09[b]			2.13[b]	
13	140.1, C	-	-	141.2, C	-	-	144.3, C	-	-
14	115.8, CH	5.06, t (7.1, 7.1)	12, 15, 16, 21	116.2, CH	5.08, t (6.5, 6.5)	12, 15, 16, 21	121.9, CH	5.36, d (8.6)	12, 21

15	29.6, CH_2	2.68, ddd (15.0, 7.1, 5.2) 2.28, ddd (15.0, 7.1, 5.2),	13, 14, 16, 17	30.5, CH_2	2.67, ddd (14.2, 6.5, 5.5) 2.32, ddd (14.2, 6.8, 5.5)	13, 14, 16, 17	67.8, CH	4.65, dd (8.6, 1.0)	13, 14
16	83.7, CH	4.89, t (5.2, 5.2)	14, 15, 17, 18	84.5, CH	4.89, t (5.5, 5.5)	14, 15, 17, 18	87.1, CH	4.81, d (1.0)	14, 15
17	167.6, C	-	-	168.4, C	-	-	166.7, C	-	-
18	116.4, CH	5.83, br s	16, 17, 19, 20	117.5, CH	5.85, s	16, 17, 19, 20	118.3, CH	5.91, s	16, 17, 19
19	172.6, CO	-	-	173.4, CO	-	-	173.3, CO	-	-
20	13.3, CH_3	2.06, s	16, 17, 18	14.1, CH_3	2.06, s	16, 17, 18	14.8, CH_3	2.15, s	16, 17, 18
21	16.0, CH_3	1.66, s	12, 13, 14	16.5, CH_3	1.66, s	12, 13, 14	17.3, CH_3	1.77, s	12, 13, 14
22	24.3, CH_3	1.18, s	7, 8, 9	23.9, CH_3	1.11, s	7, 8, 9	24.6, CH_3	1.13[b]	7, 8, 9
23	23.1, CH_3	1.34, s	3, 4, 5	179.3, C	-	-	179.3, CO	-	-
24	-	-	-	16.6, CH_3	1.13, s	3, 4, 5, 23	16.6, CH_3	1.14[b]	3, 4, 5, 23
25	15.8, CH_3	0.79, s	1, 5, 9, 10	16.0, CH_3	0.82, s	1, 5, 9, 10	16.5, CH_3	0.84, s	1, 5, 9, 10
OMe	-	-	-	52.1, CH_3	3.67, s	23	52.2, CH_3	3.67, s	23

[a] *J* values are in parentheses and reported in Hz; chemical shifts are given in ppm; assignments were confirmed by DQF-COSY, 1D-TOCSY and HSQC experiments. [b] Overlapped signal

Table 9. ^{1}H and ^{13}C NMR Spectroscopic Data of Compounds **4**, **5** and **6** ($CDCl_3$, 600 MHz)[a]

	4			5			6		
position	δ_C, type	δ_H	HMBC	δ_C, type	δ_H	HMBC	δ_C, type	δ_H	HMBC
1a	38.7, CH_2	1.66[b]	2, 3, 5, 9, 10, 25	40.9, CH_2	1.64[b]	2, 3, 5, 9, 10, 25	42.0, CH	1.62[b]	2, 3, 5, 9, 10, 25
1b		1.00, ddd (13.0, 12.0, 2.7)			0.97, ddd (13.0, 12.8, 5.6)			0.90[b]	
2a	17.8, CH_2	1.63[b]	1, 3, 4	19.1, CH_2	1.63[b]	1, 3, 4, 10	19.9, CH_2	1.58[b]	1, 3, 4, 10
2b		1.54[b]			1.59[b]			1.53[b]	
3a	37.1, CH_2	1.74[b]	1, 2, 4, 5, 23, 24	31.4, CH_2	1.57[b]	1, 2, 4, 5, 23, 24	32.4, CH_2	1.51[b]	2, 4, 5
3b		1.54[b]			1.45[b]			1.38[b]	
4	47.7, C	-	-	43.5, C	-	-	44.5, C	-	-
5	51.0, CH	1.80, dd (13.2, 1.9)	1, 3, 4, 6, 7, 9, 10, 23, 24, 25	56.5, CH	1.49, d (11.4)	4, 6, 7, 9, 10, 23, 24, 25	57.9, CH	1.44, d (11.4)	1, 3, 4, 6, 7, 9, 10, 24, 25
6a	22.8, CH_2	1.38, dddd (13.3, 13.2, 13.2, 3.1)	4, 5, 7, 8, 10	73.6, CH	3.72, ddd (11.4, 11.3, 4.4)	4, 5, 10, 23	74.8, CH	3.65, ddd (11.4, 11.3, 4.4)	4, 5, 10
6b		1.10[b]							
7a	42.7, CH_2	1.71[b]	5, 6, 8, 9, 22	51.1, CH_2	2.36[b]	5, 6, 8, 9, 22	52.3, CH_2	2.28, dd (11.2, 4.4)	5, 6, 8, 9, 22
7b		1.45[b]			1.50[b]			1.50[b]	
8	76.1, C	-	-	75.4, C	-	-	76.4, C	-	-
9	58.6, CH	1.33, dd (11.5, 2.4)	1, 5, 8, 10, 11, 12, 25	60.0, CH	1.09, t (5.2, 5.2)	1, 7, 8, 10, 11, 22, 25	61.1, CH	1.06[b]	7, 8, 10, 11, 12, 25
10	36.4, C	-	-	36.4, C	-	-	36.4, C	-	-
11a	16.1, CH_2	1.58[b]	8, 9, 10, 12, 13	22.9, CH_2	1.58[b]	8, 9, 10, 12, 13	24.2, CH_2	1.62[b]	8, 9, 10, 12, 13
11b		1.52[b]			1.37[b]			1.39[b]	
12a	36.4, CH_2	2.24, ddd (12.7, 2.9, 2.7)	9, 11, 13, 14	41.5, CH_2	2.17, ddd (14.0, 8.4, 8.0)	9, 11, 13, 14, 21	42.9, CH_2	2.18, ddd (14.2, 8.2, 8.2)	9, 11, 13, 14, 21
12b		1.55[b]			2.12, ddd (14.0, 8.8, 5.6)			2.06[b]	

13	73.2, C	-	-	141.4, C	-	-	145.1, C	-	-
14	136.7, CH	6.26, d (16.5)	12, 13, 15, 16, 21	116.2, CH	5.02, t (7.1, 7.1)	12, 15, 16, 21	123.2, CH	5.16, d (8.6)	12, 21
15a	112.6, CH	6.16, d (16.5)	13, 14, 16, 17	30.3, CH_2	2.72, ddd (15.0, 7.1, 4.7)	13, 14, 16, 17	69.2, CH	4.66, dd (8.6, 3.5)	-
15b					2.32 [b]				
16	116.8, C	-	-	84.5, CH	4.91, t (4.7, 4.7)	14, 15, 17, 18, 19	88.0, CH	4.80, d (3.5)	14, 15, 17, 18
17	148.6, CH_3	-	-	168.3, C	-	-	168.0, C	-	-
18	114.7, CH	6.22, d (1.8)	16, 17, 19, 20	117.9, CH	5.88, s	16, 17, 19, 20	119.3, CH	5.84, s	16, 17, 19, 20
19a	140.9, CH	7.25, d (1.8)	16, 17, 18	173.5, CO	-	-	174.4, CO	-	-
19b									
20	10.2, CH_3	2.06, s	17, 18	14.1, CH_3	2.06, s	16, 17, 18	15.9, CH_3	2.10, s	16, 17, 18
21	33.1, CH_3	1.23, s	12, 13, 14	16.4, CH_3	1.65, s	12, 13, 14	18.1, CH_3	1.66, s	12, 13, 14
22	24.5, CH_3	1.22, s	7, 8, 9	24.7, CH_3	1.12, s	7, 8, 9	25.8, CH_3	1.05, s	7, 8, 9
23	179.0, C	-	-	112.6, CH	4.43, s	4, 5, 6, 24	113.6, CH_3	4.35, s	4, 5, 6, 24, 1’
24	16.4, CH_3	1.12, s	3, 4, 5, 23	19.6, CH_3	1.01, s	3, 4, 5, 23	20.1, CH_3	0.94, s	3, 4, 5, 23
25	16.3, CH_3	0.75, s	1, 5, 9, 10	15.4, CH_3	0.83, s	1, 5, 9, 10	16.3, CH_3	0.84, s	1, 5, 9, 10
OMe	52.0, CH_3	3.66, s	-	54.9, CH_3	3.34, s	23	55.8, CH_3	3.27, s	23

[a] *J* values are in parentheses and reported in Hz; chemical shifts are given in ppm; assignments were confirmed by DQF-COSY, 1D-TOCSY and HSQC experiments. [b] Overlapped signal.

Table 10. ^{1}H and ^{13}C NMR Spectroscopic Data of Compounds **7**, **8** and **9** ($CDCl_3$, 600 MHz)[a]

	7			8			9		
position	δ_C, type	δ_H	HMBC	δ_C, type	δ_H	HMBC	δ_C, type	δ_H	HMBC
1a	39.2, CH_2	1.67[b]	-	39.6, CH_2	1.60[b]	2, 3, 9, 10, 25	40.3, CH_2	1.63[b]	2, 3, 5, 10, 25
1b		0.96[b]			0.93, ddd (13.3, 13.0. 3.3)			0.94[b]	
2a	18.1, CH_2	1.70[b]	-	17.9, CH_2	1.62[b]	1, 3, 4	19.1, CH_2	1.56[b]	1, 3, 4
2b		1.62[b]			1.49[b]			1.42[b]	
3a	30.6, CH_2	1.59[b]	-	35.3, CH_2	1.46[b]	1, 2, 4, 5, 24	43.0, CH_2	1.36 [b]	1, 2, 3, 4
3b		1.47[b]			1.22[b]			1.14[b]	
4	42.2, C	-	-	37.8, C	-	-	39.0, C	-	-
5	55.5, CH	1.51[b]	-	48.8, CH	1.24[b]	1, 3, 4, 6, 7, 9, 10, 23, 24, 25	56.5, CH	0.91[b]	1, 6, 7, 10, 23, 24
6a	72.3, CH	3.70, dd (11.3, 11.1, 4.2)	-	20.4, CH_2	1.58[b]	5, 7, 8, 10	21.8, CH_2	1.63[b]	5, 7, 8, 10
6b					1.26[b]			1.24[b]	
7a	49.8, CH_2	2.38 [b]	-	44.3, CH_2	1.48[b],	5, 6, 8, 9, 22	44.6, CH_2	1.83, dt (12.2, 3.1, 3.1)	5, 6, 8, 9
7b		1.57[b]			1.84, ddd (13.9, 3.0, 3.0)			1.36[b]	
8	74.1, C	-	-	74.0, C	-	-	74.3, C	-	-
9	59.4, CH	1.13[b]	7, 8	60.6, CH	1.05, t (4.2, 4.2)	8, 10, 11, 12, 22, 25	61.6, CH	1.03, t (4.0, 4.0)	8, 10, 11, 12
10	35.2, C	-	-	39.2, C	-	-	38.9, C	-	-
11a	22.1, CH_2	1.64[b]	-	23.4, CH_2	1.53[b]	8, 9, 10, 12	23.4, CH_2	1.46[b]	8, 9, 10, 12
11b		1.42[b]			1.32, dddd (14.1, 9.0, 5.4, 5.3)			1.37[b]	
12a	41.2, CH_2	2.14[b]	-	42.9, CH_2	2.10[b]	9, 11, 13, 14, 21	43.2, CH_2	2.09[b]	9, 11, 13, 14, 21
12b		2.12[b]			2.07[b]			2.05[b]	
13	139.8, C	-	-	141.2, C	-	-	140.4, C	-	-

14	115.4, CH	5.03, t (7.2, 7.2)	-	116.4, CH	5.02, t (6.8, 6.8)	12, 15, 16, 21	119.8, CH	5.13, t (7.4, 7.4)	12, 15, 16, 21
15a	29.2, CH	2.72, ddd (14.9, 7.2, 5.5)	-	30.2, CH_2	2.70, ddd (14.9, 6.8, 4.9)	13, 14, 16, 17	34.5, CH	2.34, ddd (14.0, 7.4, 6.9)	14, 16, 17
15b		2.32 [b]			2.31, ddd (14.9, 6.8, 4.9)			2.19, ddd (14.0, 7.4, 6.9)	
16	83.2, CH	4.91, t (5.5, 5.5)	-	84.5; CH	4.90, t (4.9, 4.9)	14, 15, 17, 18	70.5, CH	4.49, t (6.9, 6.9)	14, 15, 17, 18, 20
17	167.2, C	-	-	168.4, C	-	-	141.0, C	-	-
18	116.5, CH	5.86, s	-	117.7, CH	5.87, s	16, 17, 19, 20	126.3, CH	5.50, dd (6.9, 6.8)	16, 19, 20
19a	172.3, CO	-	-	173.5, CO	-	-	58.4, CH_2	4.18, dd (12.6, 6.8)	17, 18
19b								4.04, dd (12.6, 6.9)	
20	13.2, CH_3	2.07, s	16, 17, 18	14.1, CH_3	2.06, s	16, 17, 18	18.4, CH_3	1.75, s	16, 17, 18
21	16,6, CH_3	1.66, s	12, 13, 14	16.0, CH_3	1.66, s	12, 13, 14	16.7, CH_3	1.64, s	12, 13, 14
22	24.0, CH_3	1.15, s	7, 8, 9	23.9, CH_3	1.12, s	7, 8, 9	24.1, CH_3	1.11, s	7, 8, 9
23	111.1, C17	4.43, s	-	72.0, CH_2	3.47, d (11.0)	3, 4, 5, 24	33.8, CH_3	0.85, s	3, 4, 24
					3.06, d (11.0)				
24	17.3, CH_3	1.00, s	3, 4, 5, 23	17.6, CH_3	0.72, s	3, 4, 5, 23	15.8, CH_3	0.78, s	3, 4, 5, 23
25	15.7, CH_3	0.87, s	1, 5, 9, 10	16.5, CH_3	0.83, s	1, 5, 9, 10	15.9, CH_3	0.79, s	1, 5, 9, 10
OMe	-	-	-	-	-	-			

[a] *J* values are in parentheses and reported in Hz; chemical shifts are given in ppm; assignments were confirmed by DQF-COSY, 1D-TOCSY and HSQC experiments. [b] Overlapped signal

7.4.3 Antibacterial activity

7.4.3.1 Microorganisms

A total of 30 strains (27 clinical strains and 3 isolates of marine origin) previously isolated from different specimens and identified according to standard procedures [84] and by MALDI TOF Vitek MS™ Biomérieux were employed in this study. Twenty-four strains belonged to seventeen Gram-positive species [*Staphylococcus aureus, S. epidermidis, S. saprophyticus, S. capitis, S. warneri, S. simulans, S. lugdunensis, S. haemolyticus, S. hominis, Streptococcus agalactiae* (MB 149), *S. pneumoniae* (MB 35), *Enterococcus faecium*, *E. faecalis*, *E. avium*, *E. casseliflavus*, *E. durans* and *E. gallinarum*], four were clinical strains of Gram-negative species [*Escherichia coli* (MB 123), *Proteus mirabilis* (MB 14), *Moraxella catarrhalis* (MB 15) and *Klebsiella pneumoniae* (MB 11)], and two were clinical strains of fungi [*Candida albicans* (MB 31) and *C. glabrata* (MB 8)]. Among the Gram-positive organisms, two *S. aureus* strains were methicillin- and multidrug-resistant (MRSA) [116]; [117] (MB 18, MB 188). Two *S. epidermidis* were methicillin- and multidrug-resistant (MRSE) (MB 165, MB 169). *S. saprofiticus* MB41, *S. simulans* MB 94 and *S. lugdunensis* MB 96 were methicillin-susceptible, while *S. capitis* MB 71, *S. warneri* MB 74, S*. haemolyticus* MB 115 and *S. hominis* MB 124 were all methicillin-resistant isolates. One *E. faecalis* was vancomycin-susceptible (MB 76), and three were vancomycin-resistant (VRE) (MB 1, MB 19, MB 51). One *E. faecium* was vancomycin-susceptible (MB 2), and two were VRE (MB 3, MB 152). *E. faecalis* MB 19 and MB 51, and *E. faecium* MB 3 were of marine origin, being isolated from sea water of the Ligurian west coast. *E. avium* MB 119 and *E. durans* MB 113 were vancomycin susceptible while *E. casseliflavus* and *E gallinarum* were vancomycin resistant.

7.4.3.2 Active constituents and control antibiotics

The preparation of solutions of test compounds and control antibiotics, including susceptibility testing were carried out as previously described [118] Minimum inhibitory concentrations (MICs) were obtained following the microdilution procedure as detailed [118].

The total extract, the two *n*-hexane - insoluble and soluble fractions and the relative 13 sub-fractions (I_a-VI_a and I_b-VII_b) showed a broad range of potencies against 12 representative clinical strains (Table **S1**, Supporting Information). The total extract showed MIC values of 128 µg/mL on *Staphylococcus aureus*, *S. epidermidis*, *Enterococcus faecium* and *E. faecalis* strains while MIC >128 µg/mL were found against the two other species of Gram positive (*Streptococcus agalactiae* and *S. pyogenes*), the four Gram negative (*Escherichia coli*, *Proteus mirabilis*, *Moraxella catarrhalis* and *Klebsiella pneumoniae*) and the two mycetes (*Candida albicans* and *C. glabrata*) isolates. Similarly, the two *n*-hexane-soluble and insoluble fractions and the relative 13 sub-fractions displayed a broad range of activity against the Gram-positive species but displayed no potency on the tree Gram negative isolates nor on the two *Candida* strains (**Table S1**, Supporting Information). 19 compounds out of the 25, isolated in suitable amount for biological assays, were analyzed for antibacterial activity by determining MIC values on a panel of 30 microbial clinical strains, mainly Gram-positive pathogens, belonging

to different clinically relevant species of *Staphylococcus* and the *Enterococcu*s genera. As depicted in **Table 11**, interesting results were obtained particularly for *Staphylococci* and *Enterococci*, while MIC values above 128 μg/ml were obtained for *S. agalactiae*, *S. pyogenes*, the 4 Gram negative species and the two mycetes (data not shown). Note that the isolated compounds displayed different antimicrobial activities against several *Enterococcus* and *Staphylococcus* species. M*anool* (**17**) and *sclareol* (**15**), hawever, showed MIC values which go from 4 to 64 μg/mL. *Sclareol* and *manool* displayed the lowest MIC values among the other pure compounds. Particularly, *Sclareol* was active against several staphylococcal and enterococcal species of clinical interest with very uniform MIC values, which go from 32 to 64 μg/ml (**Table 11**). *Manool*, on the contrary, was particularly powerful against the enterococcal genera, reaching MIC values of 4 μg/ml on several Enterococcal species isolates (**Table 11**). Nevertheless we couldn't demonstrate any valuable effect of these two labdane diterpenes against the selected aerobic Gram negative species, Souza and colleagues [119] reported antimicrobial activity of the same compounds also against few Gram negative periodontal bacteria, maybe because these organisms were endowed with an anaerobic metabolism. We couldn't confirm any significant antimicrobial activity of *manool* against *S. aureus* as reported by Ulubelen, [120] maybe because of the clinical origin and the multidrug resistant characteristics of the staphylococcal strains we utilized.

Table 11. MIC Values of compounds **2**-**8**, **10**-**17**, **22**-**25**[a]

bacterial strains	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**11**	**12**	**13**
S. aureus MB 18*	>128	128 (286)	128 (309)	128 (296)	128 (286)	>128	128 (317)	128 (286)	128 (308)	128 (296)	>128
S. aureus MB 188*	128 (296)	>128	>128	128 (296)	>128	>128	>128	>128	>128	>128	>128
S. epidermidis MB 165*	128 (296)	>128	128 (309)	64 (148)	>128	>128	128 (317)	128 (286)	128 (308)	128 (296)	>128
S. epidermidis MB 169*	>128	128 (286)	64 (155)	64 (148)	128 (286)	>128	>128	>128	>128	>128	>128
S. saprophyticus MB 41	128 (296)	128 (286)	128 (309)	128 (296)	128 (286)	>128	128 (317)	>128	>128	>128	>128
S. capitis MB 71*	64 (148)	128 (286)	64 (155)	32 (74.1)	128 (286)	>128	128 (317)	128 (286)	64 (154)	128 (296)	>128
S. warneri MB 74*	64 (148)	64 (143)	128 (309)	64 (148)	>128	>128	128 (317)	128 (286)	128 (308)	128 (296)	>128
S. simulans MB 94	>128	>128	>128	128 (296)	>128	>128	>128	>128	>128	>128	>128
S. lugdunensis MB 96	128 (296)	128 (286)	>128	128 (296)	>128	>128	>128	>128	128 (308)	>128	>128
S. haemolyticus MB 115*	128 (296)	>128	>128	128 (296)	>128	>128	>128	>128	>128	128 (296)	>128
S. hominis MB 124*	128 (296)	128 (286)	128 (309)	64 (148)	128 (286)	>128	128 (317)	128 (286)	>128	>128	>128
E. faecalis MB 1°	32 (74.1)	64 (143)	>128	128 (296)	64 (143)	>128	128 (317)	64 (143)	64 (154)	64 (148)	>128
E. faecalis MB 19°§	64.0 (148)	64 (143)	128 (309)	64 (148)	128 (286)	>128	32 (79.2)	128 (286)	128 (308)	128 (296)	>128
E. faecalis MB 51°§	128 (296)	128 (286)	128 (309)	128 (296)	64 (143)	>128	64 (158)	64 (143)	64 (154)	128 (296)	>128
E. faecalis MB 76	64 (148)	64 (143)	128 (309)	128 (296)	64 (143)	>128	64 (158)	128 (286)	128 (308)	128 (296)	>128
E. faecium MB 2	128 296	128 (286)	128 (309)	128 (296)	128 (286)	>128	128 (317)	128 (286)	>128	128 (296)	>128
E. faecium MB 3°§	64 (148)	64 (143)	128 (309)	128 (296)	64 (143)	>128	128 (317)	128 (286)	128 (308)	128 (296)	>128
E. faecium MB 152°	128 (296)	128 (286)	>128	64 (148)	128 (286)	>128	64 (158)	64 (143)	128 (308)	64 (148)	>128
E. avium MB 119	128 (296)	128 (286)	>128	128 (296)	64 (143)	>128	64 (158)	64 (143)	64 (154)	64 (148)	>128

E. casseliflavus MB 159°	128	(296)	64	(143)	128	(309)	64	(148)	128	(286)	>128	64	(158)	64	(143)	128	(308)	128	(296)	>128
E. durans MB 113	128	(296)	128	(286)	>128		128	(296)	>128		>128	>128		128	(286)	>128		128	(286)	>128
E. gallinarum MB 111°	64	(148)	64	(143)	128	(309)	128	(296)	64	(143)	>128	64	(158)	128	(286)	64	(154)	64	(148)	>128

bacterial strains	14	15	16	17	22	23	24	25	O	V
S. aureus MB 18*	128 (276)	32 (104)	128 (395)	>128	>128	128 (390)	>128	>128	256 (638)	n.t.
S. aureus MB 188*	>128	32 (104)	128 (395)	>128	128 (344)	>128	>128	>128	512 (1275)	n.t.
S. epidermidis MB 165*	128 (276)	64 (207)	128 (395)	>128	>128	>128	>128	>128	256 (638)	n.t.
S. epidermidis MB 169*	>128	64 (207)	128 (395)	>128	128 (344)	128 (390)	>128	>128	256 (638)	n.t.
S. saprophyticus MB 41	>128	32 (104)	128 (395)	>128	>128	>128	>128	>128	1 (2.49)	n.t.
S. capitis MB 71*	128 (276)	32 (104)	128 (395)	>128	128 (344)	128 (390)	>128	128 (407)	256 (638)	n.t.
S. warneri MB 74*	64 (138)	32 (104)	64 (198)	>128	128 (344)	128 (390)	>128	>128	128 (319)	n.t.
S. simulans MB 94	>128	64 (207)	128 (395)	>128	>128	>128	>128	>128	0.25 (0.62)	n.t.
S. lugdunensis MB 96	>128	32 (104)	64 (198)	>128	>128	>128	>128	128 (407)	0.5 (1.25)	n.t.
S. haemolyticus MB 115*	128 (276)	64 (207)	128 (395)	>128	>128	>128	>128	>128	16 (39.9)	n.t.
S. hominis MB 124*	64 (138)	32 (104)	128 (395)	>128	128 (344)	128 (390)	>128	>128	16 (39.9)	n.t.
E. faecalis MB 1°	64 (138)	32 (104)	32 (99)	16 (55)	32 (86)	64 (195)	64 (186)	64 (204)	n.t.	32 (22.1)
E. faecalis MB 19°§	128 (276)	32 (104)	64 (198)	32 (110)	128 (344)	64 (195)	64 (186)	128 (407)	n.t	32 (22.1)
E. faecalis MB 51°§	64 (138)	64 (207)	32 (99)	16 (55)	64 (172)	128 (390)	128 (372)	128 (407)	n.t	64 (44.2)
E. faecalis MB 76	128 (276)	64 (207)	64 (198)	32 (110)	128 (344)	128 (390)	64 (186)	128 (407)	n.t	128 (88.3)
E. faecium MB 2	128 (276)	32 (104)	64 (198)	4 (14)	128 (344)	128 (390)	128 (372)	128 (407)	n.t	2 (1.38)
E. faecium MB 3°§	128 (276)	32 (104)	32 (99)	8 (28)	128 (344)	64 (195)	>128	64 (204)	n.t	128 (88.3)
E. faecium MB 152°	64 (138)	64 (207)	64 (198)	8 (28)	64 (172)	64 (195)	128 (372)	127 (407)	n.t	256 (177)
E. avium MB 119	64 (138)	64 (207)	32 (99)	8 (28)	128 (344)	128 (390)	64 (186)	64 (204)	n.t	1 (0.69)
E. casseliflavus MB 159°	128 (276)	64 (207)	64 (198)	16 (55)	64 (172)	128 (390)	128 (372)	128 (407)	n.t	4 (2.76)
E. durans MB 113	64 (138)	32 (104)	64 (198)	16 (55)	128 (344)	64 (195)	>128	128 (407)	n.t	1 (0.69)
E. gallinarum MB 111°	128 (276)	64 (207)	32 (99)	4 (14)	64 (172)	64 (195)	64 (186)	32 (102)	n.t	16 (11)

[a] MIC values, expressed in μg/mL and micromolarity (μM), of the pure compounds on the selected bacterial strains; *: Methicillin resistant *Staphylococcus* strain; °: Vancomycin resistant *Enterococcus* strain; §: Strain isolated from sea water of the Ligurian west coast (Italy); n.t.: not tested

7.4.4 Time killing curves

For the two labdane diterpenes, *sclareol* (**15**) and *manool* (**17**), as well as for *salvileucolide methylester* (**10**) and *salvileucolide-6,23-lactone* (**11**), that displayed the best antimicrobial activity with respect to other isolated sesterterpenes, the mechanism of action on the most clinically relevant and susceptible species such as *S. aureus*, *S. epidermidis*, *E. faecium* and *E. faecalis* was investigated. Time killing curves, carried out on selected representative resistant and multi-resistant isolates, are shown in **Fig. 9**. All the four compounds were proved to be active with a clear bacteriostatic mechanism, because they prevented the growth of the starting inoculum of the bacterium or produced a decrease from the starting inoculum concentration that ranged from 1 to 2 log within the 24 hours.

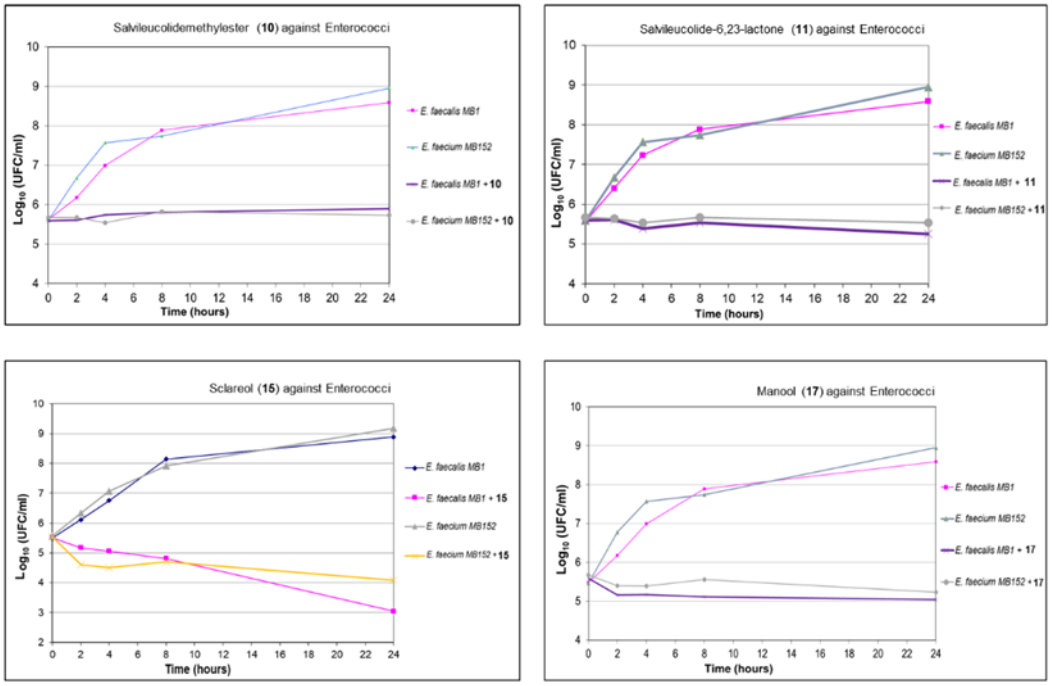

Figure 9. Effect of *salvileucolide methylester* (**10**), *salvileucolide-6,23-lactone* (**11**), *sclareol* (**15**) and *manool* (**17**) on viable cell number of selected susceptible Enterococcal strains. Time-kill curves were recorded in the absence or presence of the selected compounds at a concentration of 4 × MIC.

7.4.5 ATP production in purified mammalian ATP synthase

The *n*-hexane-insoluble and soluble fractions, the thirteen sub-fractions (I_a-VI_a and I_b-VII_b) and the nineteen pure compounds were investigated for the modulation of ATP synthase activity. Purified mammalian rod outer segments (OS) were utilized as a subcellular system allowing the rapid assay of the oxidative phosphorylation. In fact, the OS are composed of a stack of membranous disks, naturally sealed vesicles expressing the molecular machinery for the complete oxidation of glucose, thereby comprising the tricarboxylic acid cycle [121], and the five complexes of respiration [122]; [123]. This could get some indication of a possible correlation between the antibacterial activity and the modulation of the ATP synthase, in view of deeper investigations. Resveratrol, a known inhibitor of rod OS ATP synthase, was used as a positive control [63]. The data were verified by one-way ANOVA (performed in MATLAB 2019a), and differences among groups evaluated with the Bonferroni test ($p < 0.05$) (**Figures 10** and **S77**, Supporting Information). The extract and the majority of sub-fractions showed activity (**Fig**. **S77** Supporting Information). ANOVA singled out five groups among the nineteen compounds. The group with the most interesting activity comprised compounds **10**, **11**, **15** and **17**, that showed an inhibition of ATP production of 60, 79, 70 and 60%, respectively. The differences within this group were not statistically significant. The obtained data, showing inhibition of ATP production in the OS (**Figure 10**) by the four pure compounds, could suggest an inhibitory action on the oxidative phosphorylation [63]; [124]; [125]. The inhibition of ATP hydrolysis activity was also evaluated, as some plant metabolites were shown to be able to hinder also the clockwise rotation, which accomplishes for the reversal of the ATP synthetic activity of the enzyme, producing ATP lysis [126]; [127]. The effect of extract, fractions, sub-fractions and pure compounds on this activity are shown in **Figures 11** and **S78** (Supporting Information). At a concentration of 80 ug/mL, manool (**17**) inhibited ATP hydrolysis by 92%. ANOVA analysis showed that this compound had a mode of action that was distinctly different from the others (**Fig. 11**). The ability to inhibit also ATP hydrolysis activity could indicate that the modulating effect on ATP synthesis is not merely due to membrane uncoupling.

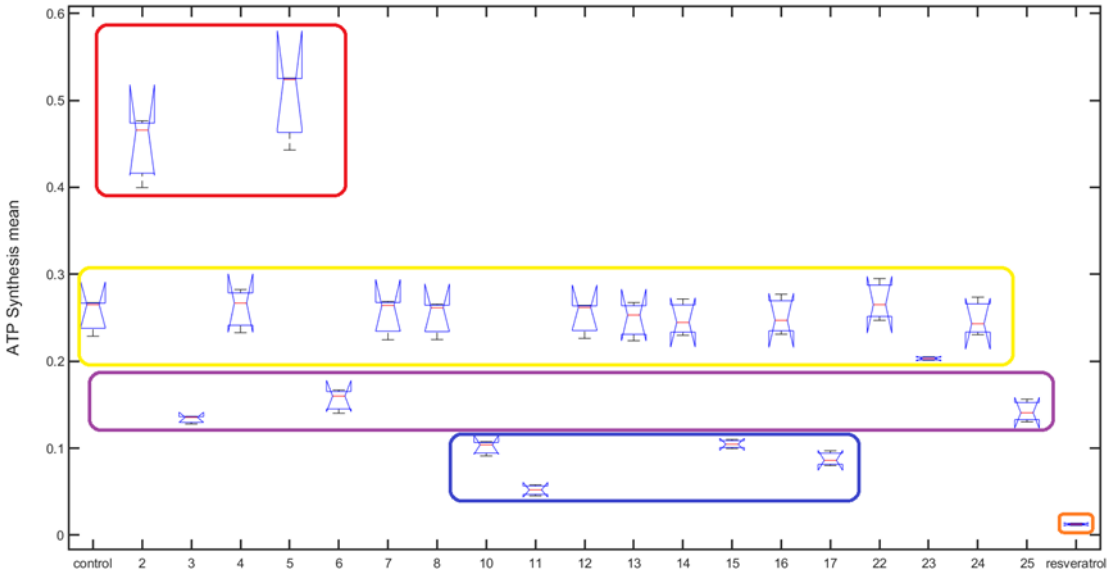

Figure 10. Effect of compounds on ATP synthesis among groups tested with one-way ANOVA. The null hypothesis is rejected and 5 groups of action can be identified.

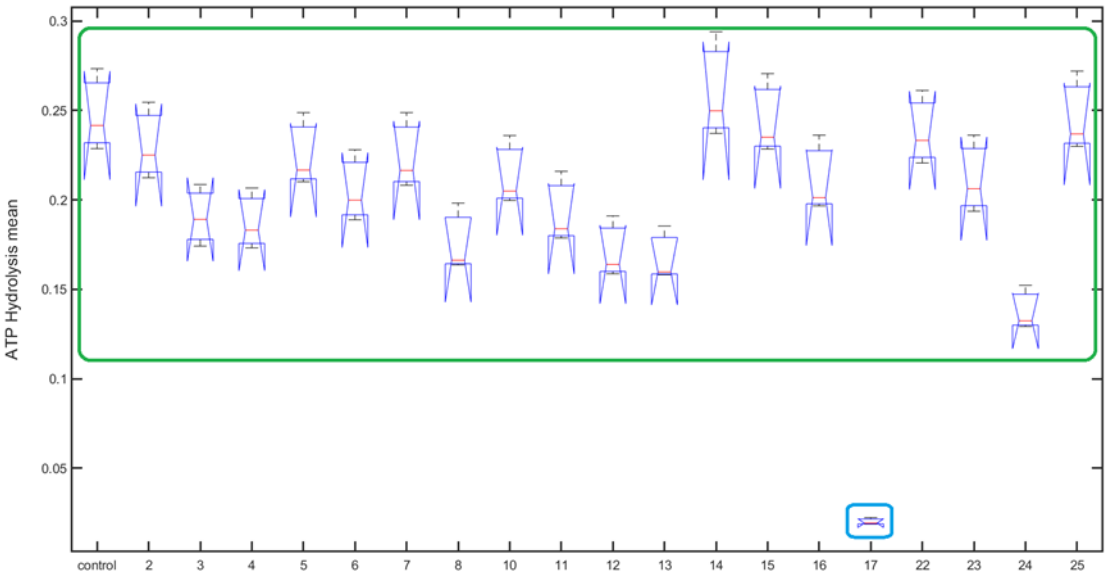

Figure 11. Effect of compounds on ATP hydrolysis among groups tested with one-way ANOVA. The null hypothesis is rejected, and 2 groups of action can be identified. The most active group contains only manool (**17**).

7.4.6 Molecular modeling

Molecular dynamics (MD) simulation studies and ligand-protein binding energy evaluations were performed in order to evaluate how **17** could interact with ATP synthase. Our analysis focused on the F1 catalytic domain of the protein (F1-ATPase), since several plant compounds such as resveratrol, piceatannol and quercetin are known to interact with F1-ATPase inhibiting ATP synthesis and hydrolysis. Precisely, X-ray structures of bovine F1-ATPase in complex with these compounds revealed a common binding site located among the α and β subunits of the protein, constituting the crown domain, and the C-terminal tip of the γ-subunit that is known to rotate inside the crown domain in association with ATP synthesis and hydrolysis. These ligands are thus supposed to inhibit ATP synthase activity by impeding this rotation, thus disrupting the catalytic machinery of the protein [126]. For this reason, manool was docked into the X-ray structure of bovine F1-ATPase in complex with quercetin (PDB code 2JJ2) [126] using a thorough AUTODOCK [128] procedure that produced good results in both virtual screening and pose prediction studies [129]; [101]. The docking protocol generated 200 different docking solutions, which were then clustered on the basis of their reciprocal root-mean square (RMSD) deviation using a threshold of 2.0 Å (see Materials and Methods for details), thus producing a total of three different clusters of poses. For each of these clusters, the docking solution associated with the best estimated binding energy was selected as a representative binding mode and further studied through MD simulations. The MD protocol was first applied on the reference X-ray structure of bovine F1-ATPase in complex with quercetin (PDB code 2JJ2), [126] which was subjected to a total of 30 ns MD simulation. The complex showed a remarkable stability during the simulation, since after less than 5 ns the system attained an equilibrium and during the rest of the simulation it maintained an approximately constant value of total energy. Moreover, the bound ligand showed an average RMSD of its position with respect to the starting coordinates of 2.0 Å (**Fig**. **S79** Supporting Information). The same MD protocol was thus applied on the three ATPase-manool complexes in order to evaluate the stability of the binding modes predicted by docking. The results were then analyzed in terms of RMSD of the ligand disposition during the simulation concerning its coordinates in the starting complex. The analysis highlighted a high stability for pose 3, in which the ligand maintained an average RMSD of about 1.9 Å during the whole simulation (**Fig. 12**). On the contrary, the other two binding poses predicted by docking did not show enough stability. In both cases the ligand moved considerably from its initial binding disposition, as demonstrated by the high RMSD of its coordinates with respect to the starting pose that reached values around 9–10 Å. Based on these results, we could already consider both pose 1 and 2 as unreliable binding dispositions with respect to pose 3. However, in order evaluate the different binding modes form an energetic point of view, relative binding free energy evaluations were performed on all the three ATPase-manool complexes with the aim of identifying the most energetically reliable binding mode [130]. Ligand-protein binding energies were calculated using the Molecular Mechanic-Poisson Boltzmann surface area (MM-PBSA) method [131] on the MD trajectories relative to the last 15 ns of simulation (Table **S2** Supporting Information). The analysis clearly confirmed the reliability of pose 3, whose estimated ligand-protein binding affinity (-21.4 kcal/mol) exceeded of about 9–12 kcal/mol those evaluated for pose 1 and pose 2 (Table **S2**, Supporting Information). **Fig.13** displays the minimized average

structure of F1-ATPase complexed with the manool in binding mode 3, as obtained from the last 15 ns of MD simulation. Due to its lipophilic nature, the ligand predominantly forms hydrophobic interactions with the binding site residues. The bicyclic core of the ligand strongly interacts with P320, as well as with V276, T318 and Q330, while its lateral chain shows lipophilic interactions with A278, V279, A293, I263, constituting a small subpocket together with by K260, E264 and E292. Interestingly the terminal vinyl group of manool shows a NH-π interaction with the backbone nitrogen of A278 [132]. Despite the polar portion of the ligand is limited to its hydroxyl group, this moiety is able to establish strong H-bonds with both K260 and E264 that account for a not negligible contribution to the total ligand-protein binding energy (Table **S2**, Supporting Information) and probably promotes the stability of the binding pose by providing the ligand with a good anchoring point.

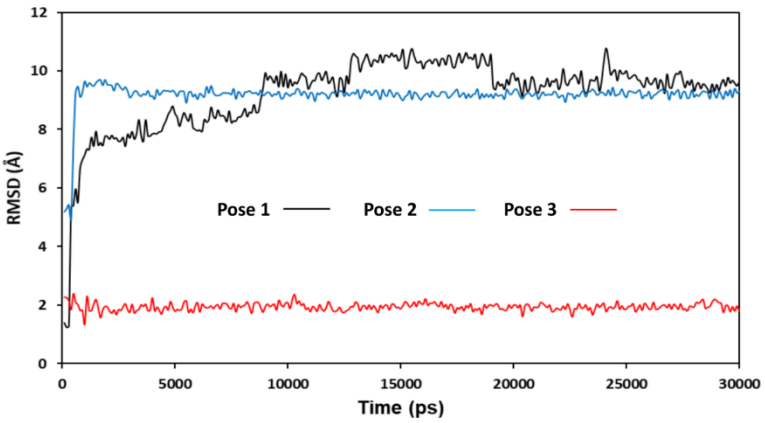

Figure 12. MD analysis of the three binding modes predicted by docking manool (**17**) into F_1-ATPase. The plot shows the RMSD of the ligand disposition during the simulation with respect to its initial docking pose.

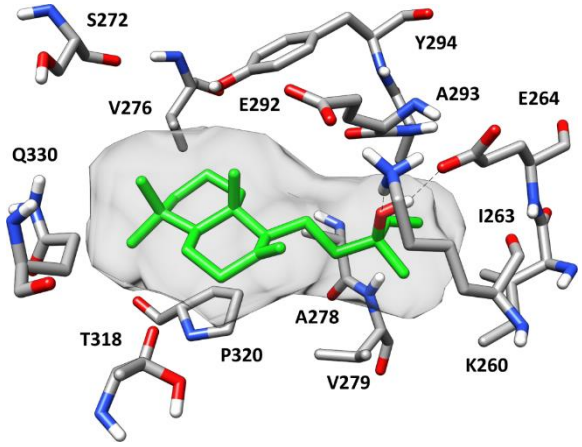

Figure 13. Minimized average structure of manool (**17**) complexed with F1-ATPase in binding mode 3. Hydrogen bonds are represented as black dashed lines. The ligand molecular surface is shown in gray.

7.4.7 Evaluation of ATP production

Finally, the ATP production in the presence or absence of manool (**17**) by *E. faecalis* MB 1 (VRE) and *E. faecium* MB 152 (VRE) was evaluated in whole-cell assay, where the bacteria were supplied with nutrients, after incubation of two hours. This timing was chosen because the duplication time of *Enterococcus* spp. is approximately 30 min [133]. An important reduction of the ATP amount of bacterial cells was observed in *E. faecium* (inhibited by 30%) (**Fig. 14**). The data on ability to regenerate ATP of bacteria are to be considered with caution as the pool of steady state ATP is dependent on many processes (glycolysis, substrate-level phosphorylation, oxidative phosphorylation, nutrient uptake systems) affecting its consumption and production. These results displayed that a correlation between the in vivo antibacterial effect and the modulation of ATPase activity could be hypothesized for manool (**17**) and this could deserve other study.

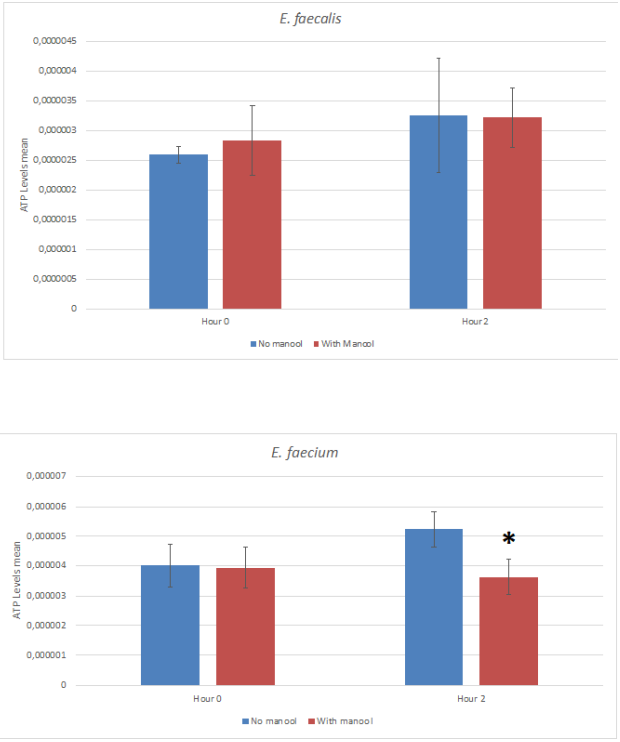

Figure 14. ATP levels determined by measuring luminescence levels and comparing with an ATP standard curve. Amount of ATP (pmol/cfu) produced by *E. faecalis* MB 1 (VRE) and *E. faecium* MB 152 (VRE) in the absence and in the presence of manool (**17**) (5 x MIC) at time of inoculum and after 2 hours of incubation at T = 37 ^{o}C. Results are expressed as mean ± SD of three separate experiments, with three replicates per experiment. Statistically significant differences between treatment and control groups were determined using Student's t-test ($p < 0.05$).

10. General experimental procedures

10.1 Solvents for extraction and chromatographic purposes

Dichloromethane was utilized as extraction solvent for the fresh aerial parts of *Salvia*. Solvents or mixtures of them, from *n*-hexane to methanol with an increasing degree of polarity were utilized for classic chromatographic methods on column of Sephadex LH-20 or Silica gel, to yield the semi-purified groups of fractions. Analytical grade solvents were filtered two times before their use in medium pressure liquid chromatography, removing any trace of impurities. Mixtures of deionized water and methanol at a decreasing degree of polarity were utilized for solid reverse-phase extractions, *n*-hexane (2.5L), dichloromethane (2.5L), chloroform (2.5L), methanol (2.5L) were of analytical grade and purchased from VWR-BDH Prolabo (Lutterworth, Leichestershire, England). Analytical grade solvents were utilized for all chromatographic purposes, with the exception of HPLC, were HPLC-grade and purchased from VWR-BDH Prolabo. HPLC-grade water (MilliQ) was prepared using a commercial water purification system (Millipore Synergy 185, Millipore, Billerica, MA Massachusetts, USA).

10.2 Extraction techniques

In addiction to the extraction with dichloromethane, freeze-dried samples, roots and leaves were extracted by homogenizing with a high throughput homogenizer, Precellys 24 (Bertin, France) at 5000 rpm for 30 s and a Precellys kit: 7mL hard tissue homogenizing mix CK28, 050 Preps, Cat.N°03961-1-302 (ceramic beads mix), using methanol.

10.3 Chromatographic techniques

Silica gel 60 F254 coated aluminium sheets (Merck, 20x20 cm, 0.2 mm layer thickness) were used for TLC (thin layer chromatography), to analyze each separation. A mixture of $CHCl_3$-CH_3OH-HCOOH (10:0.5:0.1) was utilized as mobile phase, and spots were detected by UV light at 254 and 366 nm, and subsequently spraying 50% H_2SO_4, followed by heating.

Various column chromatography have been utilized for the separations of complex mixtures, comprising both Sephadex, less accurate method, and silica gel, with a better separation capacity. With the stationary phase, mixtures can be separated by adsorption, partition, ion exchange or size exclusion processes. Based on the affinity of plant constituents for stationary phase and the different solvents or solvent mixtures with increasing polarity flushing, different extracts were obtained. Sephadex LH-20(GE Healthcare, Little Chalfont, Buckinghamshire, UK), was utilized for preliminary column chromatography, always using a solvent blend composed by chloroform and methanol in proper proportions for the whole analysis time; Silica gel 60 was purchased from Merck and was of 230-400 meshes. In this latter case, solvent or solvents blends, from the most lipophilic to the most polar, were utilized for column chromatography.

MPLC (medium pressure liquid chromatography) was carried out on Normal Phase Si60 Cartridge Supervarioflash and LiChroprep RP-18 (40-63 um) (Merck, Darmstadt, Germany). For the use of a medium pressure, MPLC provided to keep a regular flux of solvents (mobile phase) through the packed silica gel (stationary phase) into columns characterized by a large

diameter. The choice of columns depended on the quantities of fractions to load. We utilized SuperVarioPrep cartridge D40 with outer dimensions LxD 185x 47 mm, SuperVarioFlash D26 (135x33mm), D22 (122x 24 mm), containing 70, 25 and 10g of silica gel respectively.

The solid phase extraction (SPE) was carried out by loading the complex sample into a preconditioned extraction cartridge, containing a chromatographic sorbent, both in normal phase with SPE Strata SI-1 Silica Cartridge and reverse-phase with SPE Strata C18-E Cartridges, either 55um, 70 A particle size and pore size, respectively; 500 mg /3 mL capacity (Phenomenex, Torrance, California, USA).

Analytical HPLC was carried out on a Thermofisher Dionex Ultimate 3000 SD chromatographic system, comprising a Dionex LPG-3400 SD pump, ACC-3000 auto-sampler column compartment, SR-3000 UltiMate 3000 solvent rack without degasser, VWD-34000 RS detector Chromeleon 7 Workstation Secure at fixed wavelength (Thermo Fisher Scientific, Waltham, Massachusetts, USA). For analytical HPLC, a Symmetry 300 C18 column, or a XBridge Shield RP18 column, 4.6 x 250mm ID, 5um particle size (Waters Corporation, Milford, Massachusetts, USA) were utilized, at room temperature, flow rate from 0.5 to 1 mL/min, sample loop and injection volume 20 uL. The elution mixtures were composed of CH_3OH-acidified H_2O or CH_3CN-H_2O, at various appropriate ratios, mostly using a linear gradient.

Semi-preparative HPLC utilized to purify fractions after classical chromatographic methods, was performed with a Waters W600 pump equipped with a Rheodyne Delta 600 injector, a 2414 refractive index detector, and a 2998 photodiode array detector (all Waters). For semi-preparative HPLC, C18 columns, SymmetryPrep C18, 7.8 x 300mm ID, 7um particle size, XBridge Prep Shield RP18, 10 x 250mm ID, 5um particle size, uBoundapack C18, 7.8 x 300mm ID, 10 um particle size (Waters) were utilized, at room temperature, flow rate from 1.0 to 2.0 mL/min, sample loops of 100uL. The elution mixture was composed of CH_3OH-H_2O at appropriate ratios, using a linear gradient. Data acquisition was controlled by Empawer 2 software (Waters). UV spectra were recorded with an HP 8453 diode array spectrophotometer (Hewlett Packard, Palo Alto, California, USA).

LC/MS analyses were performed using a system consisting of an Agilent 1100 chromatography apparatus coupled with an API200 ESI mass spectrometer equipped by a triple quadrupole analyser. Chromatography separation was performed on a Luna C18 column, 2.0 x 100 mm ID, 5 um particle size (Phenomenex, Torrance, CA, USA) using 0.1% formic acid in water (A) and (CH_3CN) (B) as mobile phase. Compound elution was attained performing a gradient of A:B from 45:55 to 10:90 over 10 min. injected volume 10 uL, flow rate 0.4 mL/min. The mass spectrometer operated in positive mode.

10.4 Spectroscopic techniques and structural elucidation

A Bruker DRX-600 (Bruker, Billerica, Massachusetts, USA) and Bruker Avance-500 (Bruker BioSpin GmbH, Rheinstetten, Germany) NMR spectrometers running the XWINNMR (Bruker software package) were used for mono-(^1H and ^{13}C NMR) and two-dimensional (COSY, HMBC, HSQC and ROESY) NMR experiments. Spectra were studied on MestreNova.

ECD spectra were measured in CH_3OH on a Chirascan CD spectrometer and were analysed with Pro-Data V2.4 software.

VCD spectra were recorded in $CDCl_3$ on a Bruker PMA 50 accessory coupled to a Tensor 27 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90, Hinds Instruments, Hilliboro, USA) was utilized to modulate the handedness of the circular polarized light.

Optical rotations were measured with a Perkin-Elmer 241 polarimeter (Perkin Elmer, Inc. Waltham, Massachusetts, MA, USA) equipped with a sodium lamp (589nm) and a 10cm microcell.

10.5 Spectrophotometric techniques used for biological analyses

Spectrophotometric measurements were conducted both on an UV/Vis spectrophotometer SPECTROstarNano (BMG Labtech) and a Tecan SPECTRA III Microplate Reader-Screen, Spectra Rainbow spectrophotometer, by using 96-well microplates. Each measurement was done in triplicate.

10.6 Microscopy technique

Light microscopy experiments were conducted using an Olympus IX 81 microscope (10x objective) and processing Olympus XCellence RT software (Olympus, Tokyo, Japan).

10.7 Purified bovine rod OS preparations.

Purified bovine rod outer segments (OS) were set under dim red light at 4 °C from fourteen retinas, by sucrose/Ficoll continuous gradient centrifugation [134] in the presence of protease inhibitor cocktail (Sigma-Aldrich) and ampicillin (100 µg/mL). OS preparations were characterized for integrity of plasma membrane as previously reported [134].

10.8 ATP synthesis assay in rod OS.

Rod OS (5 µg) [63] were incubated for 5 min at 37 °C in 50 mM Tris/HCl (pH 7.4), 5 mM KCl, 1 mM EGTA, 5 mM $MgCl_2$, 0.6 mM ouabain, 0.25 mM di(adenosine)-5-pentaphosphate (Ap5A, adenylate kinase inhibitor), 5 mM KH_2PO_4, 20 mM succinate, 0.35 mM NADH, and 25 µg/mL ampicillin. ATP synthesis was induced by adding 0.1 mM ADP. Reaction was stopped with 7% perchloric acid. ATP concentration was measured by the luciferin/luciferase chemiluminescent method (Roche Diagnostics Corporation, Indianapolis, IN, USA) in a luminometer (Lumi-Scint, Bioscan Inc, Washington, DC, USA). Where necessary, the incubation medium contained the incubation medium contained 30 µM resveratrol or 80 µg/mL of different purified *S. tingitana* extracts, sub-fractions or pure compounds.

10.9 ATP hydrolysis assay in rod OS.

The ATPase activity of rod OS was analyzed by the pyruvate kinase/lactate dehydrogenase system in which hydrolysis of ATP is coupled to the oxidation of NADH followed at 340 nm (ε340 for NADH = 6.22 $mM^{-1} \cdot cm^{-1}$), as previously described [63]. Rod OS (40 µg) were added to a reaction mixture containing 50 mM HEPES, pH 7.4, 100 mM KCl, 150 mM NaCl, 1 mM EGTA, 2.5 mM $MgCl_2$, 0.8 mM ouabain, 0.15 mM NADH, 0.4 mM Ap5A (adenylate kinase

inhibitor), 1.5 mM phosphoenolpyruvate, pyruvate kinase and lactate dehydrogenase, and 25 µg/mL ampicillin. ATP hydrolysis was subsequently induced by adding 1 mM ATP. Where necessary, the incubation medium contained 80 µg of different purified *S. tingitana* extracts, sub-fractions or pure compounds.

10.10 Determination of ATP concentration in bacterial culture in the presence of manool

Strain was grown in Mueller Hinton II (MH II) Broth (BD Cat.# 297963;) at 37 °C overnight. The overnight culture was diluted 1:106 in 50 mL of fresh MH II Broth and incubated at 37 °C for 2 hours. Cultures were then diluted up to OD600 and, when necessary, manool was added at concentrations corresponding to 5 x MICs. Aliquots of samples were collected at two time points (0 and 2 hours) to determine ATP concentration using BacTiter-Glo™ Microbial Cell Viability Assay Reagent (Promega, Madison, WI). It is a luciferase – based assay and the ATP level is determined by measuring luminescence levels and comparing to an ATP standard curve. One hundred microliters of culture were mixed with an equal volume of BacTiter-Glo™ Microbial Cell Viability Assay Reagent in Eppendorf tubes and incubated at room temperature for 5 min. After incubation, luminescence was read in a luminometer (Lumi-Scint, Bioscan Inc, Washington, DC, USA). ATP standard solutions were prepared using adenosine 5-triphosphate disodium salt hydrate (A2383, Sigma Aldrich, St. Louis, MO), and a standard curve using ATP standard at concentrations between 1 and 0.001 pmol was recorded. ATP concentrations in bacterial samples were determined by comparison with the ATP standard curve for each assay. MH was included in all assays as the negative control.

10.11 Computational methods.

Conformational analysis was carried out with Schrödinger MacroModel 9.8 (Schrödinger, LLC, New York, USA) employing the OPLS2005 (optimized potential for liquid simulations) force field in H_2O or chloroform for ECD or VCD calculations, respectively. The five conformers with the lowest energy were selected for geometrical optimization and energy calculation applying DFT with the Becke's nonlocal three parameter exchange and correlation functional, and the Lee-Yang-Parr correlation functional level (B3LYP), using the 6-31G(d, p) basis set and the SCRF method with the CPMC model for solvation (MeOH for ECD calculations) with the Gaussian 09 program package [135]. Vibrational evaluation was done at the same level to confirm minima. Excitation energy (denoted by wavelength in nm), rotator strength (Rstr), dipole velocity (Rvel), and dipole length (Rlen) were calculated in MeOH by TD-DFT/B3LYP/6-31G(d,p). ECD curves were obtained based on rotator strengths with a half-band of 0.3 eV using SpecDis v1.71.73

Vibrational frequencies (given as wavenumbers in cm^{-1}), rotator strength (Rstr), IR intensity (IRinten) and dipole strength (Rstr) were calculated in chloroform with B3LYP/6-31+G(d, p). VCD curves were obtained based on rotator strengths with a bandwidth of 7 cm^{-1} using CDspecTech v22.0.74, 75 ECD and VCD spectra were calculated from the spectra of individual conformers according to their contribution calculated by Boltzmann weighting. Comparison was done visually as by calculation of similarity indices (SimVA, SimVCD) which were generated by VCDspecTech v22.0.31 The SimVCD values were plotted against the scaling factors of the x axis, and graphs compared between the different stereoisomers.

10.12 Statistical analysis

All determinations were performed in triplicate, and the results indicated as mean ± standard deviation (SD). Data were considered statistically significant at $p \leq 0.05$. The null hypothesis of equality in action for all compounds was tested with one-way ANOVA [136]. In all cases the null hypothesis was rejected and the possible differences among formed groups were tested with the Bonferroni method.

10.13 Docking Studies.

Manool (**17**) was built using Maestro [137] and subjected to minimization with Macromodel [138], employing the generalized Born/surface area model to simulate a water environment. The conjugate gradient algorithm, the MMFFs force field and a distance-dependent dielectric constant of 1.0 were utilized for the minimization, performed until a convergence value of 0.05 kcal/(Å·mol) was reached. The ligands were docked into the X-ray structure of bovine F1-ATPase in complex with inhibitor quercetin (PDB code 2JJ2) [126] using AUTODOCK4.2. [128] AUTODOCK TOOLS [139] were utilized to define the torsion angles in the ligand, to add the solvent model and to assign partial atomic charges (Kollman for the protein and Gasteiger for the ligand). A grid box of 56, 50, and 50 points in the x, y, and z directions, respectively, centered on the co-crystallized inhibitor was used to define the docking site for AUTODOCK calculations. The energetic maps required for docking were generated with a grid spacing of 0.375 Å and a distance-dependent function of the dielectric constant. The three ligands were docked using 200 Lamarckian genetic algorithm runs of the AUTODOCK search. During each docking run, 10'000'000 steps of energy evaluation were carried out and a maximum of 10'000'000 generations were simulated starting from an initial population of 500 individuals. The final docking solutions were clustered together using a rms cut-off of 2.0 Å and leaving all other settings as their defaults. The clusters of solutions with a population higher than 5%, i.e. including more than 5% of all the generated docking poses, were considered.

10.14 Molecular Dynamic simulations.

All simulations were carried out using AMBER 1485 using the X-ray structure of bovine F1-ATPase in complex with quercetin (PDB code 2JJ2) already employed for docking. The initial and terminal segments of all protein monomers whose residues were placed more than 30 Å away from the bound ligand were not taken into account in the simulations. All ligand-protein complexes obtained by docking were solvated with a 15 Å water cap within a parallelepiped box; chloride ions were then added as counterions for neutralizing the system. General amber force field (GAFF) parameters were assigned to the ligands, while partial charges were calculated using the AM1-BCC method. Initially, the complexes were subjected to energy minimization through 5'000 steps of steepest descent followed by conjugate gradient, until a convergence of 0.05 kcal/(mol·Å2) was reached. The minimized systems were used as starting point for an MD simulations protocol composed of three steps. In the first one, 0.5 ns of constant-volume simulation were performed, raising the temperature of the system from 0 to 300 K. In the second step, the system was equilibrated through a 3 ns constant-pressure simulation where the temperature was kept constant at 300 K by using the Langevin thermostat. In the third and last MD step, additional 26.5 ns of

constant-pressure simulation were performed, thus reaching a total simulation time of 30 ns. In both the minimization and the three MD steps, a harmonic potential of 10 kcal/(mol·Å2) was applied to the protein α carbons. All MD steps were run using particle mesh Ewald electrostatics and periodic boundary conditions, 86 while a cut-off of 10 Å were employed for the non-bonded interactions and SHAKE algorithm was used to keep rigid all bonds involving hydrogens.

10.15 Binding Energy Evaluation.

Relative binding free energy evaluations were performed using AMBER 14. The trajectories extracted from the last 15 ns of each simulation were used for the calculation, for a total of 150 snapshots (at time intervals of 100 ps). Van der Waals, electrostatic and internal interactions were calculated with the SANDER module of AMBER 14, whereas the Poisson−Boltzman method was employed to estimate polar energies through the MM-PBSA module of AMBER 14 as previously reported [129]; [130]. Gas and water phases were represented using dielectric constants of 1 and 80, respectively, while nonpolar energies were calculated with MOLSURF program. The entropic term was considered as approximately constant in the comparison of the ligand-protein energetic interactions.

10.16 Plant material

Fresh aerial parts of *Salvia tingitana* Etl. were obtained from CREA FSO San Remo, Italy. The plant material is identified by Prof. Ammar Bader, and a voucher specimen (UQU-IT-2019/1) was deposited in the Laboratory of Pharmacognosy at Umm Al-Qura University, Saudi Arabia.

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12 Appendix

Table 1. *Salvia* species containing quinone diterpenes[a]

Species name [65]	Protologue [65]	Subgeneric classification	Hedge's 'species-groups'	Molecular phylogenetic studies	References
***Salvia absconditiflora* Greuter & Burdet**	Willdenowia 15: 77 (1985)	Sect. *Hymenosphace* Benth. (as *S. cryptantha*) [140] Subg. *Schraderia* (Moench) Briq. Sect. *Hymenosphace* (as *S. cryptantha*) [141]	Group C of Flora of Turkey [142]	*Salvia* s.s. clade I-C [17]	[140], [141], [142], [17], [143], [23]
***Salvia aegyptiaca* L.**	Sp. Pl.: 23 (1753)	Sect. *Notiosphace* Benth. [140], [144], [145]; Sect. *Eremosphace* (*Notiosphaces* Benth.) Bunge [146], [147]; Subg. *Viasala* Briq. Sect. *Eremosphace* Bunge [148], [149], [141]	Group F of *Salvia* in Africa [11] Group 2 of Flora Iranica [150]	*Salvia* clade III first lineage [30], [32]; *Salvia* s.l. clade III-A (*Pleudia* Raf.) [17]; *S. aegyptiaca* clade [19]	[19], [140], [141], [17], [144], [145], [146], [147], [149], [11], [150], [30], [32], [151], [28]
***Salvia aerea* H.Lév.**	Repert. Spec. Nov. Regni Veg. 12: 532 (1913)	Subg. *Eusalvia* Stib. (Subg. *Salvia* Benth.) Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Benth. Sect. *Eurysphace* Stib. Subsect. *Perennes* C.Y.Wu Ser. *Digitaloidites* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		Chinese clade, subclade iii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [17], [28], [152], [153]
***Salvia aethiopis* L.**	Sp. Pl. 27 (1753)	Sect. *Aethiopis* Benth. [140], [145]; Sect. *Gongrosphace* Briq. (sect. *Aethiopis* Benth. *ex parte*) [146]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Gongrosphaceae* (Boiss.) Briq. Ser. *Lanatae* Pobed. [141], [154]	Group G of Flora of Turkey [142]; Group 3 of Flora Iranica [150]	*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-C [18], [17]	[140], [141], [142], [17], [145], [146], [150], [30], [32], [28], [154], [18], [155], [156]
***Salvia amplexicaulis* Lam.**	Tabl. Encycl. i. 68 (1791)	Sect. *Plethiosphace* Benth. [155]	Group F of Flora of Turkey [142]	*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-C [17]; *S. officinalis* clade [19]	[19], [142], [17], [30], [32], [155], [156]
***Salvia anastomosans* Ramamoorthy**	J. Arnold Arbor. 65: 135 (1984)	Subg. *Calosphace* Benth. Sect. *Tometellae* Epl. [157]			[157]
***Salvia apiana* Jeps.**	Muhlenbergia 3: 144 (1908)	Sect. *Audibertia* Benth. Subsect. *Jepsonia* Epl. [158]; Sect. *Audibertia* (Benth.) Epling. Subsect. *Jepsonia* Epl. Ser. *Ramona* (Greene) Neisess [159]		*Salvia* clade II [30], [32]; California *Salvia* clade (subclade *Audibertia*) [31]	[30], [32], [158], [159], [31], [160]

		Subg. *Audibertia* J.B.Walker, B.T.Drew, & K.J.Sytsma Sect. *Audibertia* J.B.Walker, B.T.Drew, & K.J.Sytsma [31]			
***Salvia argentea* L.**	Sp. Pl. ed. 2: 38 (1762)	Sect. *Aethiopis* Benth. [140], [145], [156] §. *Gongrosphaceae* Sect. *Gongrosphace* Bunge [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Gongrosphaceae* (Boiss.) Briq. [141]	Group R of *Salvia* in Africa [11]; Group D of Flora of Turkey [142]	*Salvia* s.s. clade I-C [17]	[140], [141], [142], [17], [143], [145], [147], [11], [155], [156]
***Salvia arizonica* A.Gray**	Syn. Fl. N. Amer. 2(1): 370 (1878)	Subg *Calosphace* Benth. Sect. *Uliginosae* Epl. [64]; Subg. *Calosphace* Benth. Sect. *Lanatae* Epl. [66]			[64], [66]
***Salvia austriaca* Jacq.**	Fl. Austriac. 2: 8 (1774)	Sect. *Plethiosphace* Benth. [140], [145], [147], [155]; Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. B. *Euplethiosphaceae* Briq. [141]; Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. Ser. *Autriacae* Pobed. [154]		*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-C [18], [17]	[140], [141], [17], [145], [147], [30], [32], [154], [18], [155], [28]
***Salvia axillaris* Moc. & Sessé ex Benth.**	Labiat. Gen. Spec. 270 (1833)	Sect. *Calosphace* Benth. §. *Axillaeflorae* Benth. [140]; Sect. *Calosphace* Benth. §. *Brachyantha* D. *Axilliflorae* Benth. [145]; Subg. *Jungia* (Moench) Briq. Sect. *Calosphace* Benth. §. *Brachyanthae* Benth. C. *Axilliflorae* Benth. [141]; Subg. *Calosphace* Benth. Sect. *Axillares* Epl. [64]; Sect. *Calosphace* Epl. [161]		*Salvia* clade II [32]; (*Axillares*) [29]; *Salvia* s.l. clade II-A (*Lasemia* Raf.) [17]; Subg. *Calosphace* [19]; *Axillares* monotypic section [151]	[19], [140], [141], [17], [145], [32], [151], [64], [161], [29], [162]
***Salvia ballotiflora* Benth.**	Labiat. Gen. Spec.: 270 (1833)	Sect. *Calosphace* Benth. §. *Brachyantha* D. *Axilliflorae* Benth. (as *S. ballotaeflora*) [140], [145]; Subg. *Jungia* (Moench) Briq. Sect. *Calosphace* Benth. §. *Brachyanthae* Benth. C. *Axilliflorae* Benth. [141]; Subg. *Calosphace* Benth. Sect. *Tomentellae* Epl. (as *S. ballotaeflora*) [64]		*Salvia* clade II [30], [32]; *Tomentellae* clade III [29]; *Tomentellae* clade II [151]	[140], [141], [145], [30], [32], [151], [64], [29]
***Salvia barrelieri* Etl.**	Salv.: 46 (1777)	Sect. *Plethiosphace* Benth. (*Species hujus sectionis dubia*) [145]; Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. B. *Euplethiosphaceae* Briq. [141]	Group U of *Salvia* in Africa [11]	*Salvia* s.s. clade I-C [17]	[141], [17], [145], [11]

***Salvia blepharochlaena* Hedge & Hub.-Mor.**	Notes Roy. Bot. Gard. Edinburgh 22: 178 (1957)	Sect. *Hymenosphace* Benth. [163]	Group A of Flora of Turkey [142]	*Salvia* s.s. clade I-D [17]	[142], [17], [143], [23], [163]
***Salvia bowleyana* Dunn**	J. Linn. Soc., Bot. 38: 363 (1908)	Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. [152], [25] Ser. *Miltiorrhizae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Drymosphace* Benth. [19]		Chinese clade, subclade i, group i [28]; *Salvia* s.l. clade IV-B (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Drymosphace* (G7) (*S. miltiorrhiza* group) [19]	[19], [17], [28], [152], [153], [25],
***Salvia bracteata* Banks & Sol.**	Nat. Hist. Aleppo, ed. 2, 2: 242 (1794)	Sect. *Eusphace* Benth. [140], [145], [147]; Subg. *Salvia* Benth. Sect. *Eusphace* Benth. §. *Pinnatae* Boiss. A. *Fruticosae* Boiss. [141]; Sect. *Salvia* Hedge (Sect. *Eusphace* Benth.) [155]	Group B of Flora of Turkey [142]; Group 1 of Flora Iranica [150]	*Salvia* s.s. clade I-D [17]	[140], [141], [142], [17], [143], [23], [145], [147], [150], [155]
***Salvia brevilabra* Franch.**	Bull. Annuel Soc. Philom. Paris, sér. 8, 3: 149 (1891)	Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Benth. Sect. *Eurysphace* Stib. Subsect. *Perennes* C.Y.Wu Ser. *Digitaloidites* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		*Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [17], [152], [153], [164]
***Salvia bucharica* Popov**	Trudy Turkestansk. Nauchn. Obshch. 1: 40 (1923)	Gen. *Schraderia* Medik. Sect. *Holochilus* Pobed. Ser. *Bucharcae* Pobed. (as *Schraderia bucharica*) (M. Pop.) Nevski [154]; Subg. *Schraderia* (Moench) Briq. Sect. *Hymenosphace* Benth. [149]	Group with *S. hydrangea* DC. (E Turkey, N & W Iran), *S. shelley* Boiss. (S & W Iran), *S. dracocephaloides* Boiss. (Transcaucasus, NW Iran) and *S. maymanica* Hedge [165]; Group 1 of Flora Iranica [150]	*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-D [17]	[17], [149], [150], [30], [32], [154], [165]
***Salvia bulleyana* Diels**	Notes Roy. Bot. Gard. Edinburgh 5: 233 (1912)	Subg. *Eusalvia* Stib. (Subg. *Salvia* Benth.) Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Benth. Sect. *Eurysphace* Stib. Subsect. *Perennes* C.Y.Wu Ser. *Castaneae* C.Y.Wu [153];		*Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [17], [152], [153]

		Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]			
***Salvia campanulata* Wall. ex Benth.**	Pl. Asiat. Rar. 1: 67 (1830)	Sect. *Drymosphace* Benth. [140], [145], [144]; Subg. *Salvia* Benth. Sect. *Drymosphace* Benth. [141]; Subg. *Salvia* Benth Sect. *Eurysphace* Stib. Subsect. *Perennes* C.Y.Wu Ser. *Campanulatae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		*Salvia* s.l. clade IV (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [140], [141], [17], [145], [144], [153]
***Salvia cana* Wall. ex Benth.**	Edwards's Bot.Reg.15: t.1292 (1830)	Subg. *Sclarea* (Moench) Benth. Sect. *Aethiopis* Benth. (as *S. lanata* Roxb.) [144]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. (Sect. *Aethiopis* Benth.) §. *Gongrosphace* (Boiss.) Briq. (as *S. lanata* Roxb.) [141]	Group 3 of Flora Iranica (as *S. lanata* Roxb.) [150]	*Salvia* s.s. clade I-C (as *S. lanata* Roxb.) [17]	[141], [17], [144], [150], [166], [167]
***Salvia canariensis* L.**	Sp. Pl.: 26 (1753)	Sect. *Hymenosphace* Benth. §. *Canariensis* [140], [145]; Subg. *Schraderia* (Monch) Briq. Sect. *Nactosphace* Briq. [141]	Group H of *Salvia* in Africa [11]	*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-C [18], [17]; *S. officinalis* clade [19]	[19,140], [145], [141], [11], [18], [30], [32], [17],
***Salvia candelabrum* Boiss.**	Elench. Pl. Nov.: 72 (1838)	Sect. *Eusphace* Benth. [145]; Subg. *Salvia* Benth. Sect. *Eusphace* Benth. §. *Simplicifoliae* Boiss. [141]; Sect. *Salvia* Hedge (Sect. *Eusphace* Benth.) [155]		*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-D [17]	[141], [17], [145], [30], [32], [155]
***Salvia candicans* M.Martens & Galeotti**	Bull. Acad. Roy. Sci. Bruxelles 11(2): 61 (1844)	Subg. *Jungia* (Moench) Briq. [141] Sect. *Calosphace* Benth. §. *Brachyantha* E. *Candicantes* [145], [141]; Subg. *Calosphace* Benth. Sect. *Tomentellae* Epl. [64]		*Salvia* clade II [30], [32]; (*Tomentellae*) [29]; *S. candicans* + *S. oaxacana* clade [151]	[141], [145], [64], [30], [32], [151], [29], [168]
***Salvia candidissima* Vahl**	Enum. Pl. Obs. 1: 278 (1804)	Sect. *Aethiopis* Benth. [140], [145]; Sect. *Aethiopis* Benth. §. *Gongrosphaceae* Sect. *Gongrosphace* Bunge [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Gongrosphaceae* (Boiss.) Briq. [141]	Group D of Flora of Turkey [142];	*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-C [17]	[140], [141], [142], [17], [143], [23], [145], [147], [30], [32], [28] [155], [156]

***Salvia candidissima* subsp. *candidissima*.**			Hedge Group D of Flora of Turkey [142]; Group 3 of Flora Iranica [150]		[142], [150]
***Salvia candidissima* subsp. *occidentalis* Hedge**	Notes Roy. Bot. Gard. Edinburgh 38: 48 (1980)		Hedge Group D of Flora of Turkey [142]	*Salvia* s.s. clade I-C [18], [17]	[142], [17], [18]
***Salvia carduacea* Benth.**	Labiat. Gen. Spec.: 302 (1833)	Sect. *Echinosphace* Benth. [140], [145]; Subg. *Leonia* (Llav. et Lex.) Benth. Sect. *Echinosphace* Benth. [141]; Sect. *Audibertia* Benth. Subsect. *Echinosphace* Epl. Ser. *Douglasiana* Epl. [158]; Sect. *Echinosphace* Benth. Subsect. *Douglasiana* Epl. Ser. *Eplingia* Neisess [159]; Subg. *Audibertia* J.B.Walker, B.T.Drew, & K.J.Sytsma Sect. *Echinosphace* J.B.Walker, B.T.Drew, & K.J.Sytsma [31]		California *Salvia* clade (subclade *Echinosphace*) [31]	[140], [141], [145], [158], [159], [160]
***Salvia castanea* Diels**	Notes Roy. Bot. Gard. Edinburgh 5: 233 (1912)	Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Benth. Sect. *Eurysphace* Stib. Subsect. *Perennes* C.Y.Wu Ser. *Castaneae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		Chinese Clade, subclade iii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [18], [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [17], [28], [152], [153], [18]
***Salvia cavaleriei* var. *simplicifolia* E.Peter-Stibal**	Acta Horti Gothob. 10: 61 (1935)	Subg. *Sclarea* Benth. Sect. *Drymosphace* Benth. sensu Stib. [169]; Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. Ser. *Miltiorrhizae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Sobiso* (Raf.) G.X.Hu, A.Takano & B.T.Drew, comb. & stat. nov. ≡ *Sobiso* Raf. [19]		Chinese clade, subclade i, group i [28]; *Salvia* s.l. clade IV-B (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Sobiso* (G8) (*S. chinensis* group) [19]	[19], [17], [28], [153], [169]

***Salvia ceratophylla* L.**	Sp. Pl.: 27 (1753)	Sect. *Aethiopis* Benth. [140], [145], [155]; Sect. *Gongrosphace* Briq. (sect. *Aethiopis* Benth. *ex parte*) [146]; Sect. *Aethiopis* Benth. §. *Gongrosphaceae* Sect. *Gongrosphace* Bunge [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don.) Briq. Subsect. *Gongrosphaceae* Briq. Ser. *Ceratophyllae* Pobed. [154]; Subg. *Sclarea* (Moench) Benth. Sect. *Gongrosphace* Benth. [149]	Group G of Flora of Turkey [142]; Group 3 of Flora Iranica [150]	*Salvia* s.s. clade I-C [17]	[140], [142], [17], [143], [23], [145], [146], [147], [149], [150], [154], [155]
***Salvia chionantha* Boiss.**	Diagn. Pl. Orient. ser. 1, 5: 8 (1844)	Sect. *Aethiopis* Benth. [145], [155]; Sect. *Aethiopis* Benth. §. *Gongrosphaceae* Sect. *Gongrosphace* Bunge [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Gongrosphaceae* (Boiss.) Briq. [141]	Group D of Flora of Turkey [142]	*Salvia* s.s. clade I-C [17]	[141], [142], [17], [143], [145], [147], [155]
***Salvia chionopeplica* Epling**	Ann. Missouri Bot. Gard. 27: 260 (1940)	Sect. *Audibertia* Benth. Subsect. *Jepsonia* Epl. [66]; Sect. *Audibertia* (Benth.) Epl. Subsect. *Jepsonia* Epl. Ser. *Nivea* (Benth.) Neisess [159]; Subg. *Audibertia* J.B.Walker, B.T.Drew, & K.J.Sytsma Sect. *Audibertia* J.B.Walker, B.T.Drew, & K.J.Sytsma [31]		*Salvia* clade II [30], [32]; California *Salvia* clade (subclade *Audibertia*) [31,170]	[30], [32], [159], [31], [160], [66], [171]
***Salvia chorassanica* Bunge**	Labiat. Persic.: 45 (1873)	Sect. *Gongrosphace* Briq. (sect. *Aethiopis* Benth. *ex parte*) [146]; Sect. *Aethiopis* Benth. §. *Gongrosphaceae* Sect. *Gongrosphace* Bunge [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Gongrosphaceae* (Boiss.) Briq. [141]; Sect. *Aethiopis* Benth. [155]	Group 3of Flora Iranica [150]	*Salvia* s.s. clade I-C [17]	[141], [17], [146], [147], [150], [155]
***Salvia cilicica* Boiss.**	Diagn. Pl. Orient., ser. 2, 4: 19 (1859)	Sect. *Aethiopis* Benth. [172]	Groups F and G of Flora of Turkey [142]	*Salvia* s.s. clade I-C [17]	[142], [17], [172], [24]

***Salvia coccinea* Buc'hoz ex Etl.**	Salv.: 23 (1777)	Sect *Calosphace* §. *Longiflorae* [140]; Subg. *Junga* (Moench) Briq. [141] Sect. *Calosphace* Benth. §. *Longiflorae* L. *Tubiflorae* [145], [141]; Subg. *Jungia* (Moench) Briq. Sect. *Calosphace* Benth. [153]; Sect. *Subrotundae* Epl. [170]	*Salvia* clade II [30]; "Core *Calosphace*" [29], [151]; Subg. *Calosphace* [19]	[19], [140], [141] (as *S. coccinea* L.), [145], [30], [151], [28], [153], [29], [170]
***Salvia columbariae* Benth.**	Labiat. Gen. Spec.: 302 (1833)	Sect. *Pycnosphace* [140], [145]; Subg. *Leonia* (Llav. et Lex.) Benth. Sect. *Pycnosphace* Benth. [141]; Sect. *Audibertia* Benth. Subsect. *Pycnosphace* Epl. [158]; Sect. *Audibertia* (Benth.) Epl. Subsect. *Parishiella* Epl. Ser. *Pycnosphace* (Benth. ex Epl.) Neisess [159]; Subg. *Audibertia* J.B.Walker, B.T.Drew, & K.J.Sytsma Sect. *Audibertia* J.B.Walker, B.T.Drew, & K.J.Sytsma [31]	*Salvia* clade II [30], [32]; California *Salvia* clade (subclade *Audibertia*) [31]	[140], [141], [145], [30], [32], [158], [159], [31], [160]
***Salvia corrugata* Vahl**	Enum. Pl. Obs. 1: 252 (1804)	Sect. *Calosphace* Benth. §. *Brachyanthae* [140]; Subg. *Jungia* (Moench) Briq. [141] Sect. *Calosphace* Benth. §. *Longiflorae* D. *Corrugatae* Benth. [145], [141]; Subg. *Calosphace* Benth. [64] Sect. *Corrugatae* (Benth.) Epl. [64], [170] Sect. *Calosphace* Epl. [161]	*Salvia* clade II [30], [32]; "*Uliginosae* clade" Sect. *Corrugatae* [29], [151]	[140], [141], [145], [30], [32], [151], [64], [161], [29], [170], [173]
***Salvia cuspidata* Ruiz & Pav.**	Fl. Peruv. 1: 23 (1798)	Subg. *Jungia* (Moench) Briq. [141] Sect. *Calosphace* §. *Brachyanthae* [140], Bentham 1848, [141] F. *Scorodoniae* [145], [141]; Subg. *Calosphace* Benth. Sect. *Tomentellae* Epl. [64]		[140], [141], [145], [64], [174]
***Salvia cuspidata* subsp. *gilliesii* (Benth.) J.R.I.Wood**	Kew Bull. 62: 186 (2007)	Sect. *Calosphace* Benth. Sect. *Brachyanthae* [140]; Subg. *Jungia* (Moench) Briq. Sect. *Calosphace* Benth. §. *Brachyanthae* Benth. E. *Scorodonieae* Benth. (as *S. gilliesii*) [141];	*Tomentellae* clade II (as *S. gilliesii*) [29], [151]	[140], [141], [151], [64], [161], [29]

		Subg. *Calosphace* Benth. Sect. *Tomentellae* Epl. [64] Sect. *Calosphace* Epl. [161]			
***Salvia cyanescens* Boiss. & Balansa**	Diagn. Pl. Orient., ser. 2, 4: 19 (1859)	Sect. *Aethiopis* Benth. §. *Gongrosphaceae* Sect. *Gongrosphace* Bunge. [147]; Sect. *Aethiopis* Benth. [155]	Group F of Flora of Turkey [142]	*Salvia* s.s. clade I-C [17]	[142], [17], [143], [23], [147], [155]
***Salvia cyclostegia* E.Peter-Stibal**	Acta Horti Gothob. 9: 118 (1934)	Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Stib. Sect. *Eurysphace* Stib. Subsect. *Perennes* Ser. *Maximowiczianae* C.Y.Wu [153]		*Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17], [18]	[17], [152], [153], [18]
***Salvia cynica* Dunn**	Notes Roy. Bot. Gard. Edinburgh 8: 164 (1913)	Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Stib. Sect. *Eurysphace* Stib. Subsect. *Perennes* Ser. *Maximowiczianae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		*Salvia* clade III [32]; Chinese Clade, subclade iii [28]; *Salvia* s.l. Clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [17], [32], [28], [152], [153], [164],
***Salvia dabieshanensis* J.Q.He**	Acta Bot. Yunnan. 11: 409 (1989)	Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. Ser. *Miltiorrhizae* C.Y.Wu [19]		Chinese clade, subclade i, group i [28]; *Salvia* s.l. clade IV (*Glutinaria* Raf.) [17]	[19], [17], [28]
***Salvia deserta* Schangin**	Index Seminum (TU, Dorpatensis) 1824: 6 (1824)	Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. Ser. *Nemorosae* Pobed. [154]; Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. Subsect. *Euplethiosphace* Briq. Ser. *Nemorosae* Pobed. [153]		*Salvia* clade I according to Walker 2007 [32] [28]; *Salvia* s.s. clade I-C [18], [17]; *S. officinalis* clade [19]	[19], [17], [28], [153], [154], [18]
***Salvia dichroantha* Stapf**	Denkschr. Kaiserl. Akad. Wiss., Wien. Math-Naturwiss. Kl. 1: 96 (1885)	Sect. *Plethiosphace* Benth. [143], [23]	Group F of Flora of Turkey [142]	*Salvia* s.s. clade I-C [17]	[142], [143], [23], [17]
***Salvia digitaloides* Diels**	Notes Roy. Bot. Gard. Edimburgh 5: 234 (1912)	Subg. *Salvia* Benth. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Stib. Sect. *Eurysphace* Stib. Subsect. *Perennes* Ser. *Digitaloidites* C.Y.Wu [153];		*Salvia* clade III second lineage [30], [32]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [18] [17];	[19], [17], [30], [32], [152], [153], [18]

		Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	
***Salvia divaricata* Montbret & Aucher ex Benth.**	Ann. Sci. Nat., Bot., sér. 2, 6: 37 (1836)	Sect. *Eusphace* Benth. [140], [145], [147]; Subg. *Salvia* Benth. Sect. *Eusphace* Benth. §. *Simplicifoliae* Boiss. [141];	Group E of Flora of Turkey [142]	*Salvia* s.s. clade I-D [17]	[140], [141], [142], [17], [143], [145], [147]
***Salvia drobovii* Botsch.**	Byull. Sredne-Aziatsk. Gosud. Univ. 22: 326 (1937)	Sect. *Salvia* Hedge (Sect. *Eusphace* Benth.) [143] Subg. *Macrosphace* Pobed. [154]		*Salvia* s.l. clade III-B (*Polakia* Stapf) [17]	[17], [154]
***Salvia eriophora* Boiss & Kotschy**	Fl. Orient. 4: 611 (1879)	Sect. *Aethiopis* Benth. §. *Homalosphaceae* Sect. *Homalosphace* Bunge [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Homalosphaceae* (Boiss.) Briq. [141]; Sect. *Aethiopis* Benth. Subsect. *Gongrosphace* (Bunge) Boiss. [163]	Group F of Flora of Turkey [142]	*Salvia* s.s. clade I-C [17]	[141], [142], [17], [143], [147], [163]
***Salvia evansiana* Hand.-Mazz.**	Anz. Akad. Wiss. Wienn, Math-Naturwiss. Kl. 62: 236 (1925)	Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Sect. *Eurysphace* Stib. Subsect. *Perennes* C.Y.Wu Ser. *Brachylomae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		Chinese clade, subclade iii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [17], [28], [152], [153], [164]
***Salvia flava* Forrest ex Diels**	Notes Roy. Bot. Gard. Edimburgh 5: 235 (1912)	Subg. *Salvia* Sect. *Eurysphace* Subsect. *Perennes* C.Y.Wu Ser. *Castaneae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		Clade III + Japanese and Taiwanese *Salvia* [171]; Chinese clade, subclade iii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [17], [28], [153], [171]
***Salvia fruticosa* Mill.**	Gard. Dict. Ed. 8: 5 (1768)	Sect. *Eusphace* Benth. (as *S. triloba*) [140]; Subg. *Salvia* Sect. *Eusphace* Benth. [Han 2010] §. *Pinnatae* Boiss. A. *Fruticulosae* Boiss (as *S. triloba*) [141];	Groups B and E of Flora of Turkey [142]; Group A of *Salvia* in Africa [11]	*Salvia* s.s. clade I-D [18], [17]	[140], [141], [142], [17], [23], [11], [18], [155] (as *S. triloba* L.f.), [156], [25], [175]

		Sect. *Salvia* Hedge (Sect. *Eusphace* Benth.) [175]			
***Salvia fruticulosa* Benth.**	Labiat. Gen. Spec.: 721 (1835)	Subg. *Jungia* (Moench) Briq. [141] Sect. *Calosphace* Benth. §. *Brachyantha* F. *Scorodoniae* [145], [141]; Subg. *Calosphace* Benth. Sect. *Tomentellae* Epl. [64]; Subg. *Calosphace* Benth. Sect. *Scorodoniae* Epl. [176]		*Tomentellae* clade I inside "*Uliginosae* clade" [29]; *Tomentellae* clade I inside "*Uliginosae* clade" [151]	[141], [145], [151], [64], [29], [176]
***Salvia glutinosa* L.**	Sp. Pl.: 26 (1753)	Subg. *Salvia* Benth. [141] Sect. *Drymosphace* Benth. [140], [145], [146], [141], [144], [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. Ser. *Miltiorrhizae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Glutinaria* [19]	Group E of Flora of Turkey [142]; Group 3 of Flora Iranica [150]	*Salvia* clade III second lineage [30], [32]; Clade III + Japanese and Taiwanese *Salvia* [171]; Chinese clade, subclade iii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Glutinaria* (G4) [19]	[19], [140], [141], [142], [17], [23], [144], [145], [146], [147], [150], [30], [32], [28],[153], [18], [171]
***Salvia grandifolia* W.W.Sm.**	Notes Roy. Bot. Gard. Edimburgh 9:123 (1916)	Subg. *Sclarea* (Moench) Benth. Sect. *Aethiopis* Benth. [152]; Subg. *Sclarea* (Moench) Benth. Sect. *Aethiopis* Benth. Subsect. *Homalosphaceae* (Boiss.) Briq. Ser. *Grandifoliae* C.Y.Wu [153]		*Salvia* s.l. clade IV (*Glutinaria* Raf.) [17]	[17], [152], [153]
***Salvia hians* Royle ex Benth.**	Bot. Misc. 3:373 (1833)	Subg. *Salvia* Benth. [141] Sect. *Drymosphace* Benth. [140], [145], [141], [144]		*Salvia* clade III second lineage [30], [32] Clade III + Japanese and Taiwanese *Salvia* [171]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]	[140], [141], [17], [144], [145], [30], [32], [171]
***Salvia honania* L.H.Bailey**	Gentes Herbarum: 43 (1920)	Subg. *Gymnosphace* (Benth.) Stib. [152]; Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. Ser. *Honaniae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Drymosphace* Benth. [19]		Chinese clade, subclade i, group i [28]; *Salvia* s.l. Clade IV (*Glutinaria* Raf.) [17];	[19], [17], [28], [152], [153]

				Subg. *Glutinaria* subclade *Drymosphace* (G7) (*S. miltiorrhiza* group) [19]	
***Salvia hydrangea* DC. ex Benth.**	Labiat. Gen. Spec.: 717 (1835)	Subg. *Schraderia* (Monch) Briq. [141] Sect. *Hymenosphace* Benth. [146], [141] §. *Mediterraneo-Ponticae* [145]; Sect. *Hymenosphace* [147]; Gen. *Schraderia* Medik. Sect. *Holochilus* Pobed. Ser. *Bucharcae* Pobed. (as *Schraderia dracocephaloides* (Boiss.) Pobed. [154]	Group A of Flora of Turkey [142]; Group 1 of Flora Iranica [150]	*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-D [18], [17]	[141], [142], [17], [145], [146], [147] (as *S. dracocephaloides*), [150], [30], [32], [154], [18], [177]
***Salvia hypargeia* Fisch. & C.A.Mey.**	Ann. Sci. Nat., Bot., ser. 4, 1: 34 (1854)	Sect. *Eusphace* Benth. [178]; Sect. *Aethiopis* Benth. [143], [23]	Group E of Flora of Turkey [142]	*Salvia* s.s. clade I-C [17]	[142], [17] [143], [23], [178]
***Salvia jaminiana* de Noè**	Bull. Soc. Bot. France 2: 581 (1855)	Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Gongrosphaceae* (Boiss.) Briq. [141]; Sect. *Plethiosphace* Benth. [179]	Group P of *Salvia* in Africa [11]	*Salvia* s.s. clade I-D [17]	[141], [17], [11], [179]
***Salvia karabachensis* Pobed.**	Fl. URSS 21: 659 (1954)	Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don.) Briq. Subsect. *Gongrosphaceae* Briq. Ser. *Kopetdaghenses* Pobed. [154]		*Salvia* s.s. clade I-C [17]	[17], [154],
***Salvia kiangsiensis* C.Y.Wu**	Fl. Reipubl. Popularis Sin. 66: 584 (1977)	Subg. *Allagospadonopsis* Briq. Ser. *Appendiculatae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Sobiso* (Raf.) G.X.Hu, A.Takano & B.T.Drew, comb. & stat. nov. ≡ *Sobiso* Raf. [19]		Chinese clade, subclade i, group ii [28]; *Salvia* s.l. clade IV (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Sobiso* (G8) (*S. chinensis* group) [19]	[19], [17], [28], [153]
***Salvia kiaometiensis* Lévl.**	Bull. Acad. Int. Géogr. Bot. 25: 25 (1915)	Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Sect. *Eurysphace* Subsect. *Perennes* C.Y.Wu Ser. *Castaneae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		Chinese Clade, subclade iii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) (as *S. kiaometiensis* f. *pubescens*) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [17], [28], [152], [153]
***Salvia korolkovii* Regel & Schmalh.**	Trudy Imp. S.-Peterburgsk. Bot. Sada,	Gen. *Schraderia* Medik. Sect. *Odontochilus* Pobed. Series. *Bucharcae* Pobed. (as *Schraderia korolkovii*) (Rgl. Et Schmalh.) Pobed [154]		*Salvia* s.s. clade I-D [17]	[17], [154]

	prepr. 6: 356 (1879)				
***Salvia kronenburgii* Rech. f.**	Oesterr. Bot.Z. 99: 50 (1952)	Sect. *Hymenosphace* Benth. [180]	Group C of Flora of Turkey [142]	*Salvia* s.s. clade I-D [18], [17]	[142], [17], [18], [180]
***Salvia lachnocalyx* Hedge**	Fl. Iranica 150: 455 (1982)	-	Group 3 of Flora Iranica [150]	*Salvia* s.s. clade I-C [17]	[17], [150]
***Salvia lachnostachys* Benth.**	Labiat. Gen. Spec.: 267 (1833)	Subg. *Jungia* (Moench) Briq. [141] Sect. *Calosphace* Benth. § *Brachyantha* H. *Rudes* [145], [141]; Subg. *Calosphace* Benth. Sect. *Uliginosae* Epl. [64]			[141], [145], [64]
***Salvia lanigera* Poir.**	Encycl. suppl. 5: 49 (1817)	Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. B. *Euplethiosphaceae* Briq. [141]	Group T of *Salvia* in Africa [11]; Group 3 of Flora Iranica [150]	*Salvia* s.s. clade I-C [17]	[141], [17], [11], [150]
***Salvia lavanduloides* Kunth**	Nov. Gen. Sp.2: 287 (1818)	Sect. *Calosphace* § *Brachyanthae* [140]; Subg. *Jungia* (Moench) Briq. Sect. *Calosphace* Benth. §. *Brachyanthae* Benth. A. *Angustifoliae* Benth. [141]; Subg. *Calosphace* Benth. Sect. *Lavanduloideae* Epl. [64]		*Salvia* clade II [30], [32]; "Core *Calosphace*" [29]; "Core *Calosphace*", *Lavanduloideae* clade [151]	[140], [141], [30], [32], [151], [64], [29], [168], [173]
***Salvia leriifolia* Benth.**	Prodr.12: 287 (1848)	Sect. *Aethiopis* Benth. (as *S. leriaefolia*) [145]; Sect. *Homalosphace Aethiopis* spec. Benth. (as *S. leriaefolia*) [146]; Sect. *Aethiopis* Benth. §. *Homalosphaceae* (as S. *leriaefolia*) [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Homalosphaceae* (Boiss.) Briq. (as *S. leriaefolia*) [141]; Subg. *Sclarea* (Moench) Benth. Sect. *Homalosphace* Benth. [149]	Group 3 of Flora Iranica [150]	*Salvia* s.s. clade I-C [17]	[141], [17], [145], [146], [147], [149], [150]
***Salvia limbata* C.A.Mey.**	Verz. Pfl. Casp. Meer.: 86 (1831)	Sect. *Aethiopis* Benth. [145], [155]; Sect. *Gongrosphace* Briq. (sect. *Aethiopis* Benth. *ex parte*) [146];	Group D of Flora of Turkey [142]; Group 3 of Flora Iranica [150]	*Salvia* s.s. clade I-C [17]	[141], [142], [17], [145], [146], [147], [150], [154], [155],

		Sect. *Aethiopis* Benth. §. *Gongrosphaceae* [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Gongrosphaceae* (Boiss.) Briq. [141]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don.) Briq. Subsect. *Gongrosphaceae* Briq. Ser. *Limbatae* Pobed. [154]		
***Salvia maximowicziana* Hemsl.**	J. Linn. Soc., Bot. 26: 285 (1890)	Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Stib. Sect. *Eurysphace* Stib. Subsect. *Perennes* Ser. *Maximoviczianae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]	Chinese clade, subclade iii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [17], [28], [152], [153]
***Salvia meiliensis* S.W.Su**	Acta Bot. Yunnan. 6: 59 (1984)	Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. Ser. *Honaniae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Drymosphace* Benth. [19]	Chinese clade, subclade i, group i [28]; *Salvia* s.l. clade IV (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Drymosphace* (G7) (*S. miltiorrhiza* group) [19]	[19], [17], [28], [153]
***Salvia mellifera* Greene**	Pittonia 2: 236 (1892)	Sect. *Audibertia* Benth. Subsect. *Parishiella* Epl. [158]; Sect. *Audibertia* (Benth.) Epl. Subsect. *Parishiella* Epl. Ser. *Stachyoides* Neisess [159]; Subg. *Audibertia* J.B.Walker, B.T.Drew, & K.J.Sytsma Sect. *Audibertia* J.B.Walker, B.T.Drew, & K.J.Sytsma [31]	*Salvia* clade II [30], [32]; *Salvia* s.s. clade II-C [17]; California *Salvia* clade (subclade *Audibertia*) [31]	[159], [158], [160], [31], [30], [32], [29], [17]
***Salvia miltiorrhiza* Bunge**	Enum. Pl. China Bor.: 50 (1833)	Subg. *Salvia* Benth. [141] Sect. *Drymosphace* Benth. (as *S. miltiorhiza*) [145], [141]; Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. [152] Ser. *Miltiorrhizae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Drymosphace* Benth. [19]	*Salvia* clade III [30], [32]; Clade III + Chinese and Japanese *Salvia* [171]; Chinese clade, subclade i, group i [28]; *Salvia* s.l. clade IV-B (*Glutinaria* Raf.) [18], [17];	[19], [141], [17], [145], [30], [32], [28], [152], [153], [18] [171]

				Subg. *Glutinaria* subclade *Drymosphace* (G7) (*S. miltiorrhiza* group) [19]	
***Salvia miltiorrhiza* var. *charbonnelii* (H.Lév.) C.Y.Wu**	Fl. Reipubl. Popularis Sin. 66: 148 (1977)				
Salvia miltiorrhiza* var. *miltiorrhiza		Subg. *Sclarea* Benth. Sect. *Drymosphace* Benth. [181], [25]		*Salvia* s.l. clade IV-B (*Glutinaria* Raf.) [17]	[17], [25], [181] (as *S. miltiorrhiza* f. *alba*),
***Salvia montbretii* Benth.**	Ann. Sci. Nat., Bot., ser.2, 6: 42 (1836)	Sect. *Aethiopis* Benth. (as *S. monbretii*) [140], [145]; Sect. *Aethiopis* Benth. §. *Homalosphaceae* Sect. *Homalosphace* [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Homalosphaceae* (Boiss.) Briq. [141]	Group E of Flora of Turkey [142]; Group 3 of Flora Iranica [150]	*Salvia* s.s. clade I-C [17]	[140], [141], [142], [17], [145], [147], [150]
***Salvia moorcroftiana* Wall. ex Benth.**	N. Wallich, Pl. Asiat. Rar. 1: 67 (1830)	Sect. *Aethiopis* Benth. (as *S. moorcroftiana*) [140], [145], [144]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Gongrosphaceae* (Boiss.) Briq. [141]; Subg. *Sclarea* (Moench) Benth. Sect. *Homalosphace* Benth. [149]	Group 3 of Flora Iranica [150]	*Salvia* s.s. clade I-C [17]	[140], [141], [17] [144], [145], [149], [150], [165]
***Salvia multicaulis* Vahl**	Enum. Pl. Obs.1: 225 (1804)	Sect. *Hymenosphace* Benth. [140] §. *Mediterraneo-Ponticae* [145]	Groups B and C of Flora of Turkey [142]; Group 1 of Flora Iranica [150]	*Salvia* s.s. clade I-D [17]	[140], [142], [17], [143], [23], [145], [150]
***Salvia munzii* Epling**	Madroño 3: 169 (1935)	Sect. *Audibertia* Benth. Subsect. *Parishiella* Epl. [158]; Sect. *Audibertia* (Benth.) Epl. Subsect. *Parishiella* Epl. Ser. *Stachyoides* Neisess [159]; Subg. *Audibertia* J.B.Walker, B.T.Drew, & K.J.Sytsma Sect. *Audibertia* J.B.Walker, B.T.Drew, & K.J.Sytsma [31]		*Salvia* clade II [30], [32]; California *Salvia* clade (subclade *Audibertia*) [31]	[30], [32], [158], [159], [31], [160]
***Salvia nanchuanensis* Y.Z.Sun**	Fl. Reipubl. Popularis Sin. 66: 582 (1977)	Subg. *Salvia* Sect. *Drymosphace* Benth. [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Drymosphace* Benth. [19]		*Salvia* s.l. clade IV (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Drymosphace* (G7) (*S. miltiorrhiza* group) [19]	[19], [17], [153]

***Salvia napifolia* Jacq.**	Hort. Bot. Vindob. 2: 71 (1773)	Subg. *Covola* (Medik.) Briq. [141] Sect. *Hemisphace* Benth. [140], [145], [141], [155]	Group F of Flora of Turkey [142]	*Verticillata* group [17]	[140], [141], [142], [17], [145], [23], [155]
***Salvia nemorosa* L.**	Sp. Pl. ed. II. 35 (1762)	Sect. *Plethiosphace* Benth. [146], [155]; Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. [149] B. *Euplethiosphaceae* Briq. [141]; Subg. *Sclarea* (Moench) Benth. Subsect. *Gongrosphaceae* Briq. Ser. *Nemorosae* Pobed. [154]	Group F of Flora of Turkey [142]; Group 3 of Flora Iranica [150]		[141], [142], [143], [146], [149], [150] [154], [155]
***Salvia nipponica* Miq.**	Ann. Mus. Bot. Lugduno-Batavi 2: 107 (1865)	Subg. *Salvia* Stib. Sect. *Eurysphace* Stib. Subsect. *Perennes* Ser. *Nipponicae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Glutinaria* [19]		Clade III + Japanese and Taiwanese *Salvia* [171]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Glutinaria* (G4) [19]	[19], [17], [153], [171], [27]
***Salvia nutans* L.**	Sp. Pl.: 27 (1753)	Sect. *Plethiosphace* Benth. [140], [145], [155], [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. B. *Euplethiosphaceae* Briq. [141]; Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. Subsect. *Gongrosphaceae* Briq. Ser. *Nutantes* Pobed. [154]	Group F of Flora of Turkey [142]	*Salvia* s.s. clade I-C [17]	[140], [141], [142], [17], [145], [147], [154], [155]
***Salvia oaxacana* Fernald**	Proc. Amer. Acad. Arts 35: 536 (1900)	Subg. *Calosphace* Benth. Sect. *Conzattiana* Epl. [64]		(Conzattiana) [29]; *Salvia* s.l. clade II-A (*Lasemia* Raf.) [17]; *S. candicans* + *S. oaxacana* clade [151]	[17], [151], [64], [29]
***Salvia officinalis* L.**	Sp.Pl.: 23 (1753)	Sect. *Eusphace* Benth. [140], [145]; Subg. *Salvia* Benth. Sect. *Eusphace* Benth [25]. §. *Simplicifoliae* Boiss. [141]; Subg. *Eusalvia* Pobed. Sect. *Eusphace* Benth. Ser. *Officinales* Pobed. [154]; Subg. *Salvia* Stib. Sect. *Eusphace* Stib. Subsect. *Simplicifolia* Boiss. Ser. *Officinales* Pobed [153]		*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-D [18], [17]; *S. officinalis* clade [19]	[19], [140], [141], [17], [145], [154], [30], [32], [153], [18], [25], [175], [182]

		Sect. *Salvia* (Benth.) Hedge (Sect. *Eusphace* Benth.) [155]			
***Salvia officinalis* subsp. l*avandulifolia* (Vahl) Gams**	Ill. Fl. Mitt.-Eur. 5(4): 2482 (1927)	Sect. *Eusphace* Benth. [140]; Subg. *Salvia* Benth. Sect. *Eusphace* Benth. §. *Simplicifoliae* Boiss. (as *S. lavandulaefolia*) [141]; Sect. *Salvia* (as *S. lavandulifolia*) [155]	Group A of *Salvia* in Africa (as *S. lavandulifolia*) [11]	*Salvia* s.s. clade I-D (as *S. lavandulifolia*) [17]	[140], [141], [155], [11], [17]; [175]
***Salvia omeiana* E.Peter-Stibal**	Acta Horti Gothob. 9: 119 (1934)	Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Stib. Sect. *Eurysphace* Stib. Subsect. *Perennes* Ser. *Maximoviczianae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		Chinese clade, subclade iii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [17], [28], [152], [153]
***Salvia pachystachya* Trautv.**	Bull. Soc. Imp. Naturalistes Moscou 41(1): 462 (1868)	Subg. *Eusalvia* Pobed. Sect. *Eusphace* Benth. Ser. *Pachystachyae* Pobed [154]	Group A of Flora of Turkey [142]	*Salvia* s.s. clade I-D [17]	[142], [17] [154],
***Salvia palaestina* Benth.**	Labiat. Gen. Spec.: 718 (1835)	Sect. *Aethiopis* Benth. [23], [145]; Sect. *Homalosphace Aethiopis* spec. Benth. [146]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Homalosphaceae* (Boiss.) Briq. [141]	Group E of Flora of Turkey [142]; Group Q of *Salvia* in Africa [11]; Group 3 of Flora Iranica [150]	*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-C [17], [18]	[146], [141], [142], [17], [23], [145], [11], [150], [30], [32], [18]
***Salvia paramiltiorrhiza* H.W.Li & X.L.Huang**	Acta Phytotax. Sin. 19: 245 (1981)	Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. Ser. *Miltiorrhizae* C.Y.Wu [19]		Chinese clade, subclade i, group i [28]; *Salvia* s.l. clade IV (*Glutinaria* Raf.) [17]	[17], [28]
***Salvia phlomoides* Asso**	Intr. Oryctogr. Aragon.: 158 (1784)	Sect. *Aethiopis* Benth. [145], [155]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Gongrosphaceae* (Boiss.) Briq. [141]	Group Q of *Salvia* in Africa [11]	*Salvia* s.s. clade I-C (as *S. phlomoides* spp. *phlomoides*) [17]	[141], [17], [145], [11], [155]
***Salvia pisidica* Boiss & Heldr. ex Benth.**	Prodr. 12: 269 (1848)	Sect. *Eusphace* Benth. [145], [147]; Subg. *Salvia* Benth. Sect. *Eusphace* Benth. §. *Pinnatae* Boiss. A. *Fruticosae* Boiss. [141]; Sect. *Salvia* Hedge (Sect. *Eusphace* Benth.) [23]	Group A of Flora of Turkey [142]	*Salvia* s.s. clade I-D [17]	[141], [142], [17] [23], [145], [147]

***Salvia plebeia* R.Br.**	Prodr. Fl. Nov. Holland.: 501 (1810)	Subg. *Leonia* (Llav. & Lex) Benth. Sect. *Notiosphace* Benth. [149], [154]; Sect. *Notiosphace* Benth. [140], [145], [144]; Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Sclarea* (Moench) Benth. Sect. *Notiosphace* Benth. [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Notiosphace* Benth. [19]		Clade III + Japanese and Taiwanese Salvia [171]; Chinese clade, subclade ii [28]; *Salvia* s.l. clade IV-C (*Glutinaria* Raf.) [17], [18]; Subg. *Glutinaria* subclade *Notiosphace* (G2) [19]	[19], [140], [17], [144], [145], [149], [28], [152], [153], [154] (as *S. plebeja*), [18], [171], [181], [27], [183]
***Salvia plectranthoides* Griff.**	Not. Pl. Asiat. 4: 199 (1854)	Sect. *Notiosphace* Benth. [144]; Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. Ser. *Plectranthoidites* C.Y.Wu [153] Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Notiosphace* Benth. [19]		*Salvia* s.l. clade IV [18] Subg. *Glutinaria* subclade *Plectranthoides* (G7) [19]	[19], [144], [153], [18]
***Salvia potentillifolia* Boiss & Heldr. ex Benth.**	Prodr.12: 270 (1848)	Sect. *Eusphace* Benth. (as *S. potentillaefolia*) [145]; Subg. *Salvia* Benth. Sect. *Eusphace* Benth. §. *Pinnatae* Boiss. A. *Fruticosae* Boiss. [141]; Sect. *Salvia* Hedge (Sect. *Eusphace* Benth.) [23]	Group A of Flora of Turkey [142]	*Salvia* s.s. clade I-D [17]	[141], [142], [17], [23], [145]
***Salvia pratensis* L.**	Sp.Pl.: 25 (1753)	Sect. *Plethiosphace* Benth. [140], [145], [155], [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. B. *Euplethiosphaceae* Briq. [141]; Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. Subsect. *Gongrosphaceae* Briq. Ser. *Pratenses* Pobed. [154]		*Salvia* clade I [[30] [32] *Salvia* s.s. clade I-C [18], [17]	[140], [141], [17], [145], [147], [154], [30] [32], [18], [155]
***Salvia pratii* Hemsl.**	J. Linn. Soc., Bot. 29: 316 (1892)	Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Stib. Sect. *Eurysphace* Stib. Subsect. *Perennes* Ser. *Hiantes* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		Chinese clade, subclade iii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [17], [28], [152], [153]
***Salvia prionitis* Hance**	J.Bot. 8: 74 (1870)	Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. Ser. *Miltiorrhizae* C.Y.Wu [153];		Chinese clade, subclade i, group ii [28];	[19], [28], [153]

		Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Sobiso* (Raf.) G.X.Hu, A.Takano & B.T.Drew, comb. & stat. nov. ≡ *Sobiso* Raf. [19]		Subg. *Glutinaria* subclade *Sobiso* (G8) (*S. chinensis* group) [19]	
***Salvia przewalskii* Maxim.**	Bull. Acab. Imp. Sci. Saint-Petersbourg, ser.3, 27: 526 (1882)	Subg. *Salvia* Benth. Sect. *Drymosphace* Benth. [141]; Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Stib. Sect. *Eurysphace* Stib. Subsect. *Perennes* Ser. *Digitaloidites* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		*Salvia* clade III second lineage [30], [32]; Clade III + Japanese and Taiwanese *Salvia* [171]; Chinese clade, subclade iii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [141], [17], [30], [32], [28], [152], [153], [171]
***Salvia pubescens* Benth.**	Labiat. Gen. Spec.: 723 (1835)	Sect. *Calosphace* Benth. §. *Longiflorae* H. *Inflatae* [145]; Subg. *Calosphace* Benth. Sect. *Erythrostachys* Epl. [64]		Sect. *Erythrostachys* [29]; *Erythrostachys* clade [151]	[145], [151], [64], [29]
***Salvia recognita* Fisch. & C.A.Mey.**	Ann. Sci. Nat., Bot., sér. 4, 1: 33 (1854	Subg. *Salvia* Benth. Sect. *Eusphace* Benth. §. *Pinnatae* Boiss. A. *Fruticosae* Boiss. [141]; Sect. *Salvia* Hedge (Sect. *Eusphace* Benth.) [23]	Group B of Flora of Turkey [142]	*Salvia* s.s. clade I-D [17]	[141], [142], [17] [143], [23]
***Salvia regla* Cav.**	Icon. 5: 33 (1799)	Sect. *Calosphace* Benth. Sect. *Longiflorae* [140], [145]; Subg. *Jungia* (Moench) Briq. Sect. *Calosphace* Benth. §. *Longiflorae* Benth. H. *Inflatae* Benth. [141]; Subg. *Calosphace* Benth. Sect. *Erythrostachys* Epl. [64]; Sect. *Platycheilos* Epl. [161]		Sect. *Erythrostachys* [29]	[140], [141], [145], [64], [161], [29]
***Salvia rythidea* Benth.**	Prodr. 12: 280 (1848)	Sect. *Aethiopis* Benth. [145]; Sect. *Homalosphace Aethiopis* spec. Benth. [146]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Homalosphaceae* (Boiss.) Briq. [141]; Sect. *Aethiopis* Benth. §. *Homalosphaceae* Sect. *Homalosphace* Bunge [147];	Group with *S. chorassanica* Bunge (NW Iran), *S. lasearica* Rech f. (SE Iran), *S. sahendica* Boiss. & Buhse and *S. frigida* Boiss. (Irani Ajerbaidjan) and *S. chrysophylla* Stapf [165]	*Salvia* s.s. clade I-C [17]	[141], [17], [145], [146], [147], [149], [150], [165]

		Subg. *Sclarea* (Moench) Benth. Sect. *Gongrosphace* Benth. [149]	Group 3 of Flora Iranica [150]		
***Salvia roborowskii* Maxim.**	Bull. Acad. Imp. Sci. Saint-Pétersbourg, sér. 3, 27: 527 (1882)	Subg. *Salvia* Benth. Sect. *Drymosphace* Benth. [141]; Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Benth. Sect. *Eurysphace* Stib. Subsect. *Annuae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Annuae* (C.Y.Wu) C.L.Xiang & H.Peng stat. nov. ≡ Subsect. *Annuae* C.Y.Wu. [19]		*Salvia* clade III second lineage [30], [32]; Chinese clade, subclade iii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Annuae* (G5) [19]	[19], [141], [17], [30], [32], [28], [152], [153]
***Salvia sahendica* Boiss. & Buhse**	Nouv. Mém. Soc. Imp. Naturalistes Moscou 12: 172 (1860)	Sect. *Gongrosphace* Briq. (sect. *Aethiopis* Benth. *ex parte*) [146]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Gongrosphaceae* (Boiss.) Briq. [141]; Sect. *Aethiopis* Benth. §. *Gongrosphaceae* Sect. *Gongrosphace* Bunge [147]; Sect. *Aethiopis* Benth. [155]	Group 3 of Flora Iranica [150]	*Salvia* s.s. clade I-C [17]	[141], [17] [146], [147], [150], [155]
***Salvia schizochila* E.Peter-Stibal**	Acta Horti Gothob. 9: 126 (1934)	Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Benth. Sect. *Eurysphace* Stib. Subsect. *Perennes* C.Y.Wu Ser. *Brachylomae* C.Y.Wu [153]		*Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]	[19], [140], [141], [17], [143], [23], [145], [146], [147], [149], [152], [153]
***Salvia sclarea* L.**	Sp. Pl.: 27 (1753)	Sect. *Aethiopis* Benth. [140], [145], [155], [143], Celep 2010]; Sect. *Gongrosphace* Briq. (sect. *Aethiopis* Benth. *ex parte*) [146]; Subg. *Sclarea* Sect. *Aethiopis* [25]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Gongrosphaceae* (Boiss.) Briq. [141] Ser. *Sclareae* Pobed [154]; Sect. *Aethiopis* Benth. §. *Gongrosphaceae* Sect. *Gongrosphace* Bunge [147];	Group R of *Salvia* in Africa [11]; Group D of Flora of Turkey [142]; Group 3 of Flora Iranica [150]	*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-C [18], [17]; *S. officinalis* clade [19]	[142], [17], [11], [150], [30], [32], [28], [154], [18], [155], [25], [171]

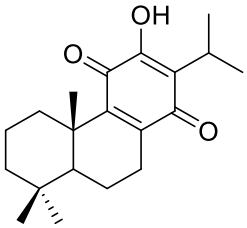
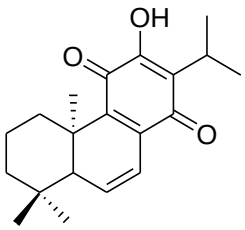
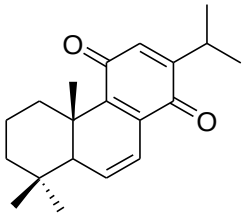
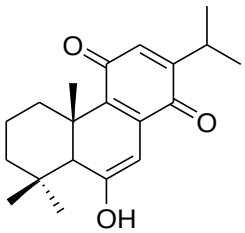
		Subg. *Sclarea* (Moench) Benth. Sect. *Gongrosphace* Benth. [149]		
***Salvia semiatrata* Zucc.**	Abh. Math.-Phys. Cl. Königl. Bayer. Akad. Wiss. 1: 298 (1829-1830 publ. 1832)	Sect. *Calosphace* Benth. §. *Brachyantha* F. *Scorodoniae* [140], [145]; Subg. *Jungia* (Moench) Briq. Sect. *Calosphace* Benth. §. *Brachianthe* Benth. E. *Scorodonieae* [141]; Subg. *Calosphace* Benth. Sect. *Atratae* [64];	*Salvia* clade II [32]; "Core *Calosphace*" [29]	[140], [141], [145], [32], [64], [29]
***Salvia sessei* Benth.**	Labiat. Gen. Spec.: 288 (1833)	Subg. *Jungia* (Moench) Briq. [141] Sect. *Calosphace* Benth. §. *Longiflorae* [140] H. *Inflatae* [145], [141]; Subg. *Calosphace* Benth. Sect. *Erythrostachys* Epl. [64]	Sect. *Erythrostachys* [29]	[140], [141], [145], [64], [29]
***Salvia sinica* Migo**	J. Shanghai Sci. Inst. Sect. 3, 3: 226 (1937)	Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. Ser. *Miltiorrhizae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Drymosphace* Benth. [19]	Chinese clade, subclade i, group i [28]; *Salvia* s.l. clade IV (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Drymosphace* (G7) (*S. miltiorrhiza* group) [19]	[19], [17], [28], [153]
***Salvia stibalii* Alziar**	Biocosme Mésogéen 6: 79 (1989)	Sect. *Calosphace* Benth. §*Brachyantha* E. *Candicantes* [145], [141]; Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. (as *S. pauciflora*) [152]; Subg. *Salvia* Benth. Sect. *Eurysphace* Stib. Subsect. *Perennes* C.Y.Wu Ser. *Brachylomes* C.Y.Wu [153]	*Salvia* s.l. clade IV-A (*Glutinaria* Raf.) (as *S. pauciflora*) [17]	[19], [17], [145] (as *S. pauciflora*), [141] (as *S. pauciflora*), [28], [152], [153], [25] (as *S. pauciflora*)
***Salvia subpalmatinervis* E.Peter-Stibal**	Acta Horti Gothob. 9: 135 (1934)	Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Benth. Sect. *Eurysphace* Stib. Subsect. *Perennes* C.Y.Wu Ser. *Castaneae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]	Chinese clade, subclade iii [28]; *Salvia* s.l. clade IV (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	
***Salvia syriaca* L.**	Syst. Nat. ed. 10, 2: 854 (1759)	Sect. *Aethiopis* Benth. [140], [145]; Sect. *Homalosphace Aethiopis* spec. Benth. [146];	*Salvia* s.s. clade I-C [17]	[140], [141], [17], [143], [23], [145], [146], [147], [154]

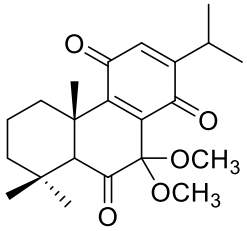
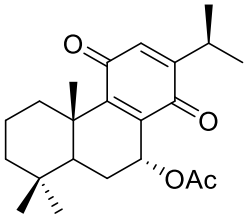
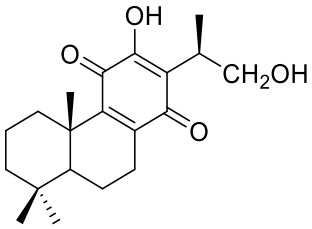
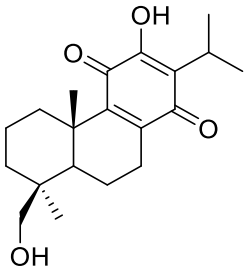
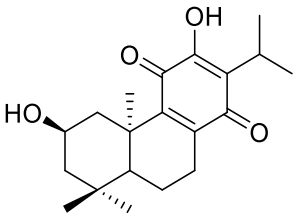
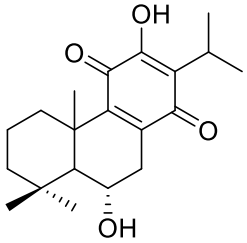
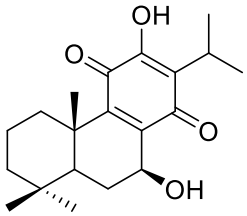
		Sect. *Aethiopis* Benth. §. *Homalosphaceae* Sect. *Homalosphace* Bunge [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Stenarrhena* (Don) Briq. §. *Homalosphaceae* (Boiss.) Briq [141]; Sect. *Stenarrhena* (Don) Briq. (Sect. *Aethiopis* Benth.) Subsect. *Homalosphace* (Bunge.) Briq. Ser. *Syriace* Pobed. [154]			
***Salvia tchihatcheffii* (Fisch. & C.A.Mey.) Boiss.**	Fl. Orient. 4: 598 (1879)	Subg. *Salvia* Benth. Sect. *Eusphace* Benth. §. *Pinnatae* Boiss. A. *Fruticosae* Boiss. [141]; Sect. *Eusphace* Benth. [147]; Sect. *Salvia* Hedge (Sect. *Eusphace* Benth.) [143], [23]	Group A of Flora of Turkey [142]	*Salvia* s.s. clade I-D [17]	[141], [142], [17], [143], [23], [147]
***Salvia tebesana* Bunge**	Labiat. Persic.: 52 (1873)	Sect. *Eremosphace Nothiosphace* Benth. [146], [147]; Subg. *Viasala* Briq. Sect. *Eremosphace* Bunge [141];	Group 2 of Flora Iranica [150]	*Salvia* clade III first lineage [30], [32]; *Salvia* s.l. clade III-A/C (*Pleudia* Raf.) [17]	[141], [17], [146], [147], [150], [30], [32],
***Salvia texana* (Scheele) Torr.**	Rep. U.S. Mex. Bound. 2(1): 132 (1858)	Nearest to *Heterosphace* Benth. [184]; Gen. *Salviastrum* Scheele (as *Salviastrum texanum* Scheele) [141]		*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-B [17]	[141], [17], [30], [32], [171], [184]
***Salvia thymoides* Benth.**	Labiat. Gen. Spec.: 255 (1833)	Sect. *Calosphace* Benth. §. *Brachyantha* [140]; Subg. *Jungia* (Moench) Briq. [141] Sect. *Calosphace* Benth. §. *Brachyantha* E. *Candicantes* [145], [141]; Subg. *Calosphace* Benth. Sect. *Flocculosae* Epl. [64]		*Salvia* clade II [32]; "Core *Calosphace*" [29]; "Core *Calosphace*", *S. chamaedryoides* + *S. thymoides* clade [151]	[140], [141], [145], [32], [151], [64], [29]
***Salvia tiliifolia* Vahl**	Symb. Bot. 3: 7 (1794)	Sect. *Calosphace* Benth. §. *Micranthae* (as *S. tiliaefolia*) [140], [145]; Subg. *Jungia* (Moench) Briq. Sect. *Calosphace* Benth. §. *Micranthae* B. *Phthartae* Briq. (as *S. tiliaefolia*) [141]; Subg. *Calosphace* Benth. Sect. *Angulatae* Epl. Subsect. *Tiliaefoliae* (as *S. tiliaefolia*) [64]; Sect. *Angulatae* [170]		*Salvia* clade II [30], [32]; "Core *Calosphace*" [29]; "Core *Calosphace*", *Angulatae* clade [151]; Subg. *Calosphace* [19]	[19], [140], [141], [145], [30], [32], [151], [64], [29], [170]

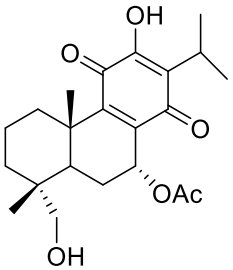
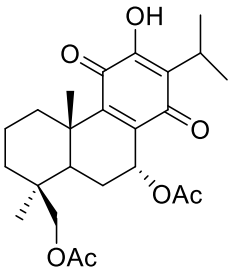
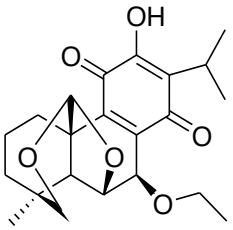
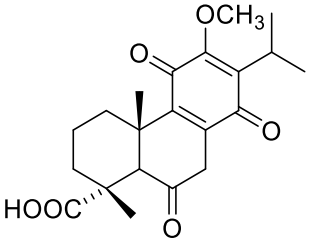
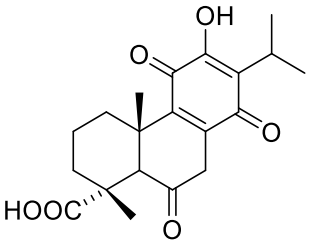
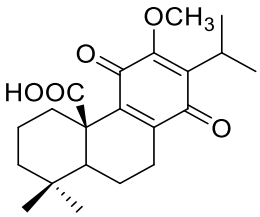
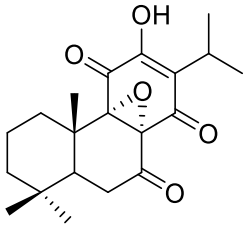
***Salvia tomentosa* Mill.**	Gard. Dict. ed. 8: n.º 2 (1768)	Sect. *Salvia* Hedge (Sect. *Eusphace* Benth.) [143], [23]	Group E of Flora of Turkey [142]	*Salvia* s.s. clade I-D [17]	[142], [17], [143], [23],
***Salvia trautvetteri* Regel**	Trudy Imp. S.-Peterburgsk. Bot. Sada, prepr. 6: 355 (1879)	Subg. *Eusalvia* Pobed. Sect. *Physosphace* Bunge. [154]		*Salvia* s.l. clade III-B (*Polakia* Stapf) [17]	[17], [154]
***Salvia tricuspis* Franch.**	Bull. Annuel Soc. Philom. Paris, sér.8, 3: 150 (1891)	Sect. *Lanatae* [66]; Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Benth. Sect. *Eurysphace* Stib. Subsect. *Annuae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Annuae* (C.Y.Wu) C.L.Xiang & H.Peng stat. nov. ≡ Subsect. *Annuae* C.Y.Wu. [19]		Chinese clade, subclade iii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Annuae* (G5) [19]	[19], [17], [28], [152], [153], [66]
***Salvia trijuga* Diels**	Notes Roy. Bot. Gard. Edimburgh 5: 237 (1912)	Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. [152]; Ser. *Miltiorrhizae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Substoloniferae* (C.Y.Wu) C.L.Xiang & B.T.Drew stat. nov. ≡ Ser. *Substoloniferae* C.Y.Wu [19]		Clade III + Japanese and Taiwanese *Salvia* [171]; Chinese clade, subclade ii [28]; *Salvia* s.l. clade IV-A (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Substoloniferae* (G3) [19]	[19], [17], [28], [152], [153], [171]
***Salvia umbratica* Hance**	J. Bot. 8: 75 (1870)	Subg. *Salvia* Benth. Sect. *Drymosphace* Benth. [141]; Subg. *Eusalvia* Stib. Sect. *Eurysphace* Stib. [152]; Subg. *Salvia* Benth. Sect. *Eurysphace* Stib. Subsect. *Annuae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Annuae* (C.Y.Wu) C.L.Xiang & H.Peng stat. nov. ≡ Subsect. *Annuae* C.Y.Wu. [19]		*Salvia* s.l. clade IV (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Annuae* (G5) [19]	[19], [141], [17], [28], [152], [153], [25], [181]
***Salvia vasta* H.W.Li**	Bull. Bot. Res., Harbin. 3: 67 (1983)	Subg. *Sclarea* (Moench) Benth. Sect. *Drymosphace* Benth. Ser. *Miltiorrhizae* C.Y.Wu [19]			[19], [185], [186]
***Salvia verbenaca* L.**	Sp. Pl.: 25 (1753)	Sect. *Plethiosphace* Benth. [140], [145], [155], [147], [156];	Group T of *Salvia* in Africa [11];	*Salvia* clade I [30], [32];	[140], [141], [142], [17], [143], [23], [145], [147],

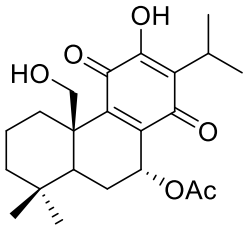
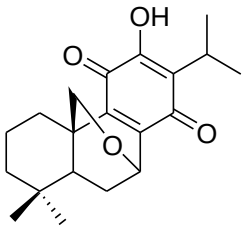
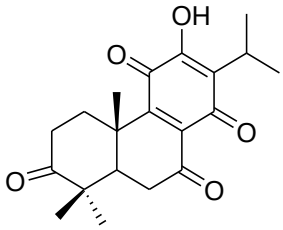
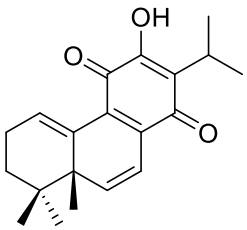
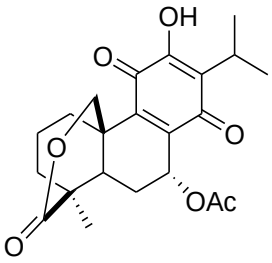
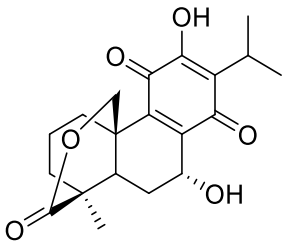
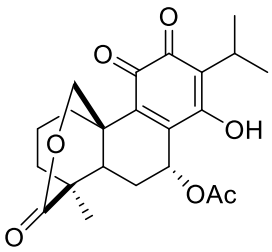
		Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. B. *Euplethiosphaceae* Briq. [141] Ser. *Verbenacae* Pobed. [154]	Group F of Flora of Turkey [142]	*Salvia* s.s. clade I-C [17]	[11], [30] [32], [154], [155], [156]
***Salvia verticillata* L.**	Sp. Pl.: 26 (1753)	Sect. *Hemisphace* Benth [140], [145], [146], [155], [156], [147]; Subg. *Covola* (Medik.) Briq. [154] Sect. *Hemisphace* Benth [141]; Sect. *Plethiosphace* Benth. [155]	Group F of Flora of Turkey [142]; Group 3 of Flora Iranica [150]	*Salvia* clade I [30], [32]; *S. verticillata* group [17]; *S. officinalis* clade [19]	[19], [142], [140], [141], [17], [143], [23], [145], [146], [147], [150], [30], [32], [154], [155], [156]
***Salvia virgata* Jacq.**	Hort. Bot. Vindob.1: 14 (1770)	Sect. *Plethiosphace* Benth. [140], [145], [146], [155], [156], [147]; Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. [Hedge 1970] B. *Euplethiosphaceae* Briq. [141]; Subg. *Sclarea* (Moench) Benth. Sect. *Plethiosphace* Benth. Subsect. *Gongrosphaceae* Briq. Ser. *Pratenses* Pobed. [154]	Groups F and G of Flora of Turkey [142]; Group 3 of Flora Iranica [150]	*Salvia* s.s. clade I-C [17]	[140], [141], [142], [17], [143], [23], [145], [146], [147], [150], [154], [155], [156]
***Salvia viridis* L.**	Species Plantarum 1: 24 (1753)	Subg. *Sclarea* (Moench) Benth. [154] Sect. *Horminum* Benth. [140], [146], [141], [156], [147], Pobedimova 1954 Flora of the URSS]; Sect. *Plethiosphace* Benth. [155]	Group S of *Salvia* in Africa [11]; Group F of Flora of Turkey [142]; Group 3 of Flora Iranica [150]	*Salvia* clade I [30], [32]; *Salvia* s.s. clade I-C [17]	[140], [141], [142], [17], [143], [23], [146], [147], [11], [150], [30] [32], [154], [155], [156]
***Salvia viridis* L. 'Blue Denim'**		Sect. *Horminum* Benth. [145]			[145]
***Salvia wardii* E.Peter-Stibal**	Repert. Spec. Nov. Regni Veg. 39: 176 (1936)	Subg. *Salvia* Benth. Sect. *Eurysphace* Stib. Subsect. *Perennes* C.Y.Wu Stib. Ser. *Hiantes* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Eurysphace* Stib. [19]		*Salvia* s.l. clade IV (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Eurysphace* (G6) [19]	[19], [17], [153]
***Salvia wiedemannii* Boiss.**	Fl. Orient. 4: 599 (1879)	Subg. *Salvia* Benth. Sect. *Eusphace* Benth. §. *Pinnatae* Boiss. A. *Fruticosae* Boiss. [141]; Sect. *Eusphace* Benth. [147]; Sect. *Salvia* Hedge (Sect. *Eusphace* Benth.) [143], [23]	Group A of Flora of Turkey [142]	*Salvia* s.s. clade I-D [17]	[141], [142], [17], [143], [23], [147]

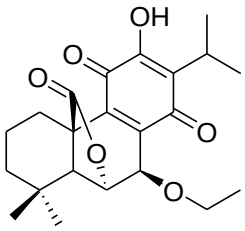
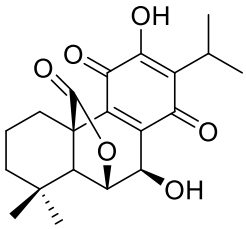
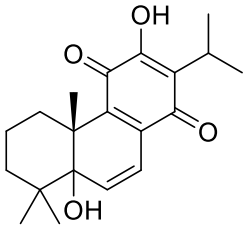
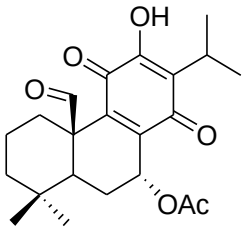
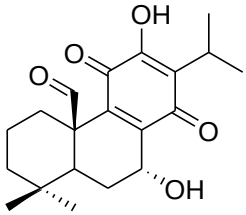
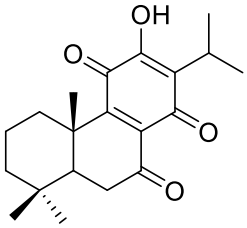
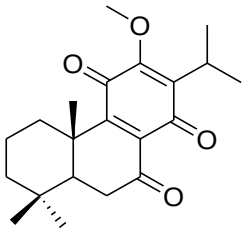
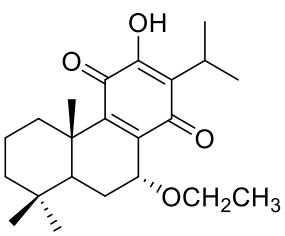
***Salvia xanthocheila* Boiss. ex Benth.**	Prodr. 12: 284 (1848)	Sect. *Aethiopis* Benth. (as *S. xanthochila*) [145]; Sect. *Gongrosphace* Briq. (sect. *Aethiopis* Benth. *ex parte*) (as *S. xanthochila*) [146]; Sect. *Aethiopis* Benth. §. *Gongrosphaceae* Sect. *Gongrosphace* Bunge [147]	Group D of Flora of Turkey [142]; Group 3 of Flora Iranica [150]	*Salvia* s.s. clade I-C [17]	[142], [17], [145], [146], [147], [150]
***Salvia yunnanensis* C.H.Wright**	Bull. Misc. Inform. Kew 1896: 164 (1896)	Subg. *Sclarea* Benth. Sect. *Drymosphace* Benth. [152] Ser. *Miltiorrhizae* C.Y.Wu [153]; Subg. *Glutinaria* (Raf.) G.X.Hu, C.L.Xiang & B.T.Drew, comb. & stat. nov. Sect. *Drymosphace* Benth [19]		Clade III + Japanese and Taiwanese *Salvia* [171]; Chinese clade, subclade i, group ii [28]; *Salvia* s.l. clade IV-B (*Glutinaria* Raf.) [17]; Subg. *Glutinaria* subclade *Drymosphace* (G7) (*S. plectranthoides* group) [19]	[19], [17], [28], [152], [153], [171]

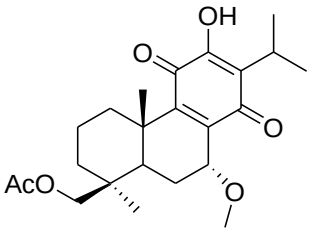
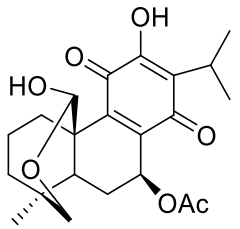
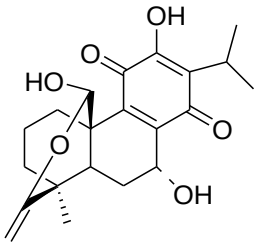
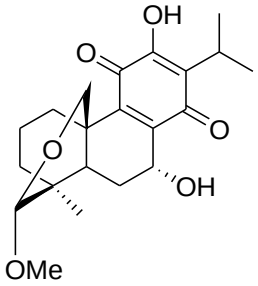
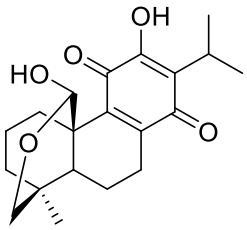
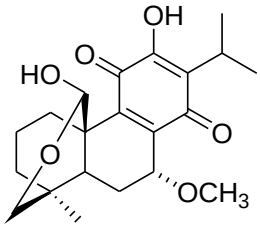
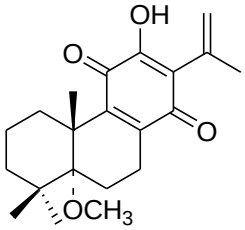
Table 2. Structures of abietane diterpene quinones isolated from *Salvia* species			
c. n.	Trivial name	Structure	*Salvia* species (organs)
1	Royleanone		*S. aethiopis* L. (roots) [187] *S. anastomosans* Ramamoorthy (roots) [188] *S. austriaca* Jacq. (hairy roots) [189] *S. ballotiflora* Benth. (aerial parts) [190] *S. barrelieri* Etl. (roots) [191] *S. blepharochlaena* Hedge & Hub.-Mor. (NS) [192] *S. bucharica* Popov (roots; NS) [193,194] *S. cana* Wall. ex Benth. (whole plant) [195] *S. deserta* Schangin (NS) [196,197] *S. fruticosa* Mill. (roots) [193] *S. hydrangea* DC. ex Benth. (roots) [194] *S. korolkovii* Regel & Schmalh. (roots) [194] *S. kronenburgii* Rech. f. (roots) [198] *S. lanigera* Poir. (roots) [199] *S. mellifera* Greene (roots) [200] *S. moocroftiana* Wall. ex Benth. (roots) [201] *S. nemorosa* L. (roots) [202] *S. nutans* L. (roots) [203] *S. officinalis* L. (whole plant) [204] *S. officinalis* subsp. *lavandulifolia* (Vahl) Gams (roots) [205] *S. pachystachya* Trautv. (aerial parts) [206] *S. phlomoides* Asso (roots) [207] *S. pratensis* L. (roots) [208] *S. prionitis* Hance (roots) [209] *S. regla* Cav. (aerial parts) [210] *S. tomentosa* Mill. (roots) [211] *S. viridis* L. (roots) [212]
2	6,7-Dehydroroyleanone		*S. bracteata* Banks & Sol. (roots) [213] *S. cana* Wall. ex Benth. (NS) [193] *S. eriophora* Boiss. & Kotschy (roots) [214] *S. jaminiana* de Noè (roots) [215] *S. lanigera* Poir. (roots) [216] *S. moocroftiana* Wall. ex Benth. (roots) [217] *S. officinalis* L. (whole plant) [204] *S. officinalis* subsp. *lavandulifolia* (Vahl) Gams (roots) [205] *S. pratensis* L. (roots) [218] *S. tchihatcheffii* (Fisch. & C.A.Mey.) Boiss. (NS) [193] *S. tomentosa* Mill. (roots) [211,219] *S. verbenaca* L. (roots) [193] *S. viridis* L. (roots) [212]
3	12-Deoxy-6,7-dehydroroyleanone		*S. nutans* L. (roots) [194,203] *S. sahendica* Boiss. & Buhse (roots) [220]
4	12-Deoxy-6-hydroxy-6,7-dehydroroyleanone		*S. nutans* L. (roots) [194]

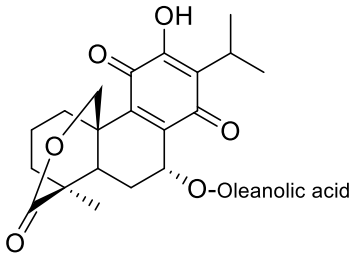
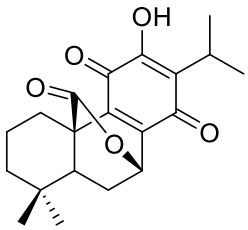
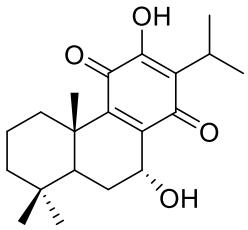
5	12-Deoxy-7,7'-dimethoxy-6-oxoroyleanone		*S. nutans* L. (roots) [203]
6	12-Deoxy-7-acetoxyroyleanone		*S. bucharica* Popov (roots) [194] *S. hydrangea* DC. ex Benth. (roots) [194] *S. korolkovii* Regel & Schmalh. (roots) [194]
7	16-Hydroxyroyleanone		*S. apiana* Jeps. (roots) [221]
8	19-Hydroxyroyleanone		*S. chionopeplica* Epling (leaves) [222]
9	2β-Hydroxyroyleanone		*S. absconditiflora* Greuter & Burdet (roots) [223]
10	6α-Hydroxyroyleanone		*S. fruticosa* Mill. (roots) [206]
11	7β-Hydroxyroyleanone		*S. lanigera* Poir. (roots) [193] *S. moocroftiana* Wall. ex Benth. (roots) [201]

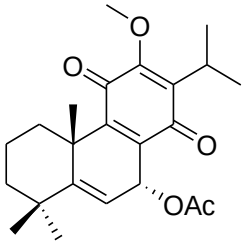
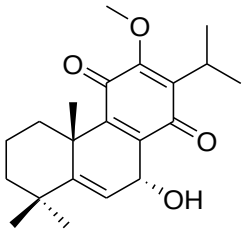
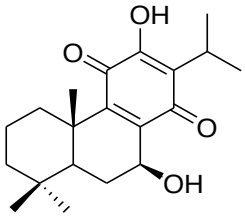
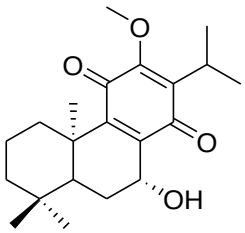
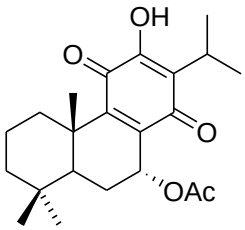
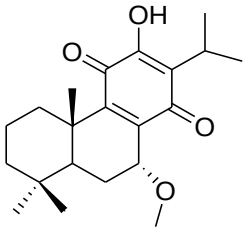
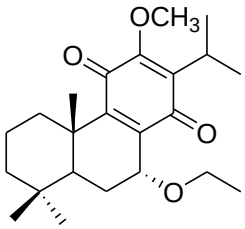
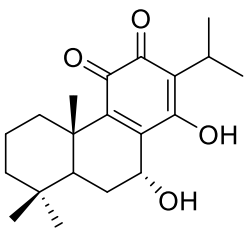
12	7α-Acetoxy-19-hydroxyroyleanone		*S. regla* Cav. (aerial parts) [210]
13	7α,19-Diacetoxy-hydroxyroyleanone		*S. corrugata* Vahl (aerial parts; *in vitro* shoots) [224,225]
14	7β-Ethoxy-6β,20:19,20-diepoxyroyleanone		*S. corrugata* Vahl (*in vitro* shoots) [224]
15	6-Oxo-12-methylroyleanon-18-oic acid		*S. divaricata* Montbret & Aucher ex Benth. (aerial parts) [226]
16	6-Oxoroyleanon-18-oic acid		*S. divaricata* Montbret & Aucher ex Benth. (aerial parts) [226]
17	Trilobic acid		*S. fruticosa* Mill. (roots) [227]
18	8,9-Epoxy-7-oxoroyleanone		*S. pratensis* L. (roots) [218]

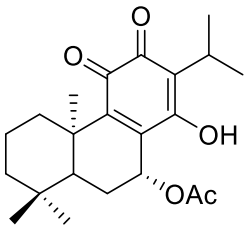
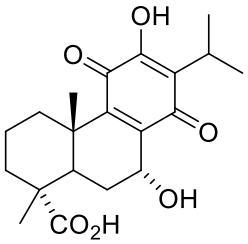
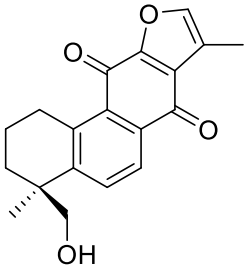
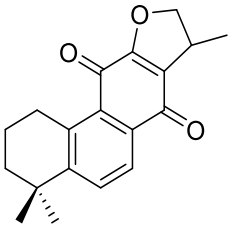
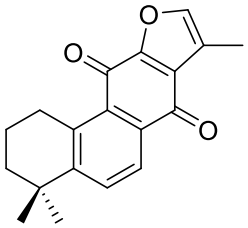
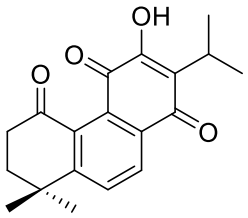
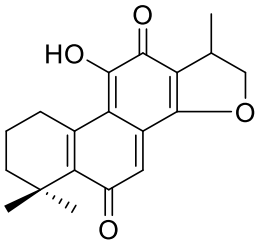
19	7α-Acetoxy-20-hydroxyroyleanone		*S. cana* Wall. ex Benth. (whole plant) [195]
20	7,20-Epoxyroyleanone		*S. candidissima* Vahl subsp. *candidissima.* (roots) [228] *S. blepharochlaena* Hedge & Hub.-Mor. (roots) [192] *S. napifolia* Jacq. (roots) [229]
21	Candelabroquinone		*S. candelabrum* Boiss. (aerial parts) [230]
22	Salviskinone A		*S. przewalskii* Maxim. (roots) [231]
23	Isosessein		*S. sessei* Benth. (aerial part) [232]
24	Deacetylsessein		*S. regla* Cav. (aerial parts) [210]
25	Sessein		*S. regla* Cav. (aerial parts) [210,233] *S. sessei* Benth. (aerial parts; roots) [232,234]

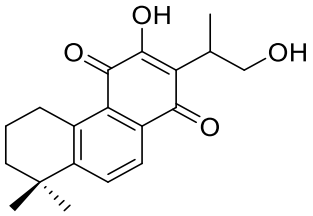
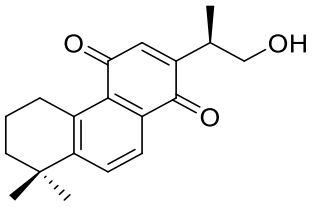
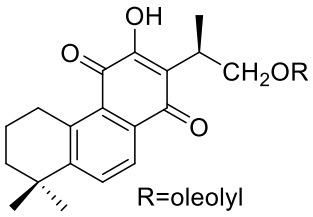
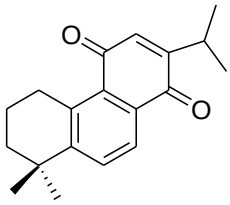
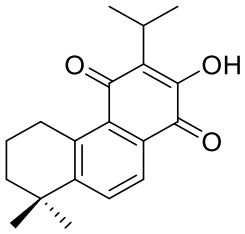
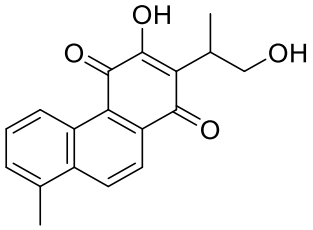
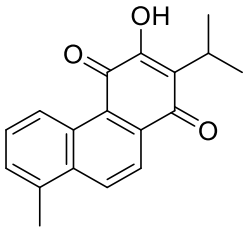
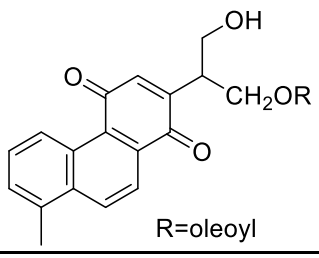
26	Canariquinone		*S. canariensis* L. (flowers) [235]
27	Atuntzensin A		*S. officinalis* L. (leaves) [236]
28	Hypargenin F		*S. hypargeia* Fisch. & C.A.Mey. (roots) [237] *S. montbretii* Benth. (roots) [202,238]
29	Nemorone		*S. ballotiflora* Benth. (aerial parts) [190] *S. nemorosa* L. (roots) [202] *S. pubescens* Benth. (aerial parts) [239]
30	Deacetylnemorone		*S. anastomosans* Ramamoorthy (roots) [188] *S. cana* Wall. ex Benth. (whole plant) [195] *S. lanigera* Poir. (roots) [216] *S. leriifolia* Benth. (roots) [240] *S. nemorosa* L. (roots) [202] *S. pubescens* Benth. (aerial parts) [239]
31	7-Oxoroyleanone		*S. sclarea* L. (whole plant) [241]
32	7-Oxoroyleanone-12-methyl ether		*S. barrelieri* Etl. (roots) [191] *S. lanigera* Poir. (roots) [193] *S. moocroftiana* Wall. ex Benth. (roots) [201] *S. pratensis* L. (roots) [218] *S. sclarea* L. (roots) [241]
33	7α-Ethoxyroyleanone		*S. officinalis* subsp. l*avandulifolia* (Vahl) Gams (roots) [205]

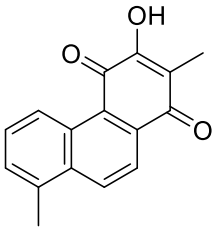
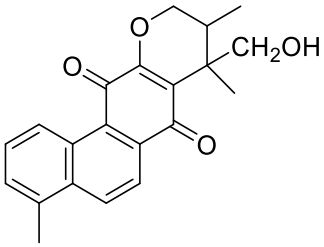
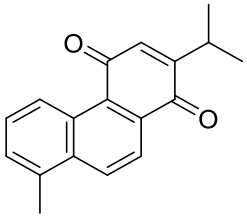
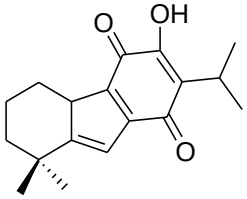
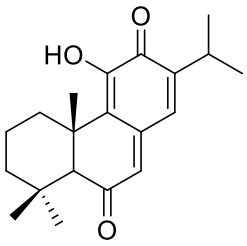
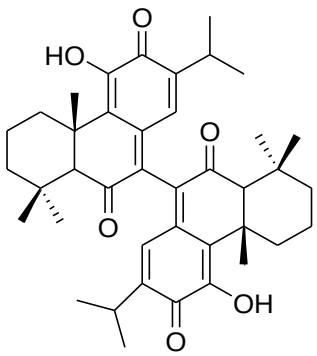
34	7α-Methoxy-19-acetoxy-royleanone		*S. corrugata* Vahl (aerial parts) [225]
35	7β-Acetoxy-20-hydroxy-19,20-epoxyroyleanone		*S. corrugata* Vahl (*in vitro* shoots) [224]
36	Conacytone		*S. anastomosans* Ramamoorthy (aerial parts) [242] *S. ballotiflora* Benth. (aerial parts) [190] *S. candicans* M.Martens & Galeotti (aerial parts) [243] *S. corrugata* Vahl (aerial parts) C [224] *S. pubescens* Benth. (aerial parts) [239]
37	19-Methoxy of isomer of conacytone		*S. candicans* M.Martens & Galeotti (aerial parts) [243]
38	7-Dehydroxyconacytone		*S. corrugata* Vahl (aerial parts) [225]
39	7-O-Methylconacytone		*S. candicans* M.Martens & Galeotti (aerial parts) [243] *S. pubescens* Benth. (aerial parts) [244] *S. corrugata* Vahl (aerial parts) [225]
40	Bractealine		*S. bracteata* Banks & Sol. (roots) [213] *S. multicaulis* Vahl (roots) [245]

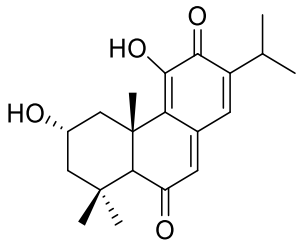
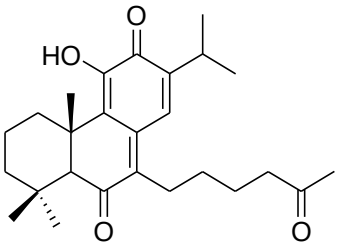
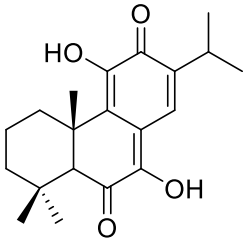
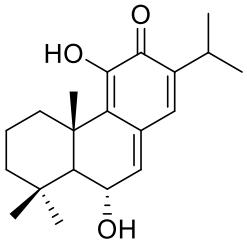
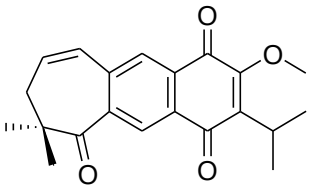
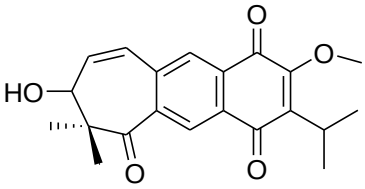
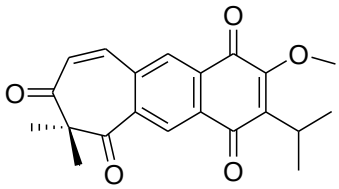
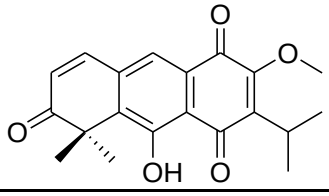
41	Reglin		*S. miltiorrhiza* Bunge (roots) [246] *S. regla* Cav. (aerial parts) [233]
42	Columbaridione		*S. columbariae* Benth. (aerial parts) [247] *S. officinalis* L. (leaves) [236] *S. pubescens* Benth. (aerial parts) [248]
43	Horminone (7α-Hydroxyroyleanone)		*S. absconditiflora* Greuter & Burdet (roots) [223] *S. amplexicaulis* Lam. (roots) [192] *S. anastomosans* Ramamoorthy (roots) [188] *S. austriaca* Jacq. (roots) [211] *S. barrelieri* Etl. (roots) [191] *S. blepharochlaena* Hedge & Hub.-Mor. (roots) [249] *S. bracteata* Banks & Sol. (roots) [213] *S. cana* Wall. ex Benth. (roots) [194] *S. candidissima* subsp. *occidentalis* Hedge (roots) [193,238] *S. carduacea* Benth. (roots) [250] *S. chionantha* Boiss. (aerial parts) [251] *S. deserta* Schangin (roots) [214] *S. eriophora* Boiss. & Kotschy (roots) [223] *S. eriophora* Boiss. & Kotschy (roots) [206] *S. fruticosa* Mill. (roots) [211];[237] *S. hypargeia* Fisch. & C.A.Mey. (roots) [214],[237] *S. korolkovii* Regel & Schmalh. (whole plant) [250] *S. kronenburgii* Rech. f. (aerial parts) [252] *S. lavanduloides* Kunth (roots) [195] *S. mellifera* Greene (roots) [200] *S. moocroftiana* Wall. ex Benth. (roots) [228] *S. multicaulis* Vahl (roots) [201,253] *S. munzii* Epling (leaves; roots) [229,254] *S. napifolia* Jacq. (roots) [241,253] *S. nemorosa* L. (aerial parts; roots) [229,255] *S. nutans* L. (whole plant) [203] *S. officinalis* L. (aerial plant) [204] *S. pachystachya* Trautv. (aerial plant) [206] *S. palaestina* Benth. (roots) [256] *S. pisidica* Boiss. & Heldr.ex Benth. (roots) [257] *S. potentillifolia* Boiss. & Heldr. ex Benth. (roots) [223] *S. pratensis* L. (roots) [258] *S. sahendica* Boiss. & Buhse (roots) [188] *S. semiatrata* Zucc. (roots) [208] *S. tomentosa* Mill. (roots) [206] *S. verbenaca* L. (roots) [216], *S. verticillata* L. (roots) [259] *S. virgata* Jacq. (roots) (ULUBELEN 1992 CHEMISTRY AND PHARMACOLOGY OF TURKISH SALVIA SPECIES) *S. viridis* L. (NS; roots) [212,260] *S. wiedemannii* Boiss. (aerial parts; roots) [193]

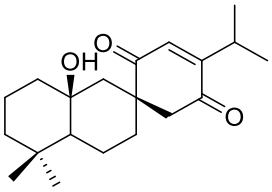
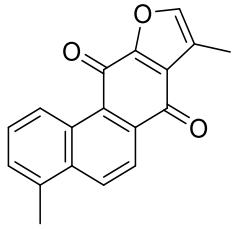
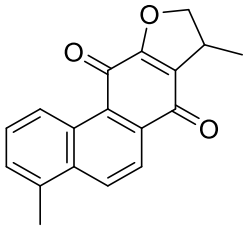
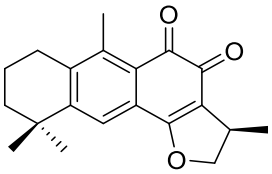
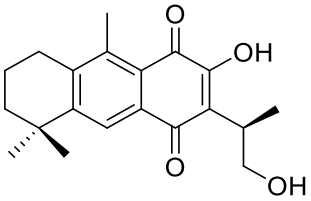
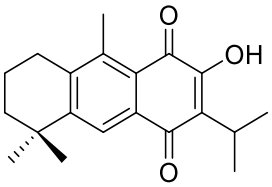
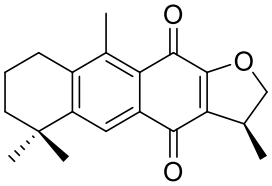
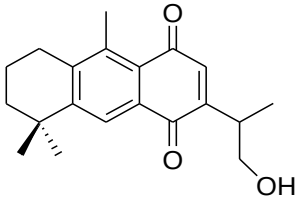
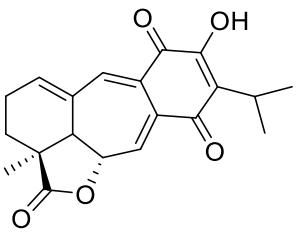
44	12-Methoxy-5,6-dehydroacetylhorminone		*S. multicaulis* Vahl (roots) [245]
45	12-Methoxy-5,6-dehydrohorminone		*S. multicaulis* Vahl (roots) [245] *S. recognita* Fisch. & C.A.Mey. (roots) [261] *S. verbenaca* L. (roots) [216]
46	Taxoquinone		*S. lanigera* Poir. (roots) [216]
47	12-Methylhorminone		*S. bracteata* Banks & Sol. (roots) [213]
48	7-Acetylhorminone		*S. blepharochlaena* Hedge & Hub.-Mor. (roots) [249] *S. bracteata* Banks & Sol (roots) [213] *S. candidissima subsp. occidentalis* Hedge (roots) [262] *S. napifolia* Jacq. (roots) [229] *S. nemorosa* L. (roots; aerial parts) [241,255]
49	7-O-Methylhorminone		*S. deserta* Schangin (NS) [197,263] *S. leriifolia* Benth. (NS) [264]
50	7-Ethyl- 12-O-methylhorminone		*S. officinalis* subsp. *lavandulifolia* (Vahl) Gams (roots) [205]
51	Horminone tautomer		*S. viridis* L. 'Blue Denim' (whole plant) [265]

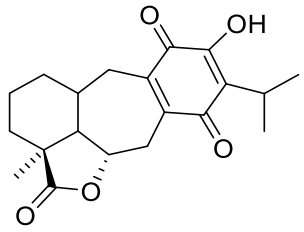
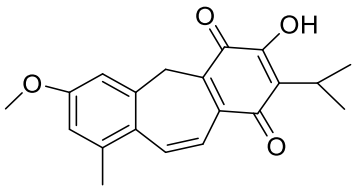
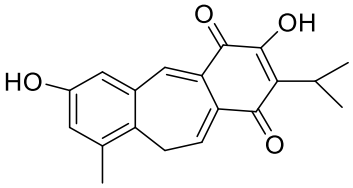
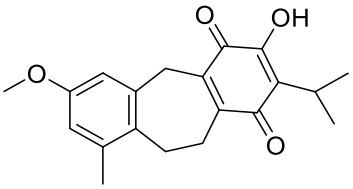
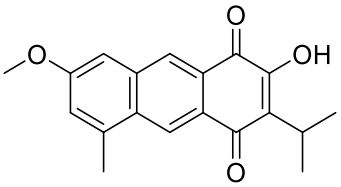
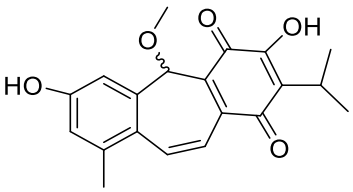
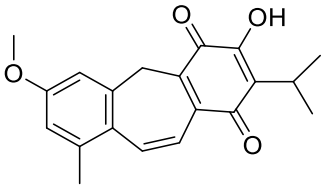
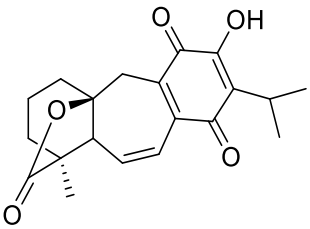
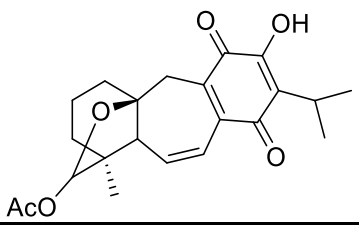
52	7-O-Acetylhorminone tautomer		*S. viridis* L. 'Blue Denim' (whole plant) [265]
53	Horminone-18-oic acid		*S. divaricata* Montbret & Aucher ex Benth. (aerial parts) [226]
54	Isotanshinone II B		*S. miltiorrhiza* Bunge (roots) [266]
55	Isocryptotanshinone (Isotanshinone III)		*S. mellifera* Greene (roots) [200] *S. miltiorrhiza* Bunge (roots) [267]
56	Isotanshinone II (Isotanshinone IIA)		*S. glutinosa* L. (roots) [211] *S. miltiorrhiza* Bunge (roots) [267,268] *S. yunnanensis* C.H.Wright (roots) [269]
57	Miltionone I		*S. miltiorrhiza* Bunge (roots) [270]
58	Miltionone II		*S. columbariae* Benth. (roots) [271] *S. miltiorrhiza* Bunge (roots) [270]

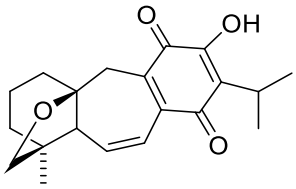
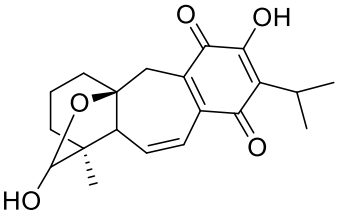
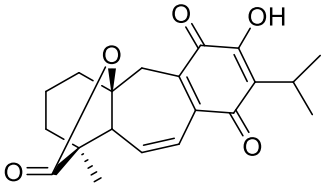
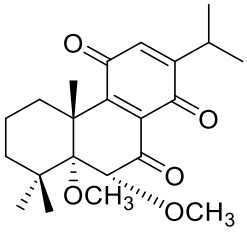
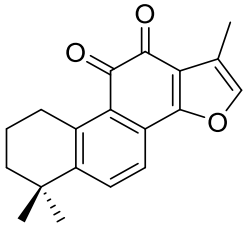
59	Neocryptotanshinone		*S. miltiorrhiza* Bunge (roots) [266,272]
60	12-Deoxyneocryptotanshinone		*S. rythidea* Benth. (roots) [273] *S. lanigera* Poir. (roots) [193] *S. miltiorrhiza* Bunge (roots) [274]
61	Oleoylneocryptotanshinone		*S. miltiorrhiza* Bunge [275]
62	Sibiriquinone B		*S. castanea* Diels (whole plant) [276]
63	Salvialerione		*S. lanigera* Poir. (roots) [277] *S. leriifolia* Benth. (whole plant) [278]
64	Danshenxinkun A		*S. miltiorrhiza* Bunge (roots) [274] *S. przewalskii* Maxim. (roots) [279]
65	Danshenxinkun B		*S. glutinosa* L. (roots) [211] *S. miltiorrhiza* Bunge (roots) [274] *S. prionitis* Hance (roots) [193] *S. przewalskii* Maxim. (roots) [279] *S. yunnanensis* C.H.Wright (roots) [280]
66	Oleoyldanshenxinkun A		*S. miltiorrhiza* Bunge (roots) [275]

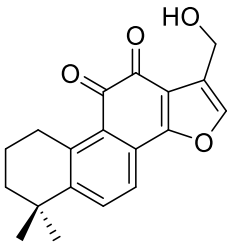
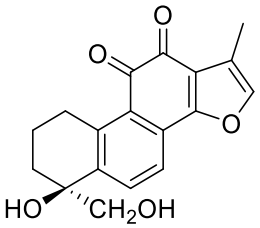
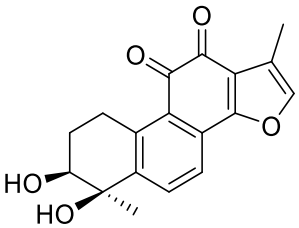
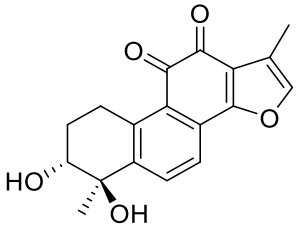
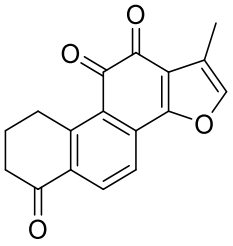
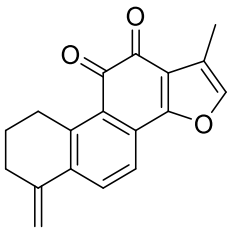
67	Danshenxinkun C		*S. miltiorrhiza* Bunge (roots) [268]
68	Danshenxinkun D		*S. miltiorrhiza* Bunge (roots) [266] *S. prionitis* Hance (roots) [193] *S. trijuga* Diels (roots) [281,282]
69	12-Deoxydanshenxinkun B		*S. glutinosa* L. (roots) [211]
70	Dichroanone		*S. dichroantha* Stapf (roots) [283]
71	Taxodione		*S. austriaca* Jacq. (hairy roots) [189,284] *S. chorassanica* Bunge (roots) [285] *S. deserta* Schangin (roots) [251] *S. hypargeia* Fisch. & C.A.Mey. (roots) [213] *S. lachnocalyx* Hedge (roots) [286] *S. lanigera* Poir. (roots) [199] *S. mellifera* Greene (roots) [200] *S. montbretii* Benth. (whole plant) [238] *S. moocroftiana* Wall. ex Benth. (roots) [287] *S. munzii* Epling (leaves; roots) [253] *S. nipponica* Miq. (roots) [274] *S. oaxacana* Fernald (aerial parts) [248] *S. pachystachya* Trautv. (aerial parts) [206] *S. phlomoides* Asso (roots) [207] *S. prionitis* Hance (roots) [288] *S. rythidea* Benth. (roots) [273] *S. verbenaca* L. (roots) [216] *S. xanthocheila* Boiss. ex Benth. (aerial parts) [289]
72	11,11'-Didehydroxy-7,7'-hydroxytaxodione		*S. montbretii* Benth. (NS) [290]

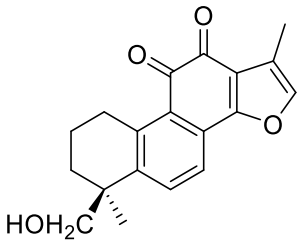
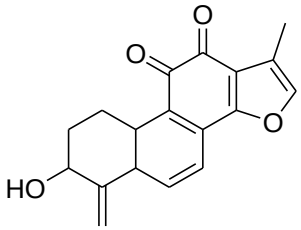
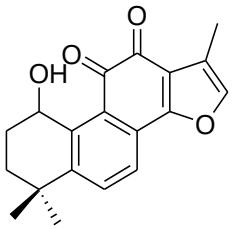
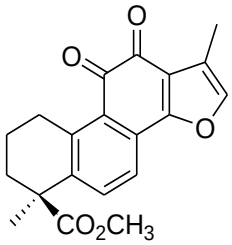
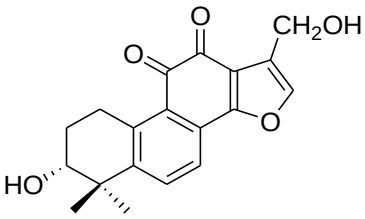
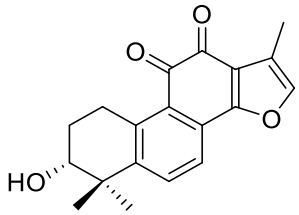
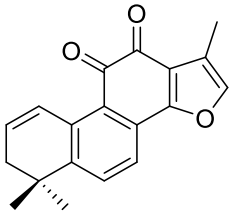
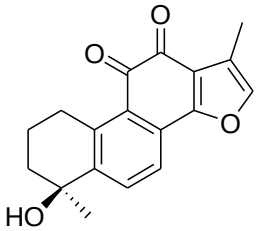
73	2α-Hydroxytaxodione		*S. texana* (Scheele) Torr. (roots) [291]
74	7-(2-Oxohexyl)-taxodione		*S.* austriaca Jacq. (hairy roots) [189]
75	7-Hydroxytaxodione		*S. montbretii* Benth. (roots) [290]
76	Taxodone		*S. austriaca* Jacq. (hairy roots) [292] *S. munzii* Epling (leaves; roots) [253] *S. oaxacana* Fernald (aerial parts) [248]
77	Tilifolidione		*S. semiatrata* Zucc. (roots) [188] *S. thymoides* Benth. (roots) [188] *S. tiliifolia* Vahl (roots) [293]
78	3-Hydroxytilifolidione		*S. thymoides* Benth. (roots) [188]
79	3-Oxotilifolidione		*S. thymoides* Benth. (roots)
80	Nor derivative of 3-Oxotilifolidione		*S. thymoides* Benth. (roots) [188]

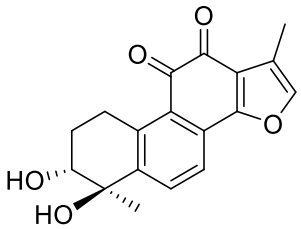
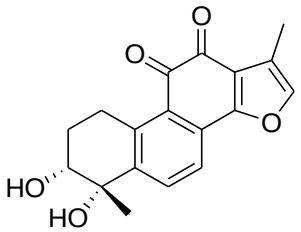
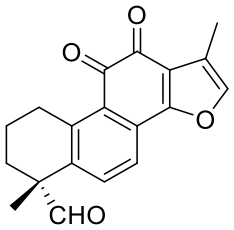
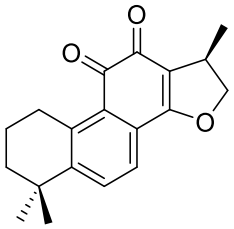
81	Martiusane		*S. leriifolia* Benth. (roots) [240]
82	Isotanshinone I		*S. glutinosa* L. (roots) [211] *S. miltiorrhiza* Bunge (roots) [267] *S. trijuga* Diels (roots) [294]
83	Dihydroisotanshinone I		*S. glutinosa* L. (roots) [211] *S. miltiorrhiza* Bunge (roots) [268] *S. prionitis* Hance (roots) [193]
84	Aegyptinone A		*S. aegyptiaca* L. (roots) [199] *S. tebesana* Bunge (roots) [295]
85	Aegyptinone B		*S. aegyptiaca* L. (roots) [199] *S. tebesana* Bunge (roots) [295]
86	Aegyptinone C		*S. aegyptiaca* L. (roots) [296]
87	Aegyptinone D		*S. aegyptiaca* L. (roots) [297]
88	Tebesinone B		*S. tebesana* Bunge (roots) [295]
89	Anastomosine		*S. anastomosans* Ramamoorthy (aerial parts) [242] *S. ballotiflora* Benth. (aerial parts) [298] *S. candicans* M.Martens & Galeotti (aerial parts) [243]

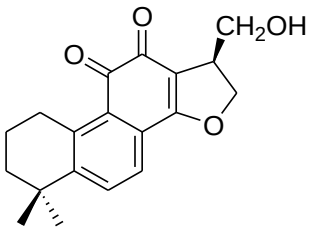
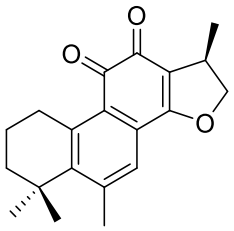
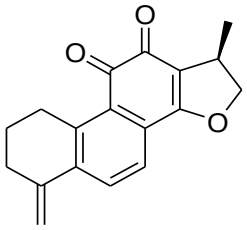
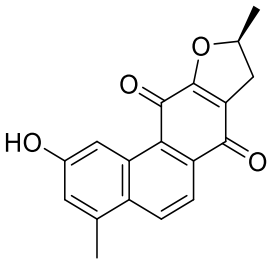
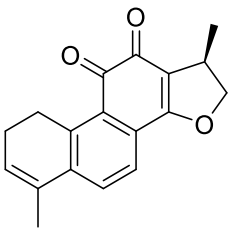
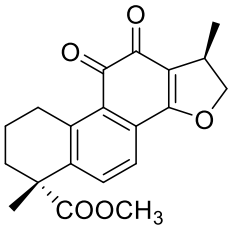
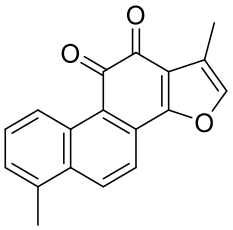
90	7,20-Dihydroanastomosine		*S. anastomosans* Ramamoorthy (roots) [188,298] *S. ballotiflora* Benth. (aerial parts) [298]
91	Fruticulin A		*S. fruticulosa* Benth. (aerial parts) [299]
92	Demethylfruticulin A		*S. arizonica* A.Gray (aerial parts) [300] *S. corrugata* Vahl (aerial parts) [67] *S. fruticulosa* Benth. (aerial parts) [299]
93	7,20-Dihydrofruticuline A		*S. corrugata* Vahl (aerial parts) [224] *S. lachnostachys* Benth. (leaves) [301]
94	Fruticulin B		*S. fruticulosa* Benth. (aerial parts) [299]
95	Fruticulin C		*S. corrugata* Vahl (aerial parts) [225]
96	Isofruticuline A		*S. lachnostachys* Benth. (leaves) [301]
97	Icetexone		*S. anastomosans* Ramamoorthy (aerial parts) [242] *S. ballotiflora* Benth. (aerial parts) [302,303] *S. candicans* M.Martens & Galeotti (aerial parts) [243] *S. pubescens* Benth. (aerial parts) [244]
98	19(R)-Acetoxy-19-deoxoicetexone		*S. pubescens* Benth. (aerial parts) [244]

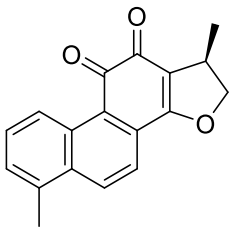
99	19-Deoxyicetexone		*S. ballotiflora* Benth. (aerial parts) [298]
100	19-Hydroxy-19-deoxo-icetexone		*S. pubescens* Benth. (aerial parts) [248]
101	5-Epi-icetexone		*S. cuspidata* subsp. *gilliesii* (Benth.) J.R.I.Wood (aerial parts) [304]
102	Xantoquinone		*S. xanthocheila* Boiss. ex Benth. (aerial parts) [305]
103	Tanshinone II Tanshinone II A		*S. aerea* H.Lév. (roots) [306] *S. bowleyana* Dunn (NS) [307] *S. brevilabra* Franch. (NS) *S. bulleyana* Diels (aerial parts, roots) [308] *S. campanulata* Wall. ex Benth. (NS) [197,307] *S. castanea* Diels (aerial parts, roots; whole plant) [197,307] *S. cavaleriei* var. *simplicifolia* E.Peter-Stibal (whole plant) [197,276,306,307] *S. coccinea* Buc'hoz ex Etl. (NS) [271] *S. columbariae* Benth. (roots) [308] *S. cynica* Dunn (NS) [197,307] *S. dabieshanensis* J.Q.He (NS) [308] *S. digitaloides* Diels (roots) [309] *S. evansiana* Hand.-Mazz. (aerial parts, roots) [197,307] *S. flava* Forrest ex Diels (aerial parts, roots) [197,307] *S. fruticosa* Mill. (roots) [193] *S. glutinosa* L.(roots) [310] *S. hians* Royle ex Benth. (roots) [311] *S. kiaometiensis* H.Lév. (roots) [312] *S. maximowicziana* Hemsl. (NS) [197,307] *S. meiliensis* S.W.Su (NS) [197,307] *S. miltiorrhiza* Bunge (roots) [313] *S. nanchuanensis* Y.Z.Sun (NS) [197,314] *S. paramiltiorrhiza* H.W.Li & X.L.Huang (aerial parts, roots) [308] *S. plectranthoides* Griff. (NS*)* [197] *S. pratii* Hemsl. (roots) [315] *S. przewalskii* Maxim. (roots) [279] *S. roborowskii* Maxim. (roots) [197] *S. schizochila* E.Peter-Stibal (NS) [197] *S. sinica* Migo (aerial parts, roots) [308] *S. stibalii* Alziar (aerial parts, roots) [197]

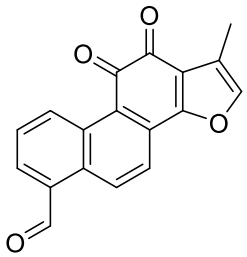
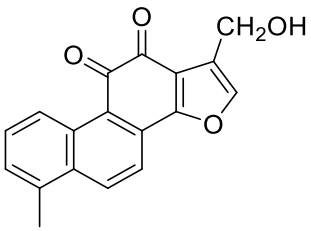
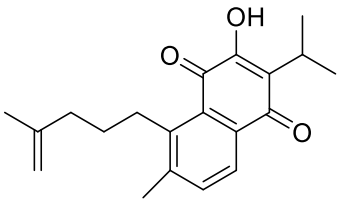
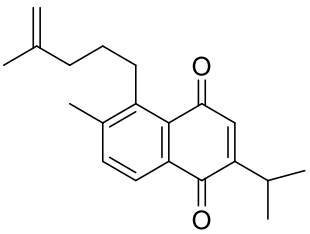
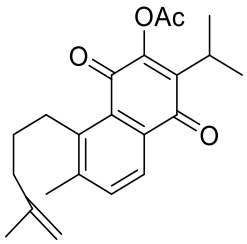
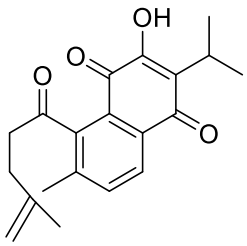
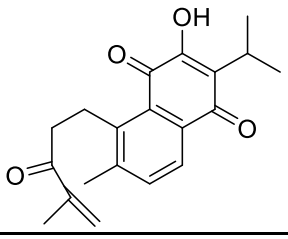
			S. subpalmatinervis E.Peter-Stibal (NS) [246] *S. tricuspis* Franch. (NS) [308] *S. trijuga* Diels (roots) [308] *S. umbratica* Hance (aerial parts, roots) [197,316] *S. vasta* H.W.Li (roots) [197] *S. yunnanensis* C.H.Wright (roots; whole plant) [317],[280]
104	17-Hydroxytanshinone II		*S. castanea* Diels (roots) [306] *S. miltiorrhiza* Bunge (roots) [318] *S. munzii* Epling (roots) [253] *S. przewalskii* Maxim. (roots) [193]
105	Tanshindiol A		*S. miltiorrhiza* Bunge (roots) [319]
106	Tanshindiol B		*S. miltiorrhiza* Bunge (roots) [319] *S. przewalskii* Maxim. (roots) [193]
107	Tanshindiol C		*S. kiaometiensis* H.Lév. (roots) [312] *S. miltiorrhiza* Bunge (roots) [268,319] *S. przewalskii* Maxim. (roots) [193]
108	Nortanshinone		*S. miltiorrhiza* Bunge (roots) [319] *S. przewalskii* Maxim. (roots) [279] *S. trijuga* Diels (roots) [316]
109	Methylene tanshinquinone		*S. brevilabra* Franch.(NS) [308] *S. castanea* Diels (roots) [276] *S. coccinea* Buc'hoz ex Etl. (NS) [308] *S. cynica* Dunn (NS) [308] *S. fruticosa* Mill. (roots) [193] *S. miltiorrhiza* Bunge (roots) [246,267,268,311,313,320] *S. nanchuanensis* Y.Z.Sun (NS) [308] *S. przewalskii* Maxim. (roots) [246,279] *S. schizochila* E.Peter-Stibal (NS) [308] *S. subpalmatinervis* E.Peter-Stibal (NS) [308] *S. tricuspis* Franch. (NS) [308] *S. trijuga* Diels (roots) [246] *S. yunnanensis* C.H.Wright (roots) [280]

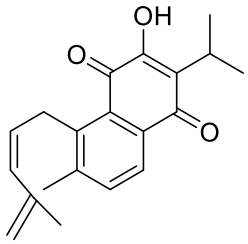
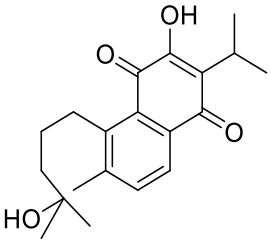
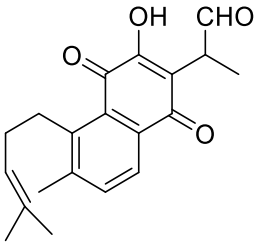
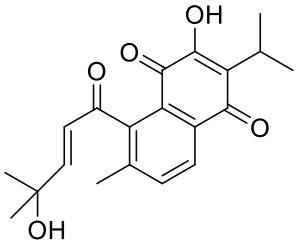
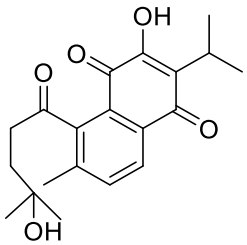
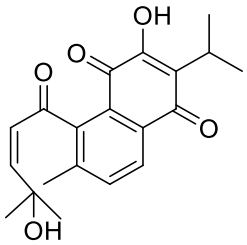
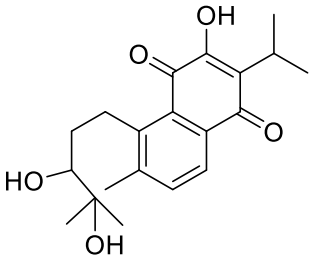
110	Tanshinone II B		*S. castanea* Diels (whole plant) [321] *S. miltiorrhiza* Bunge (roots) [267] *S. przewalskii* Maxim. (roots) [279] *S. trijuga* Diels (roots) [246]
111	3-Hydroxymethylene tanshinquinone		*S. trijuga* Diels (roots) [246]
112	1-Hydroxytanshinone II A		*S. miltiorrhiza* Bunge (roots) [313,319,320] *S. przewalskii* Maxim. (roots) [193] *S. trijuga* Diels (roots) [219]
113	Methyl tanshinonate		*S. przewalskii* Maxim. (roots) [246]
114	3α,17-Dihydroxytanshinone II A		*S. hians* Royle ex Benth. (roots) [311] *S. przewalskii* Maxim. (roots) [193]
115	3α-Hydroxytanshinone II A		*S. miltiorrhiza* Bunge (roots) [319] *S. trijuga* Diels (roots) [193]
116	1,2 Dehydrotanshinone II A		*S. cuspidata* Ruiz & Pav. (aerial parts) [322] *S. cuspidata* subsp. *gilliesii* (Benth.) J.R.I.Wood (aerial parts) [304] *S. honania* L.H.Bailey (NS) [307] *S. kiangsiensis* C.Y.Wu (NS) [307] *S. miltiorrhiza* Bunge (roots) [277] *S. sahendica* Boiss. & Buhse (roots) [258]
117	Przewaquinone C		*S. przewalskii* Maxim. (roots) [193]

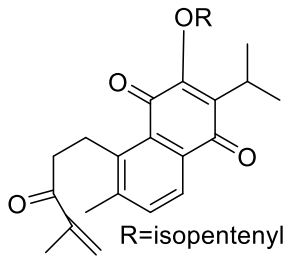
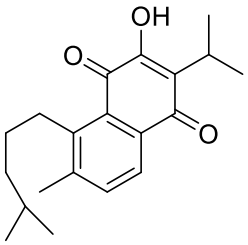
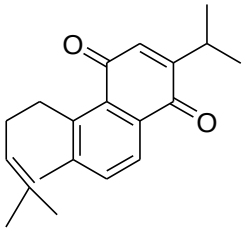
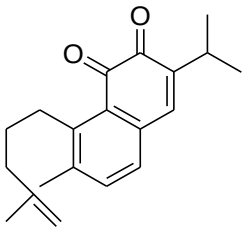
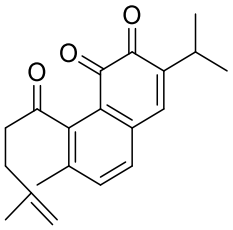
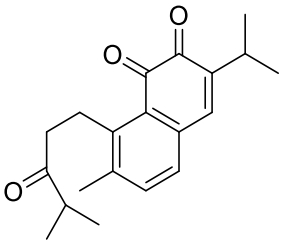
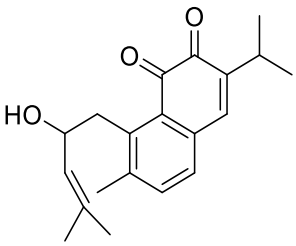
118	Przewaquinone D		*S. przewalskii* Maxim. (roots) [323]
119	Przewaquinone E		*S. przewalskii* Maxim. (roots) [323]
120	Tanshinalehyde (Tanshononal)		*S. miltiorrhiza* Bunge (roots) [313] *S. przewalskii* Maxim. (roots) [193]
121	Cryptotanshinone		*S. aerea* H.Lév. (roots) [306] *S. apiana* Jeps. (roots) [221] *S. axillaris* Moc. & Sessé ex Benth. (aerial parts; roots) [193,298] *S. bulleyana* Diels (aerial parts; roots) [197,307] *S. campanulata* Wall. ex Benth. (NS) [197,307] *S. castanea* Diels (aerial part; roots; whole plant) [197,276,306,307] *S. cavaleriei* var. *simplicifolia* E.Peter-Stibal (herbs) [197,307] *S. columbariae* Benth. (roots) [271] *S. dabieshanensis* J.Q.He (NS) [197,307] *S. digitaloides* Diels (roots) [309] *S. drobovii* Botsch. (roots) [193] *S. evansiana* Hand.-Mazz. (aerial part; roots) [197,307] *S. flava* Forrest ex Diels (aerial part; roots) [197,307] *S. glutinosa* L. (roots) [211] *S. karabachensis* Pobed. (NS) [193] *S. kiaometiensis* H.Lév. (roots) [312] *S. maximowicziana* Hemsl. (NS) [197,307] *S. meiliensis* S.W.Su (NS) [197,307] *S. mellifera* Greene (roots) [253] *S. miltiorrhiza* Bunge (roots) [253,267,274] *S. munzii* Epling (leaves;roots) [253] *S. paramiltiorrhiza* H.W.Li & X.L.Huang (aerial part; roots) [197] *S. plectranthoides* Griff. (aerial part; roots) [197] *S. pratii* Hemsl. (roots) [315] *S. przewalskii* Maxim. [279] *S. roborowskii* Maxim. (roots) [197] *S. sinica* Migo (aerial part; roots) [197] *S. stibalii* Alziar (NS) [197] *S. trautvetteri* Regel (roots) [193] *S. trijuga* Diels (roots) [193] *S. umbratica* Hance (aerial part; roots) [197] *S. vasta* H.W.Li (NS) [197,307] *S. yunnanensis* C.H.Wright (roots; whole plant) [280,324]

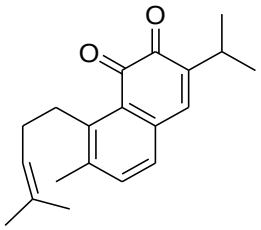
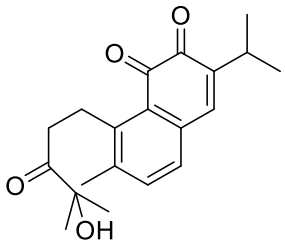
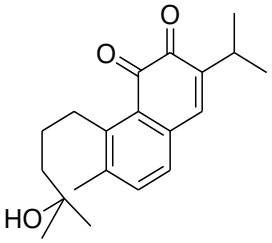
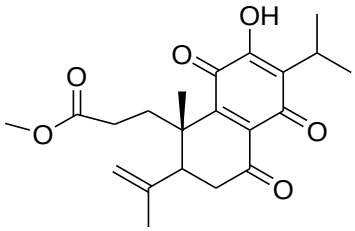
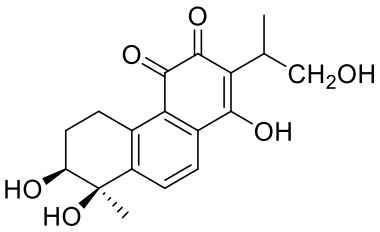
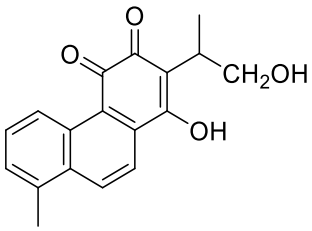
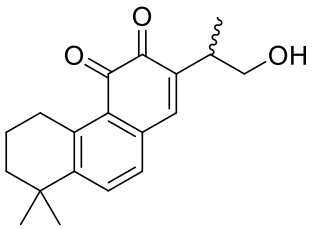
122	17-Hydroxcryptotanshinone		*S. munzii* Epling (roots) [253]
123	6-Methylcryptotanshinone		*S. aegyptiaca* L. (whole plant) [325]
124	Methylene cryptotanshinquinone		*S. miltiorrhiza* Bunge (roots) [326]
125	Trijuganone A		*S. trijuga* Diels (roots) [282]
126	Trijuganone B		*S. castanea* Diels (whole plant) [276] *S. miltiorrhiza* Bunge (roots) [246]
127	Trijuganone C		*S. trijuga* Diels (roots) [193]
128	Tanshinone I		*S. aerea* H.Lév. (roots) [306] *S. bowleyana* Dunn (NS) [307] *S. brevilabra* Franch. (NS) [308] *S. bulleyana* Diels[197,307] *S. campanulata* Wall. ex Benth. (NS) [197,307] *S. castanea* Diels (roots) [197,276,306,307] *S. cavaleriei* var. *simplicifolia* E.Peter-Stibal (NS) [197,307] *S. coccinea* Buc'hoz ex Etl. (NS) [308] *S. cynica* Dunn (NS) [308] *S. dabieshanensis* J.Q.He (NS) [197,307] *S. digitaloides* Diels (roots) [309] *S. drobovii* Botsch. (roots) [193] *S. evansiana* Hand.-Mazz. (aerial parts, roots) [197,307]

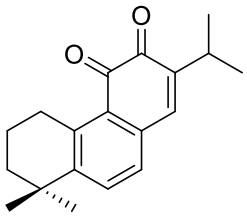
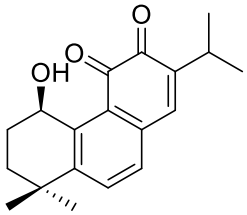
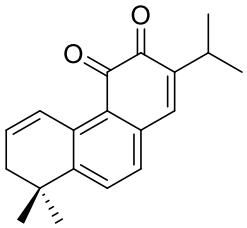
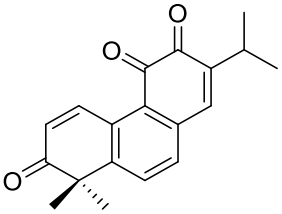
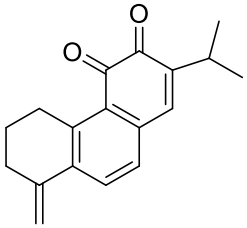
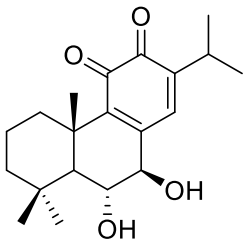
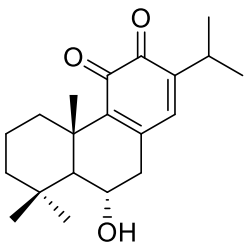
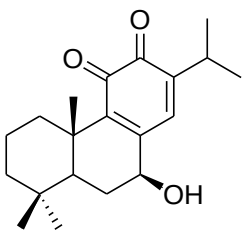
			S. flava Forrest ex Diels (aerial parts, roots) [197,307] *S. fruticosa* Mill. (roots) [193] *S. glutinosa* L. (roots) [211] *S. kiaometiensis* H.Lév. (roots) [312] *S. maximowicziana* Hemsl. (aerial parts, roots) [197,307] *S. meiliensis* S.W.Su (NS) [197,307] *S. miltiorrhiza* Bunge (roots) [274] *S. nanchuanensis* Y.Z.Sun (NS) [308] *S. paramiltiorrhiza* H.W.Li & X.L.Huang (aerial parts, roots) [197,307] *S. plectranthoides* Griff. (NS) [197] *S. pratii* Hemsl. (NS) [197] *S. przewalskii* Maxim. (roots) [193] *S. roborowskii* Maxim. (roots) [197] *S. schizochila* E.Peter-Stibal (NS) [308] *S. sinica* Migo (aerial parts, roots) [197] *S. stibalii* Alziar (aerial parts, roots) [197] *S. subpalmatinervis* E.Peter-Stibal (NS) [308] *S. tricuspis* Franch. (NS) [308] *S. trijuga* Diels (roots) [193] *S. umbratica* Hance (aerial parts, roots) [197] *S. vasta* H. W.Li (roots) [197,307] *S. wardii* E.Peter-Stibal (NS) [308] *S. yunnanensis* C.H.Wright (roots) [280,317]
129	Dihydrotanshinone I		*S. castanea* Diels (whole plant) [276] *S. digitaloides* Diels (roots) [309] *S. aerea* H.Lév. (roots) [306] *S. campanulata* Wall. ex Benth. (NS) [197,307] *S. castanea* Diels (aerial parts, roots) [197,307] *S. cavaleriei* var. *simplicifolia* E.Peter-Stibal (herbs) [197,307] *S. castanea* Diels (roots) [306] *S. dabieshanensis* J.Q.He (NS) [197,307] *S. evansiana* Hand.-Mazz. (aerial parts, roots) [197,307] *S. flava* Forrest ex Diels (aerial parts, roots) [197,307] *S. glutinosa* L. (roots) [211] *S. kiaometiensis* H.Lév. (roots) [312] *S. maximowicziana* Hemsl. [197,307] *S. meiliensis* S.W.Su (NS) [197,307] *S. nipponica* Miq. (roots) [274] *S. paramiltiorrhiza* H.W.Li & X.L.Huang (aerial parts, roots) [197,318] *S. stibalii* Alziar (aerial parts, roots) [197] *S. plectranthoides* Griff. (NS) [197] *S. przewalskii* Maxim. (roots) [279] *S. roborowskii* Maxim. (roots) [197] *S. sinica* Migo (aerial parts, roots) [197] *S. trijuga* Diels (roots) [246] *S. umbratica* Hance (aerial parts, roots) [197] *S. vasta* H.W.Li (NS) [197,307] *S. yunnanensis* C.H.Wright (roots) [269] *S. omeiana* E.Peter-Stibal (NS) [197] *S. pratii* Hemsl. (aerial parts, roots) [197]

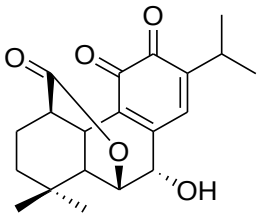
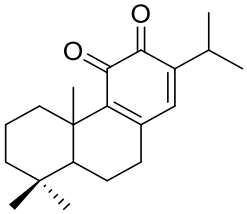
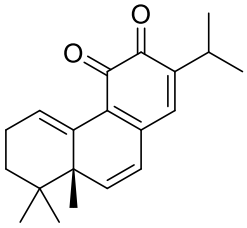
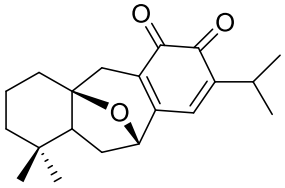
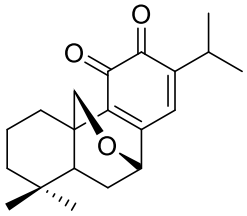
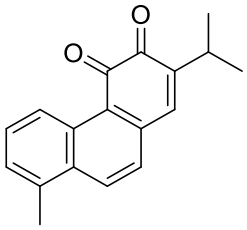
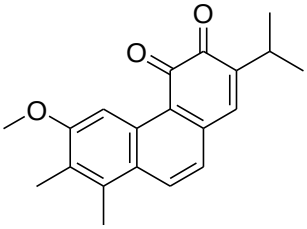
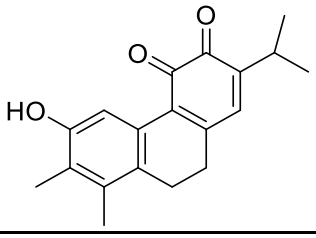
130	Formyltanshinone		*S. miltiorrhiza* Bunge (roots) [268]
131	Przewaquinone B		*S. castanea* Diels (roots) [306] *S. miltiorrhiza* Bunge (roots) [318] *S. przewalskii* Maxim. (roots) [246]
132	Salvipisone		*S. aethiopis* L. (roots) [187] *S. argentea* L. (roots) [205] *S. candidissima* Vahl subsp. *candidissima.* (roots) [228] *S. candidissima* subsp. *occidentalis* Hedge (roots) [238] *S. ceratophylla* L. (roots) [327] *S. cyanescens* Boiss. & Balansa (aerial parts) [328] *S. eriophora* Boiss. & Kotschy (roots) [214] *S. kronenburgii* Rech. f. (NS) [198] *S. nemorosa* L. (aerial parts) [241] *S. sclarea* L. (hairy roots; roots) [228,329] *S. verticillata* L. (roots) [330]
133	12-Deoxysalvipisone		*S. rythidea* Benth. (roots) [331]
134	Acetylsalvipisone		*S. sclarea* L. (roots) [228]
135	1-Oxosalvipisone		*S. candidissima* Vahl (aerial parts) [332] *S. candidissima* subsp. *occidentalis* Hedge (roots) [262]
136	3-Oxosalvipisone (3-ketosapriparaquinone)		*S. candidissima* Vahl subsp. *occidentalis* Hedge (aerial parts) [332] *S. prionitis* Hance (NS; roots) [209,333]

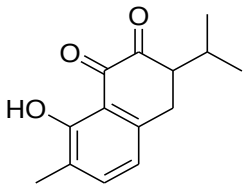
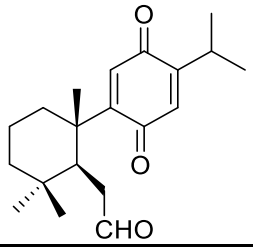
137	2,3-Dehydrosalvipisone		*S. argentea* L. (roots) [306] *S. candidissima* Vahl subsp. *candidissima.* (roots) [228] *S. sclarea* L. (roots) [241] *S. verticillata* L. (roots) [330]
138	4-Dehydro,4-hydroxysalvipisone		*S. eriophora* Boiss. & Kotschy (roots) [214] *S. prionitis* Hance (NS) [204,209]
139	Limbinal		*S. limbata* C.A.Mey. (aerial parts) [259] *S. mellifera* Greene (aerial parts) [228]
140	Prineoparaquinone		*S. prionitis* Hance (roots) [288]
141	Prionoid D		*S. prionitis* Hance (roots) [334]
142	Prionoid E		*S. prionitis* Hance (roots) [334]
143	Prionoid F		*S. prionitis* Hance (roots) [334]

144	12-Isopentenyl-3-oxosalvipisone		*S. cyanescens* Boiss. & Balansa (aerial parts) [328]
145	4-Dihydrosalvipisone		*S. eriophora* Boiss. & Kotschy (roots) [214] *S. kronenburgii* Rech. f. (roots) [198] *S. limbata* C.A.Mey. (roots) [290] *S. prionitis* Hance (NS) [193] *S. rythidea* Benth. (roots) [273]
146	Sahandinone		*S. lachnocalyx* Hedge (roots) [286] *S. sahendica* Boiss. & Buhse (roots) [258] *S. rythidea* Benth. (roots) [331]
147	Aethiopinone		*S. aethiopis* L. (ns) [325] *S. argentea* L. (roots) [205] *S. candidissima* subsp. *occidentalis* Hedge (roots) [262] *S. ceratophylla* L. (roots) [327] *S. cyanescens* Boiss. & Balansa (aerial parts) [328] *S. eriophora* Boiss. & Kotschy (roots) [214] *S. hypargeia* Fisch. & C.A.Mey. (roots) [335] *S. palaestina* Benth. (aerial parts) [336] *S. sclarea* L. (hairy roots; roots) [228,329] *S. viridis* L. (roots) [337]
148	1-oxoaethiopinone		*S. argentea* L. (roots) [205] *S. sclarea* L. (hary roots) [338]
149	Salvisyrianone		*S. syriaca* L. (roots) [337]
150	2-Hydroxysaprorthoquinone		*S. limbata* C.A.Mey. (roots) [339]

151	Saprorthoquinone		*S. hypargeia* Fisch. & C.A.Mey. (roots) [335] *S. prionitis* Hance (roots) [340]
152	Sclareapinone		*S. prionitis* Hance (roots) [341] *S. sclarea* L. (roots) [228]
153	3,4-Dihydro-4-Hydroxysaprorthoquinone		*S. prionitis* Hance (roots) [341]
154	Candesalvoquinone		*S. candelabrum* Boiss. (aerial parts) [230]
155	Tanshinone V		*S. miltiorrhiza* Bunge (roots) [342]
156	Tanshinone VI		*S. miltiorrhiza* Bunge (roots) [193]
157	Grandifolia D		*S. grandifolia* W.W.Sm. (roots) [343]

158	Miltirone		*S. argentea* L. (roots) [205] *S. drobovii* Botsch. (roots) [193] *S. kiaometiensis* H.Lév. (roots) [312] *S. miltiorrhiza* Bunge (roots) [344] *S. officinalis* L. (roots) [236] *S. prionitis* Hance (roots) [209] *S. rythidea* Benth. (roots) [331]
159	1(R)-Hydroxymiltirone		*S. argentea* L. (roots) [205]
160	1,2-Didehydromiltirone		*S. castanea* Diels (whole plant) [276] *S. miltiorrhiza* Bunge (roots) [268,326] *S. przewalskii* Maxim. (roots) [246] *S. trijuga* Diels (roots) [294] *S. yunnanensis* C.H.Wright (whole plant) [317]
161	Saligerone		*S. lanigera* Poir. (roots) [193]
162	4-Methylenemiltirone		*S. miltiorrhiza* Bunge (roots) [268,326]
163	Salviphlomone		*S. phlomoides* Asso (roots) [207]
164	7-Deoxysalviphlomone		*S. recognita* Fisch. & C.A.Mey. (roots) [261]
165	6-Deoxysalviphlomone		*S. nutans* L. (roots) [203]

166	Rosmaquinone		*S. canariensis* L. (flowers) [235]
167	6,7-Dideoxisalviphlomone		*S. candidissima* Vahl subsp. *candidissima.* (roots) [228] *S. hypargeia* Fisch. & C.A.Mey. (roots) [335] *S. miltiorrhiza* Bunge (roots) [268] *S. napifolia* Jacq. (roots) [229]
168	Viridoquinone		*S. viridis* L. 'Blue Denim' (whole plant) [265]
169	Przewalskin E		*S. przewalskii* Maxim. (whole plant) [345]
170	Przewalskin G		*S. przewalskii* Maxim. (whole plant) [345]
171	R0-09-0680 [18,20-Dinorabieta-1,3,5(10),6,8,1 3-hexaene-11, 12-dione)]		*S. glutinosa* L. (roots) [211] *S. kronenburgii* Rech. f. (roots) [198]
172	Multiorthoquinone		*S. blepharochlaena* Hedge & Hub.-Mor. (roots) [249] *S. multicaulis* Vahl (roots) [228]
173	2-Demethylmultiorthoquinone		*S. blepharochlaena* Hedge & Hub.-Mor. (roots) [249] *S. multicaulis* Vahl (roots) [228]

174	Lanigerone		*S. lanigera* Poir. (roots) [277]
175	7,8-seco-para-ferrugginone		*S. prionitis* Hance (roots) [341]

SUPPORTING INFORMATION

Salvia tingitana Etl.

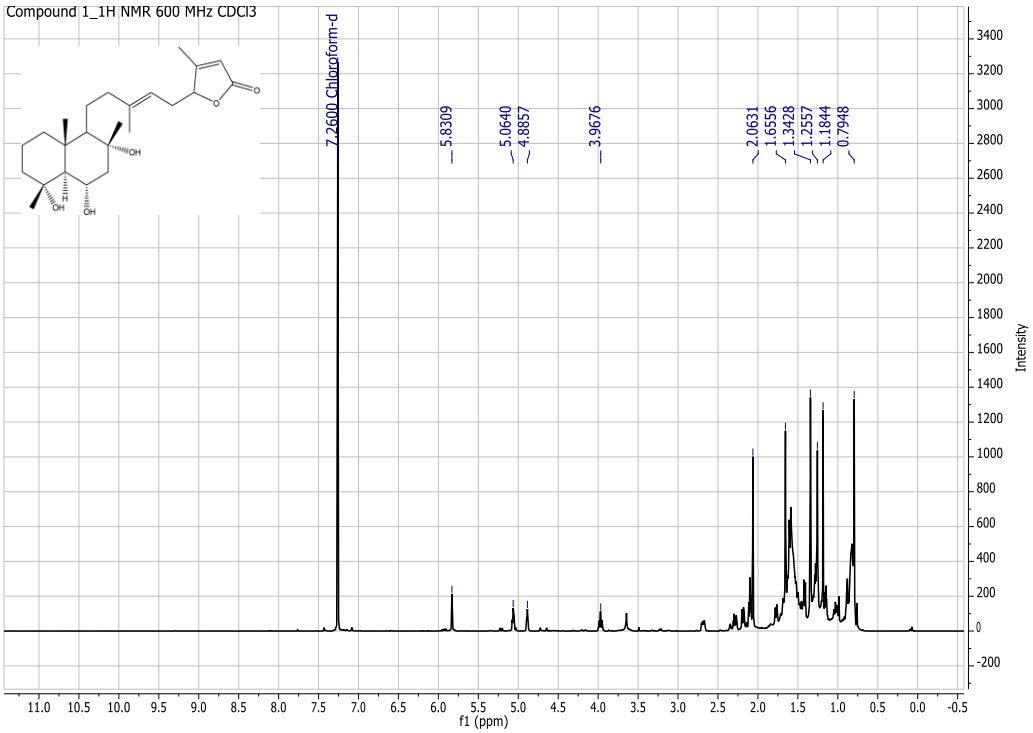


Figure S1: ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of compound **1**

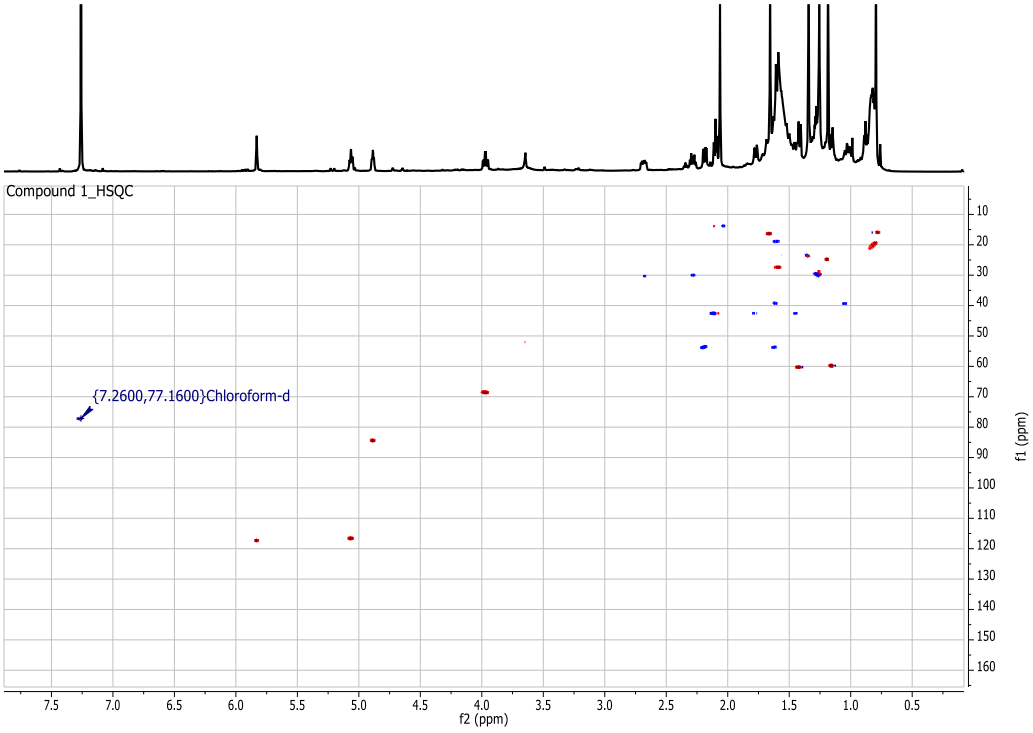


Figure S2. HSQC (600 MHz, $CDCl_3$) spectrum of compound **1**

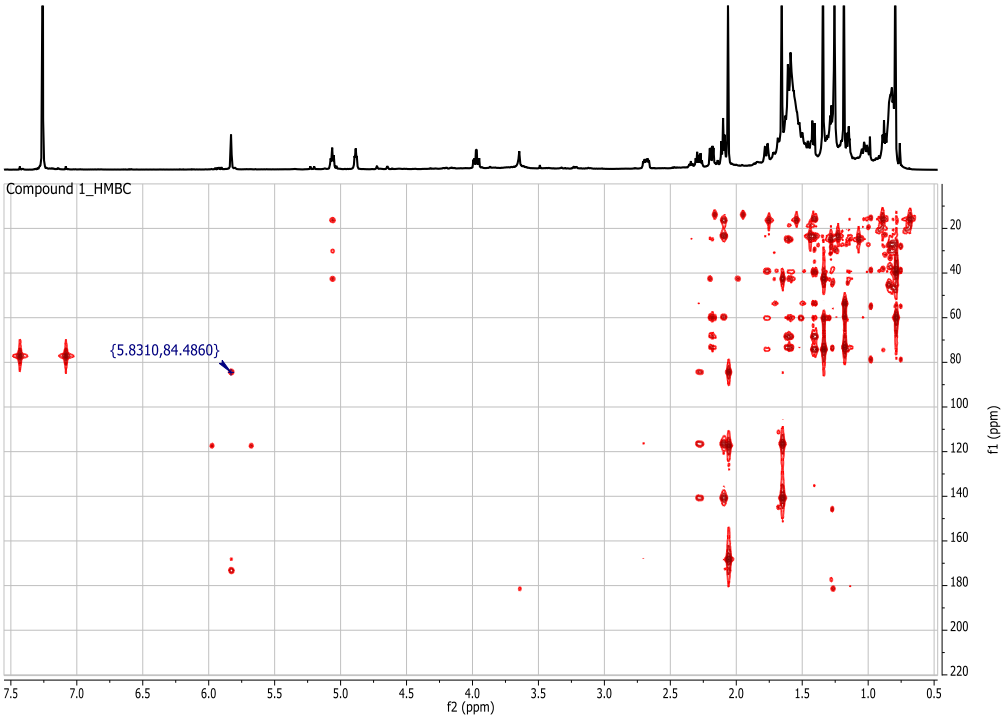


Figure S3. HMBC (600 MHz, $CDCl_3$) spectrum of compound **1**

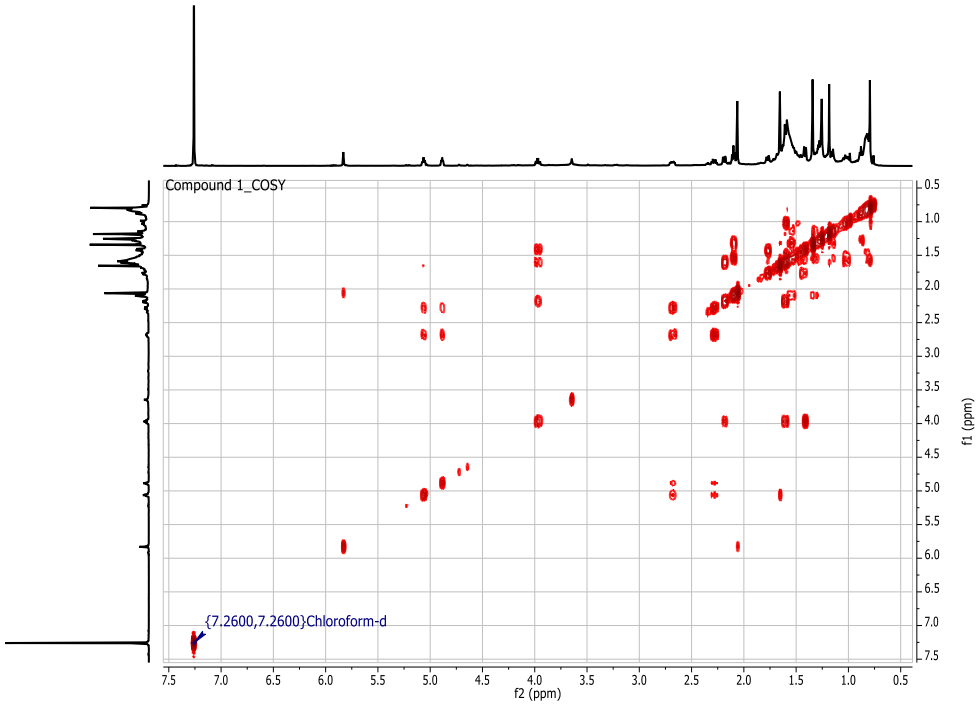


Figure S4. COSY (600 MHz, $CDCl_3$) spectrum of compound **1**

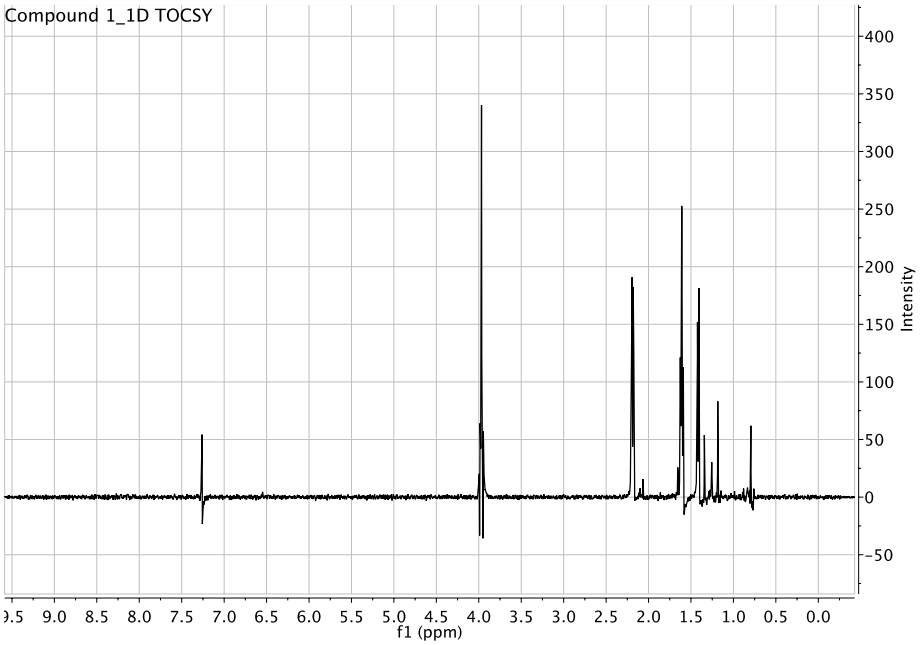


Figure S5. 1D TOCSY (600 MHz, $CDCl_3$) spectrum of compound **1**

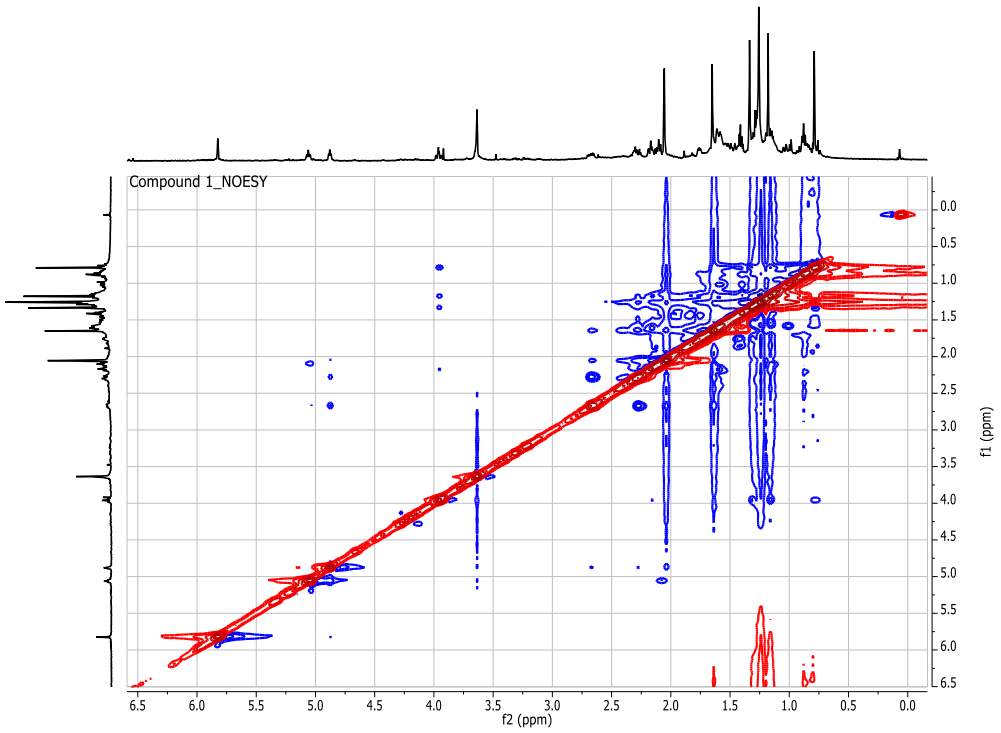


Figure S6. NOESY (600 MHz, $CDCl_3$) spectrum of compound **1**

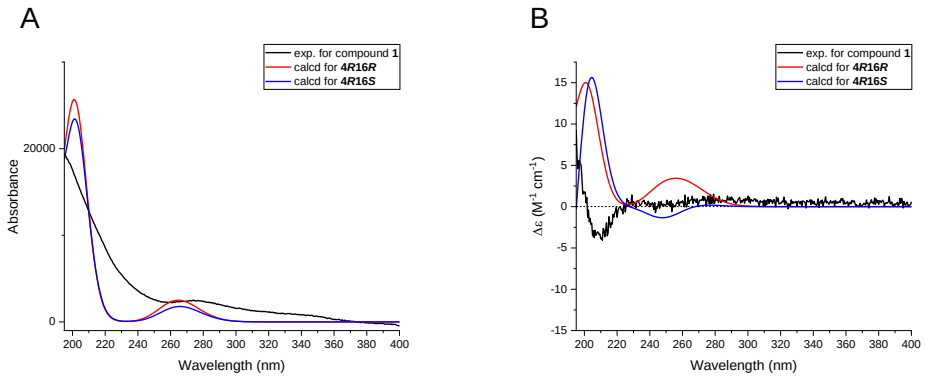


Figure S7. Comparison of experimental and computed UV (A) and ECD (B) (CH_3OH) spectra for compound **1,** where 4R stands for *4R5S6S8R9R10R*

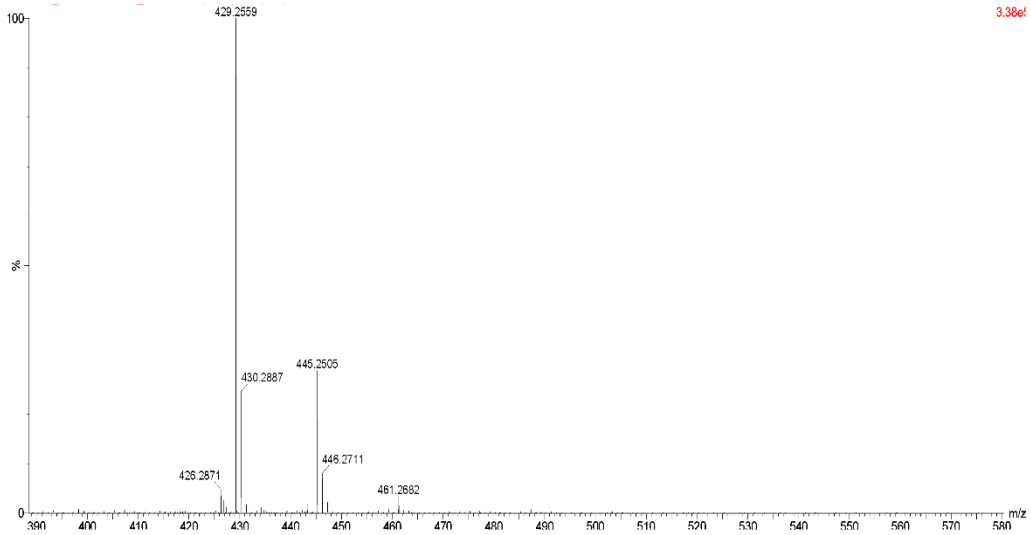


Figure S8. HRESIMS spectrum of compound **1**

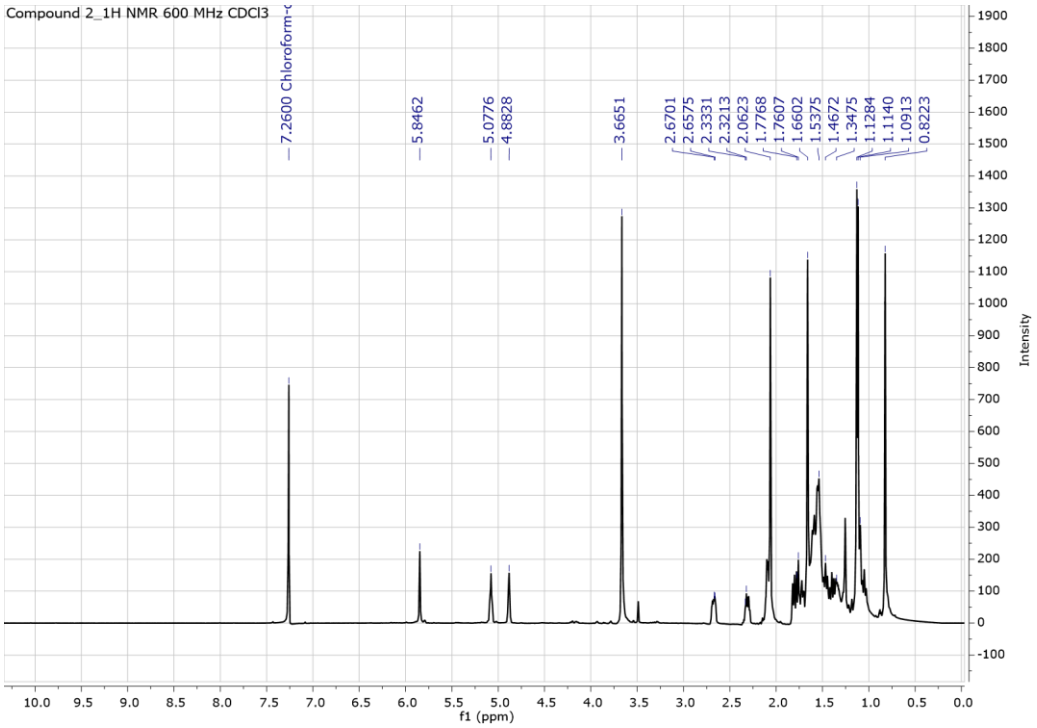


Figure S9. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of compound **2**

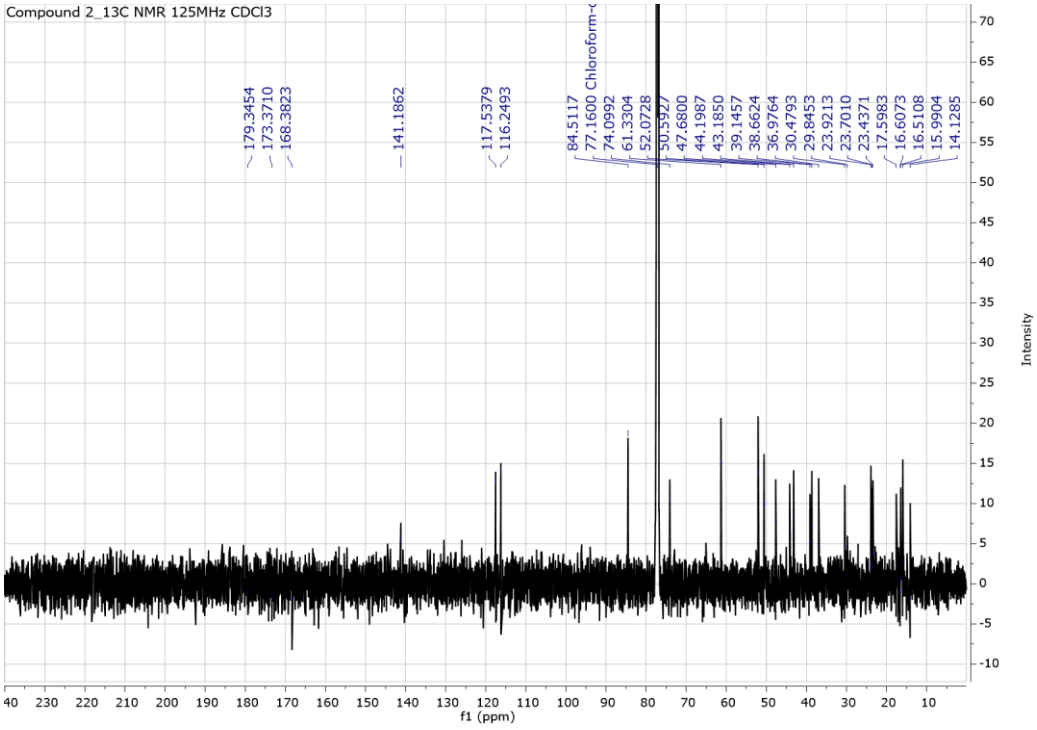


Figure S10. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **2**

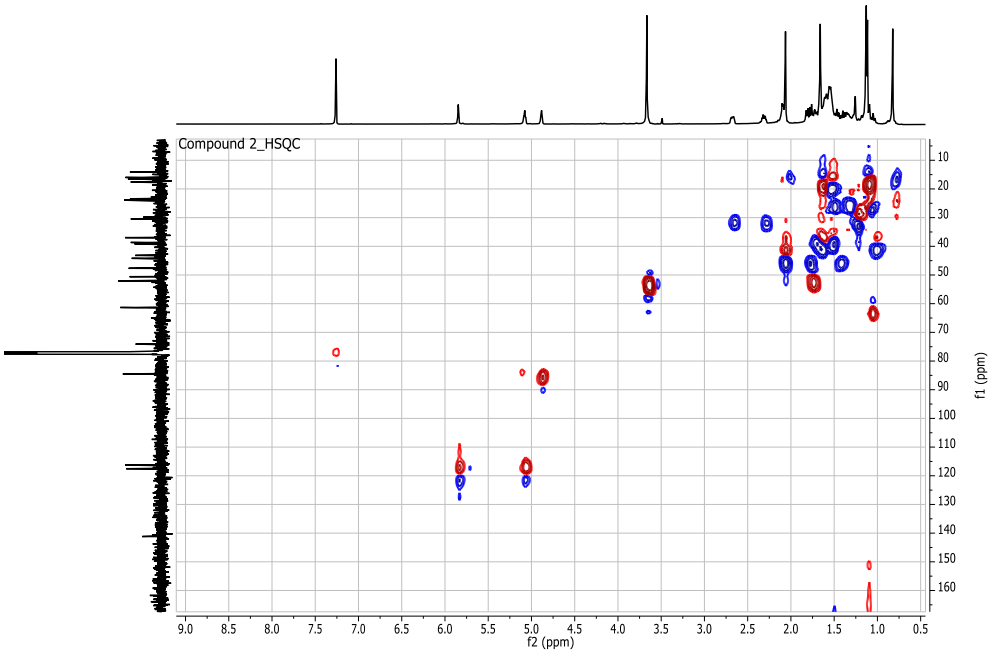


Figure S11. HSQC (600 MHz, $CDCl_3$) spectrum of compound **2**

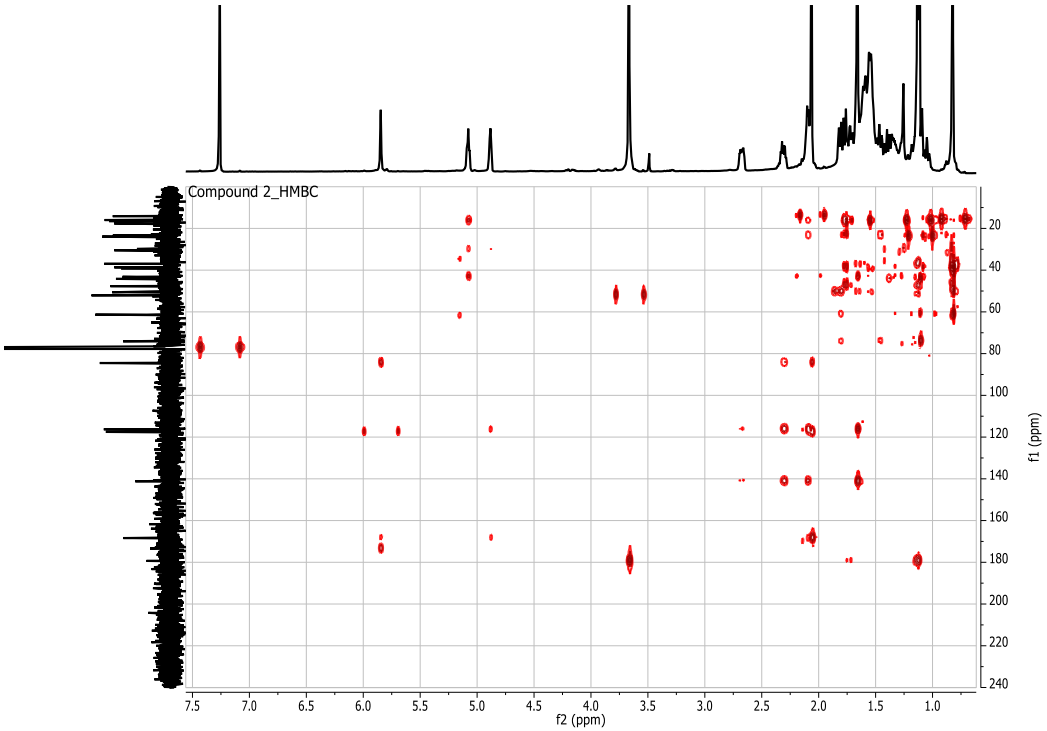


Figure S12. HMBC (600 MHz, $CDCl_3$) spectrum of compound **2**

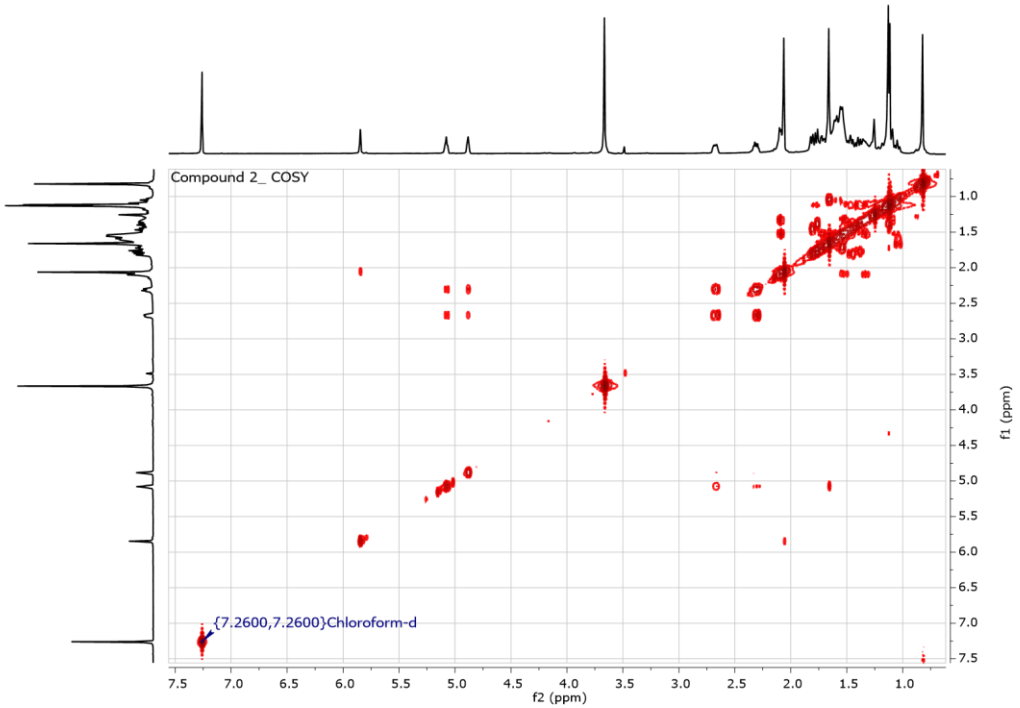


Figure S13. COSY (600 MHz, $CDCl_3$) spectrum of compound **2**

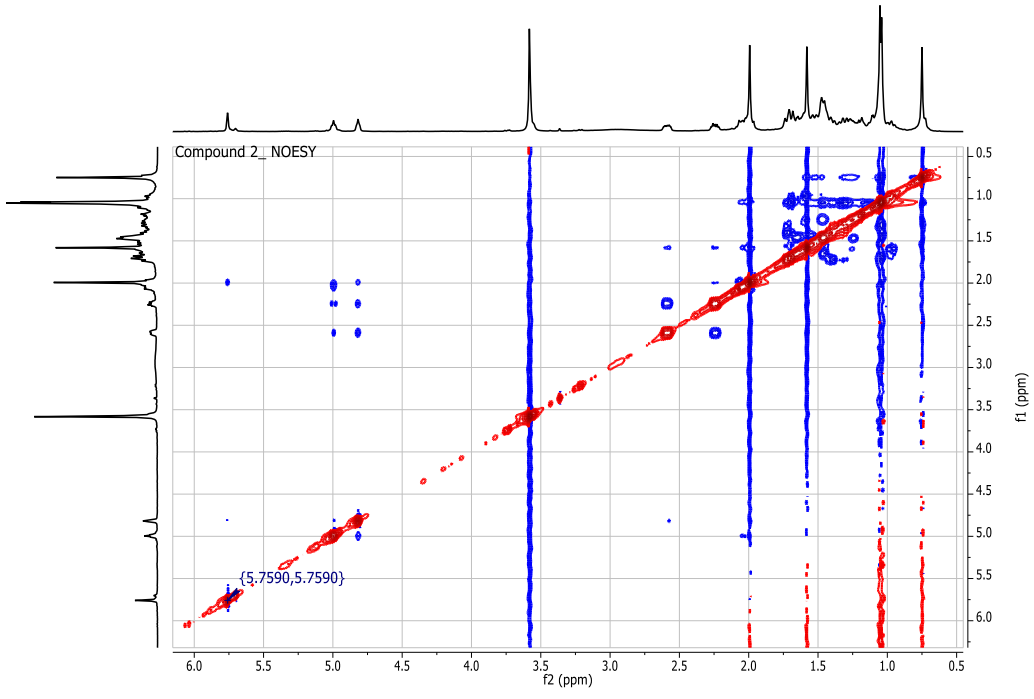


Figure S14. NOESY (600 MHz, $CDCl_3$) spectrum of compound **2**

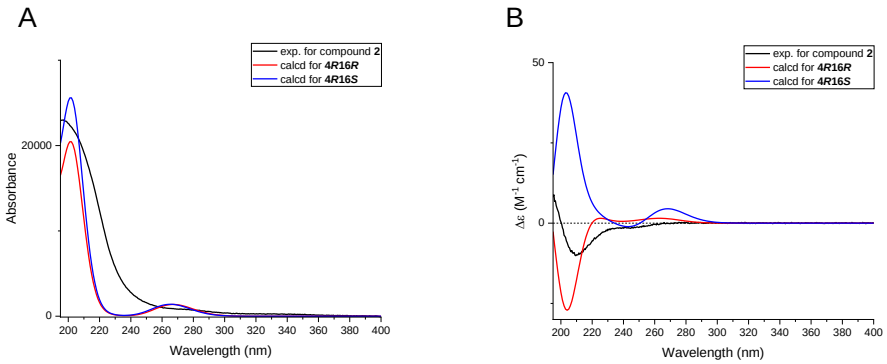


Figure S15. Comparison of experimental and computed UV (A) and ECD (B) (CH_3OH) spectra for compound **2,** where 4R stands for *4R5R8R9R10S*

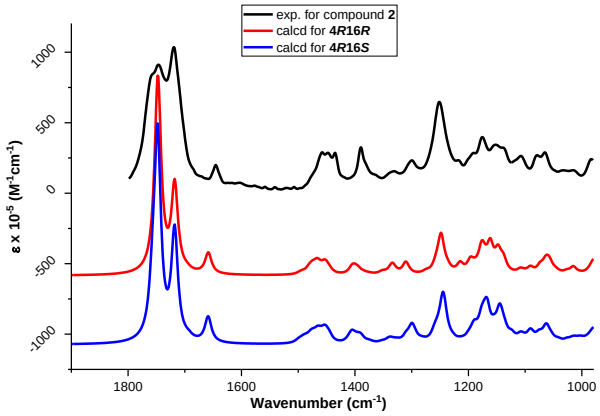


Figure S16. Comparison of experimental and computed IR ($CDCl_3$) spectra for compound **2**, where 4R stands for *4R5R8R9R10S*. The wavenumber scale factor 0.9835 was used to scale the computed spectra

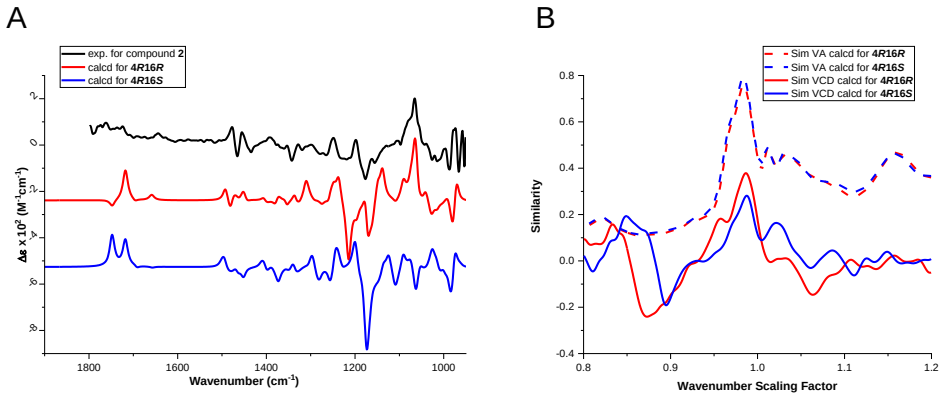


Figure S17. Comparison of experimental and computed VCD in $CDCl_3$ spectra for compound **2** (A). Similarities (SimVA and SimVCD) between experimental and computed VA and VCD spectra of **2** were plotted as functions of wavenumber scale factor (B). 4R stands for *4R5R8R9R10S*. The wavenumber scale factor corresponding to the maximal SimVA value in B (0.9835) was used to scale the computed spectra in A.

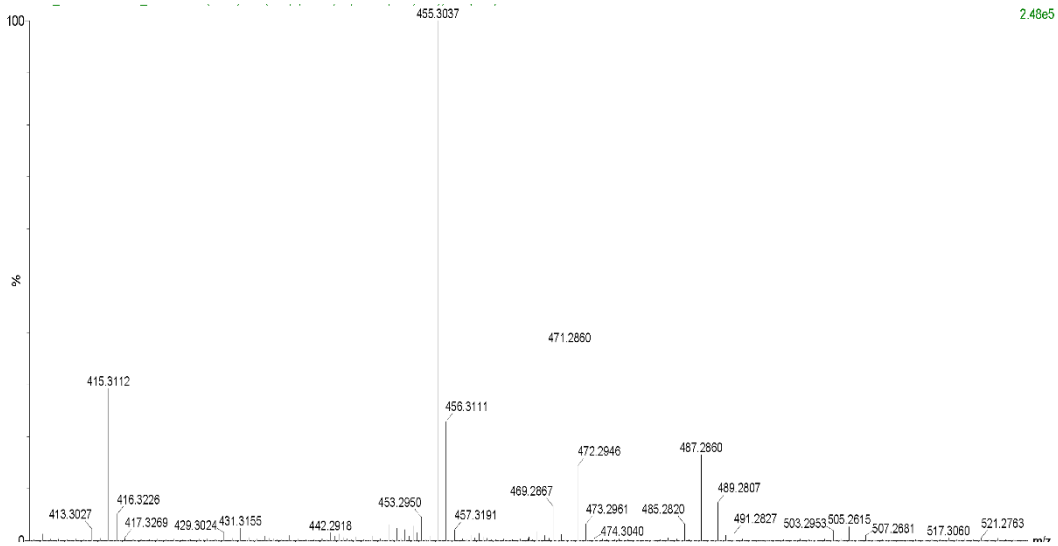


Figure S18. HRESIMS spectrum of compound **2**

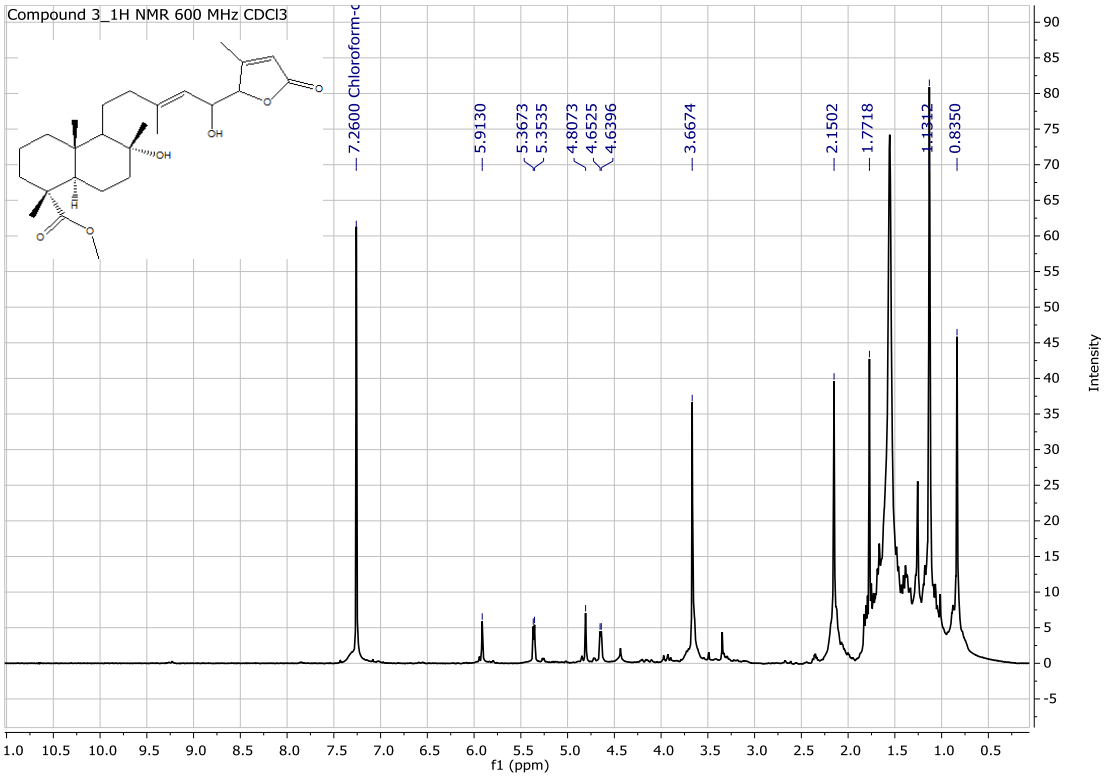


Figure S19. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of compound **3**

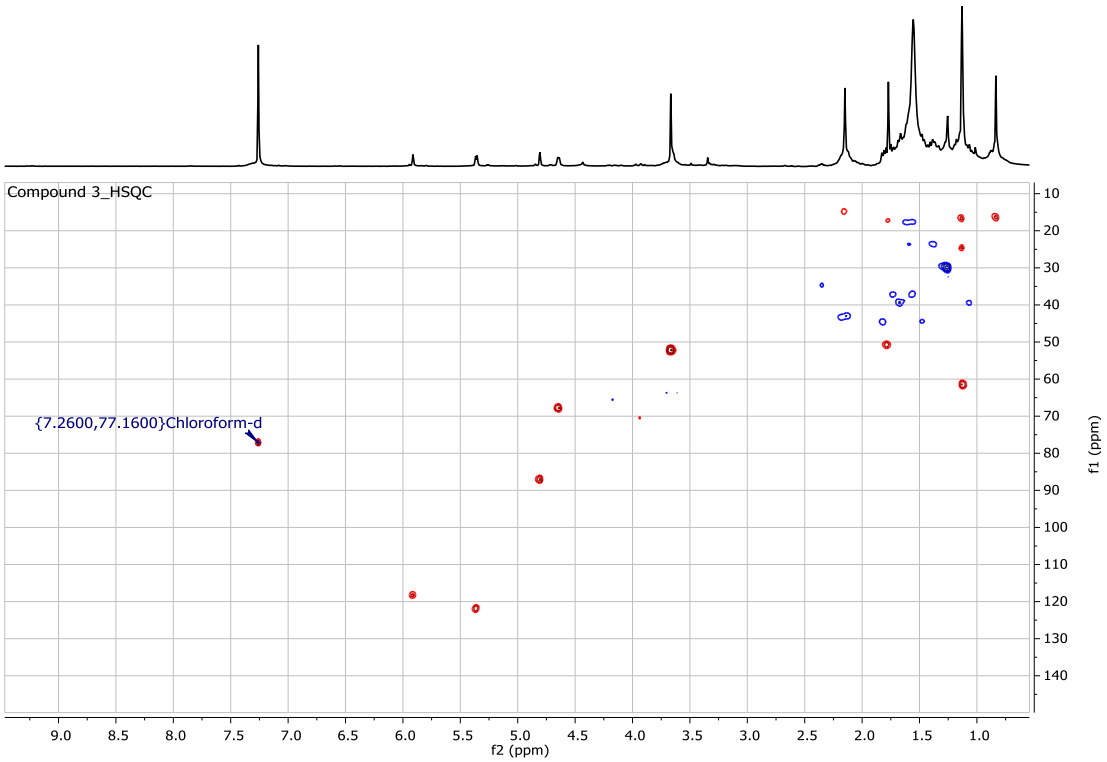


Figure S20. HSQC (600 MHz, $CDCl_3$) spectrum of compound **3**

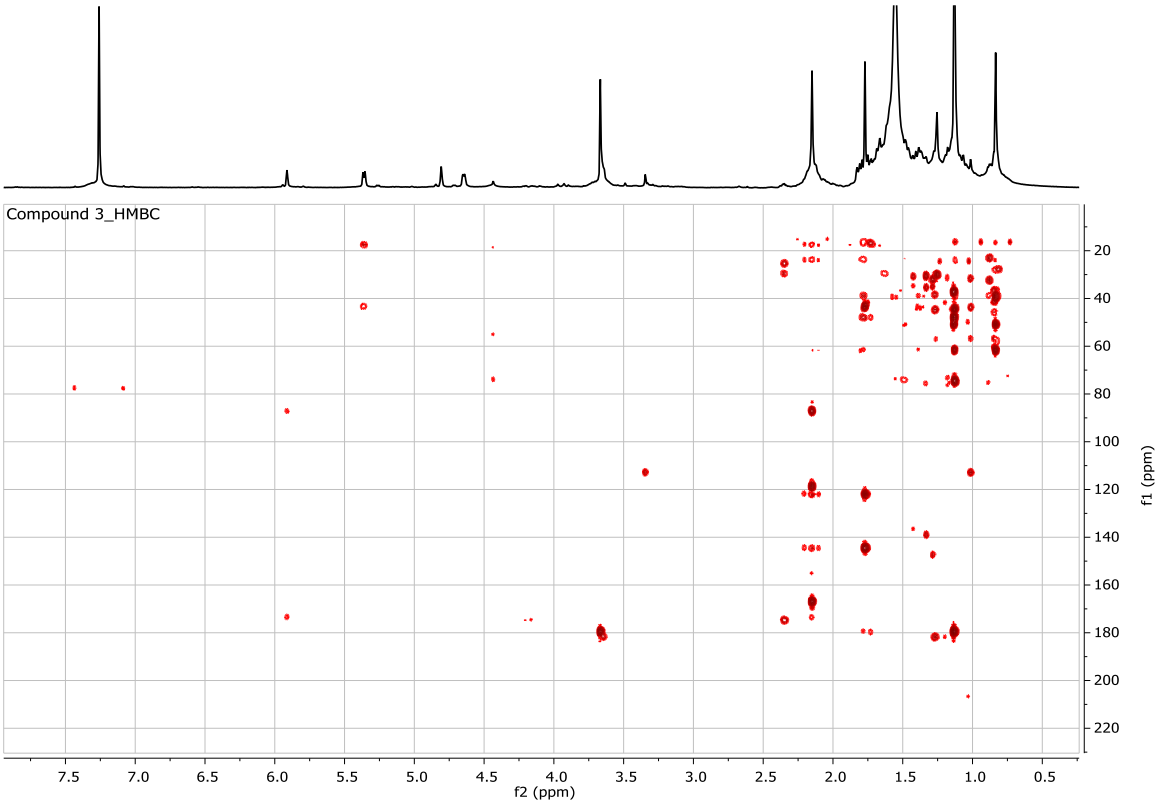


Figure S21. HMBC (600 MHz, $CDCl_3$) spectrum of compound **3**

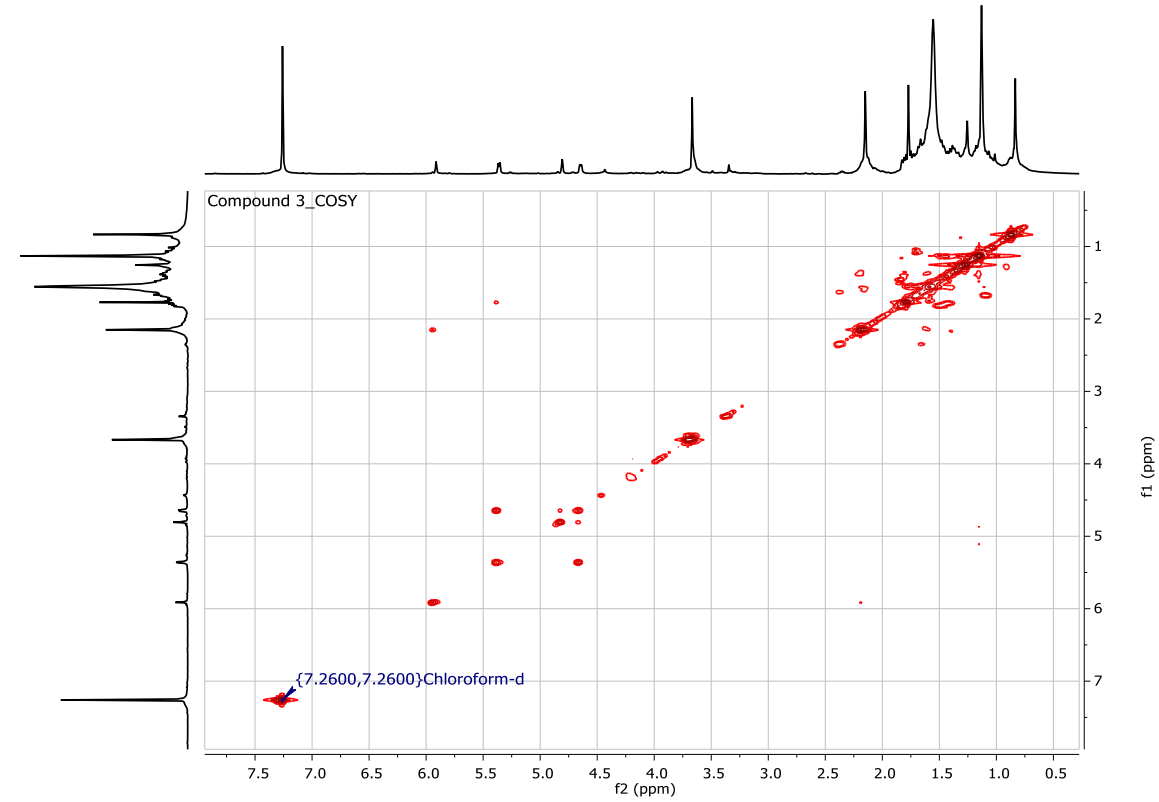


Figure S22. COSY (600 MHz, $CDCl_3$) spectrum of compound **3**

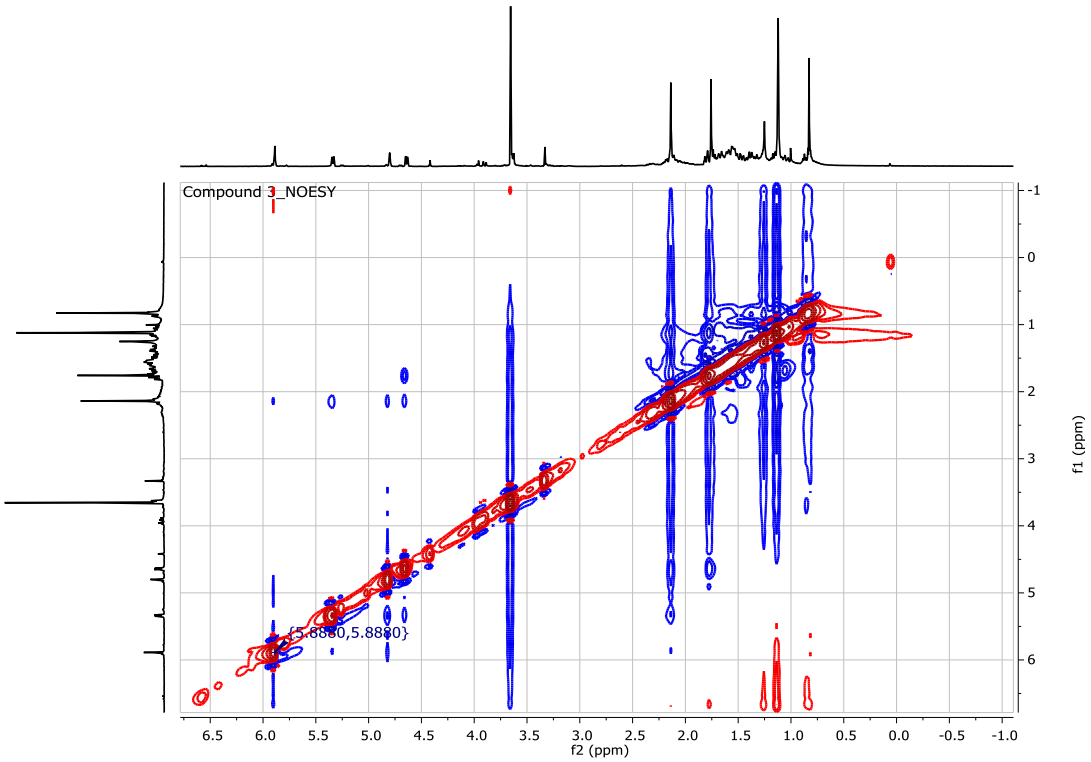


Figure S23. NOESY (500 MHz, $CDCl_3$) spectrum of compound **3**

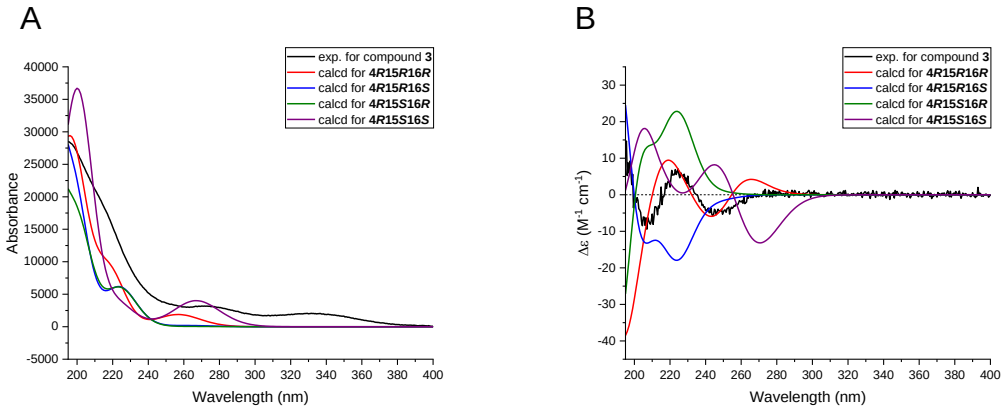


Figure S24. Comparison of experimental and computed UV (A) and ECD (B) (CH_3OH) spectra for compound **3,** where 4R stands for *4R5R8R9R10S*

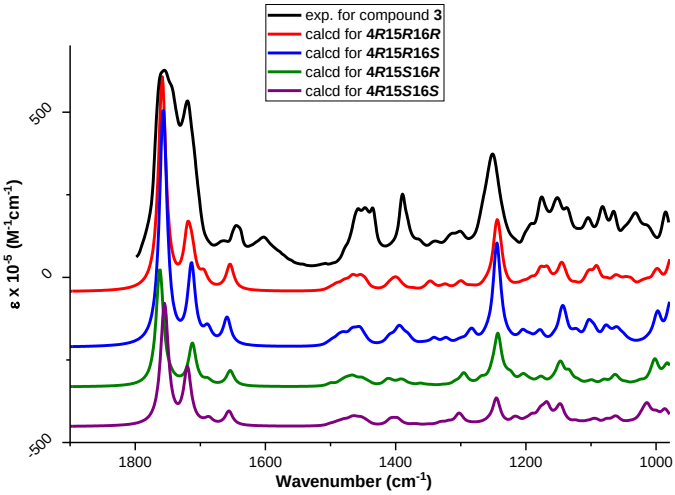


Figure S25. Comparison of experimental and computed IR ($CDCl_3$) spectra for compound **3**, where 4R stands for 4R5R8R9R10S. The wavenumber scale factor 0.9845 was used to scale the computed spectra

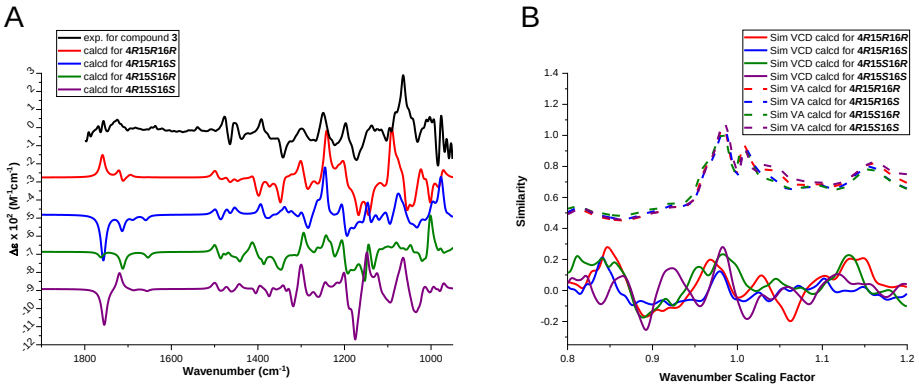


Figure S26. Comparison of experimental and computed VCD in $CDCl_3$ spectra for compound 3 (A). Similarities (SimVA and SimVCD) between experimental and computed VA and VCD spectra of **3** were plotted as functions of wavenumber scale factor (B). 4R stands for *4R5R8R9R10S*. The wavenumber scale factor corresponding to the maximal SimVA value in B (0.9845) was used to scale the computed spectra in A

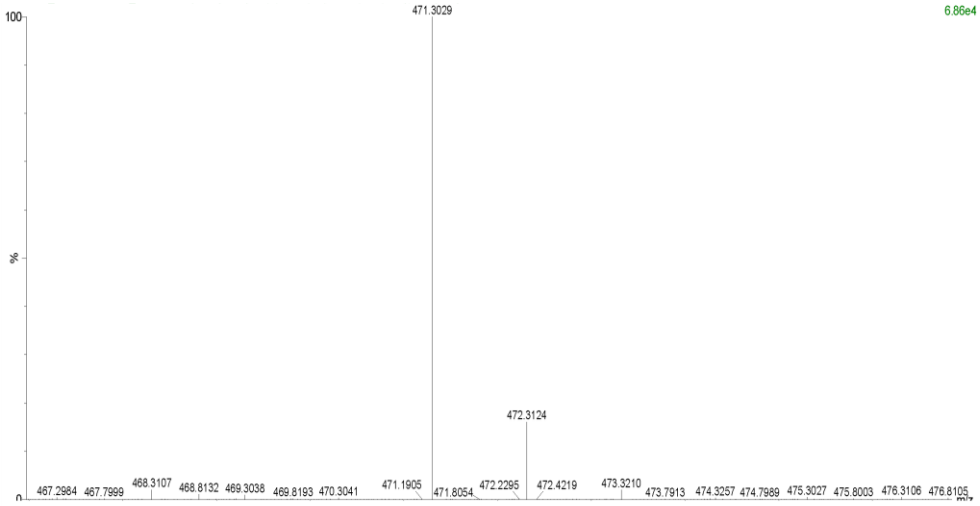


Figure S27. HRESIMS spectrum of compound **3**

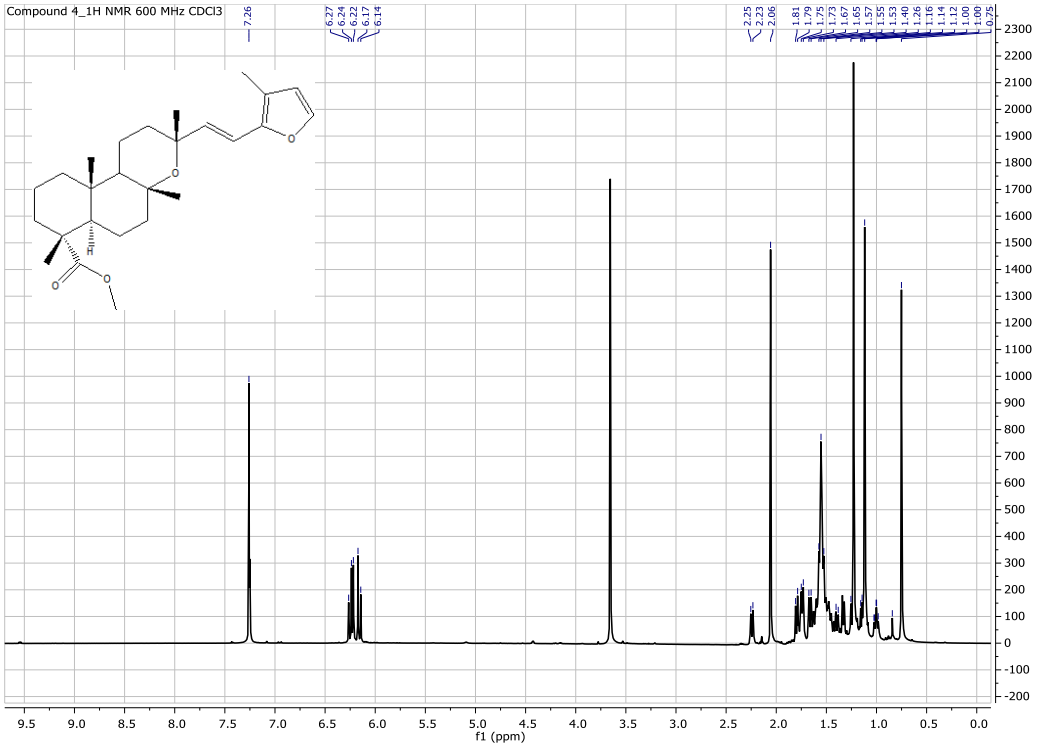


Figure S28. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of compound **4**

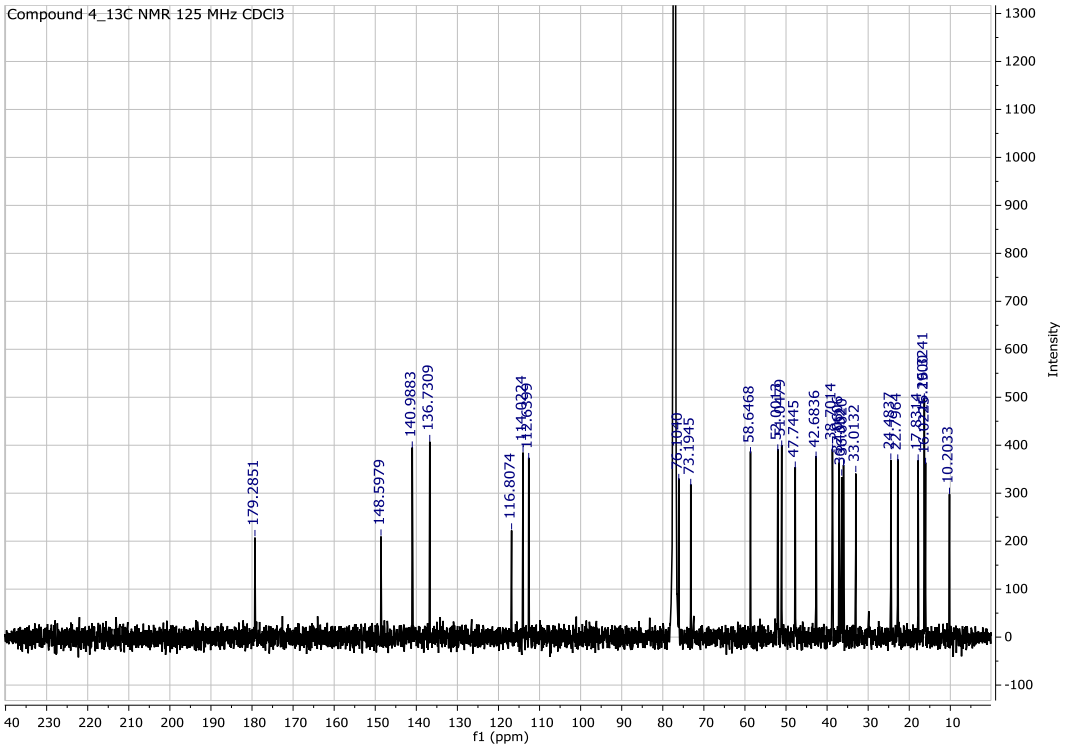


Figure S29. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **4**

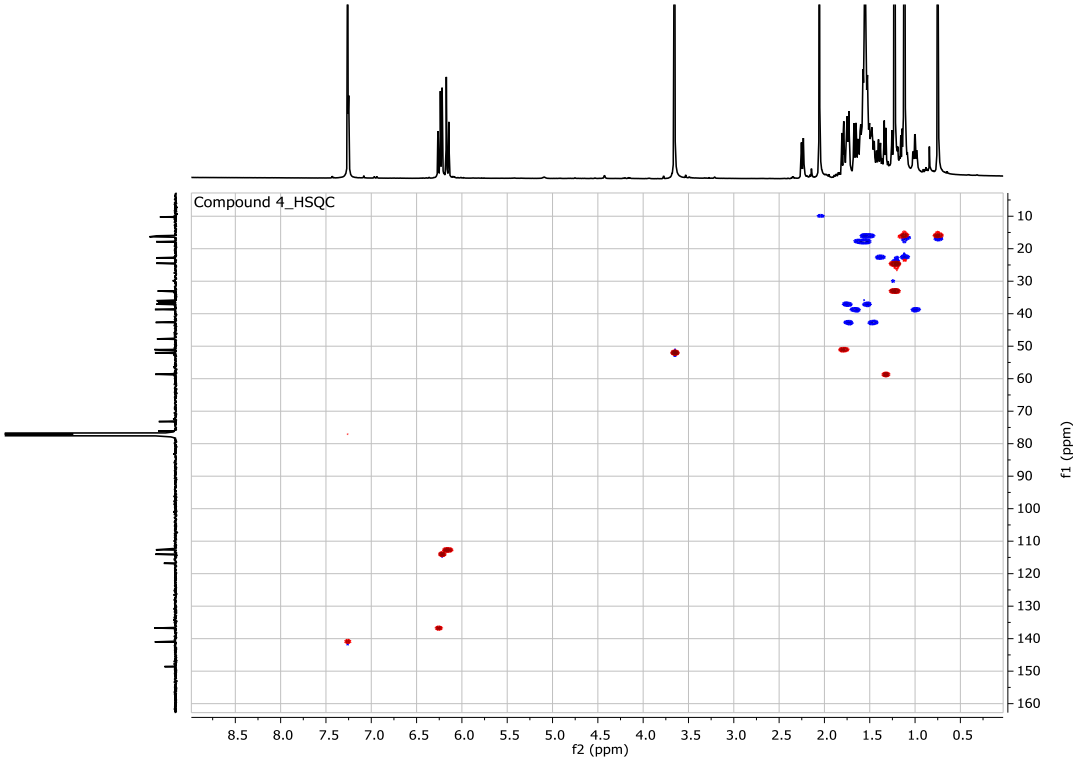


Figure S30. HSQC (600 MHz, $CDCl_3$) spectrum of compound **4**

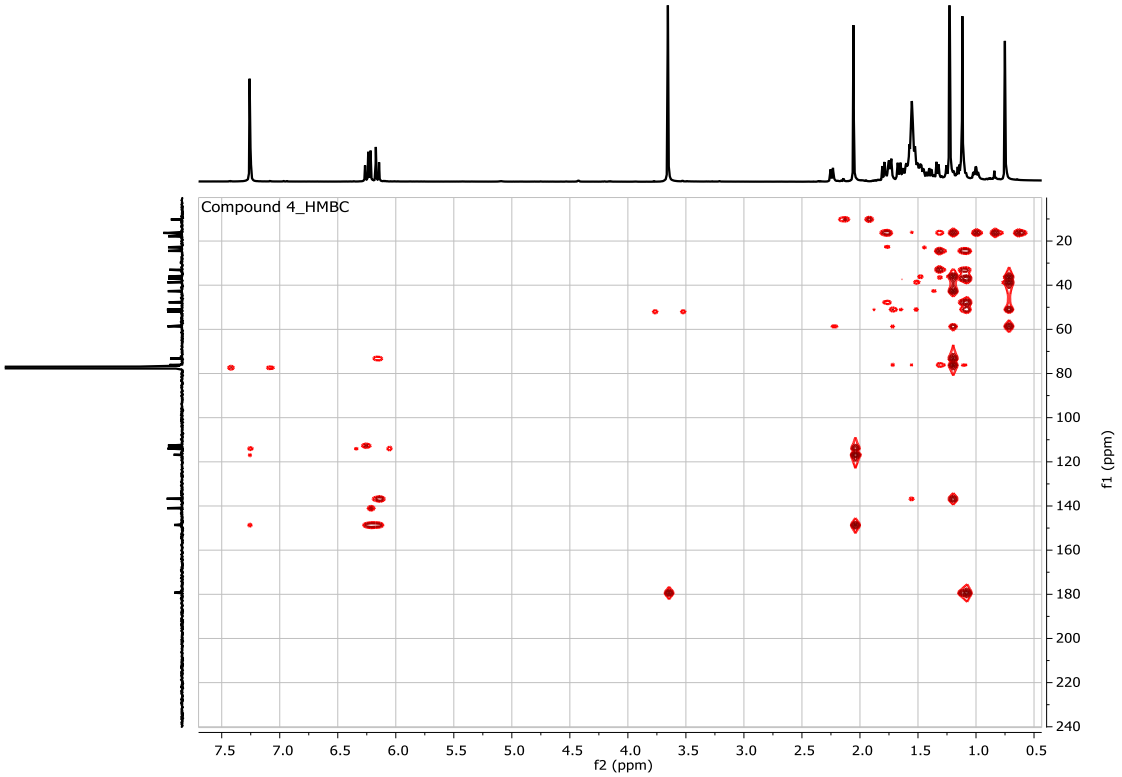


Figure S31. HMBC (600 MHz, $CDCl_3$) spectrum of compound **4**

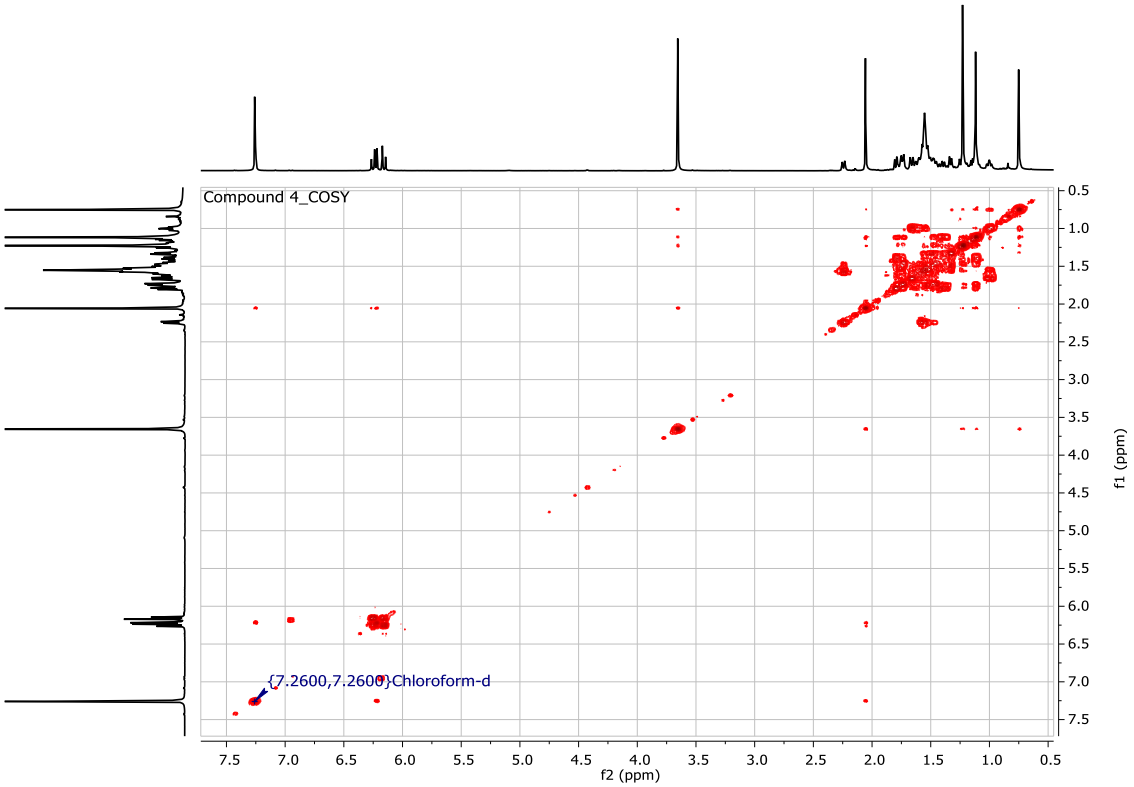


Figure S32. COSY (600 MHz, $CDCl_3$) spectrum of compound **4**

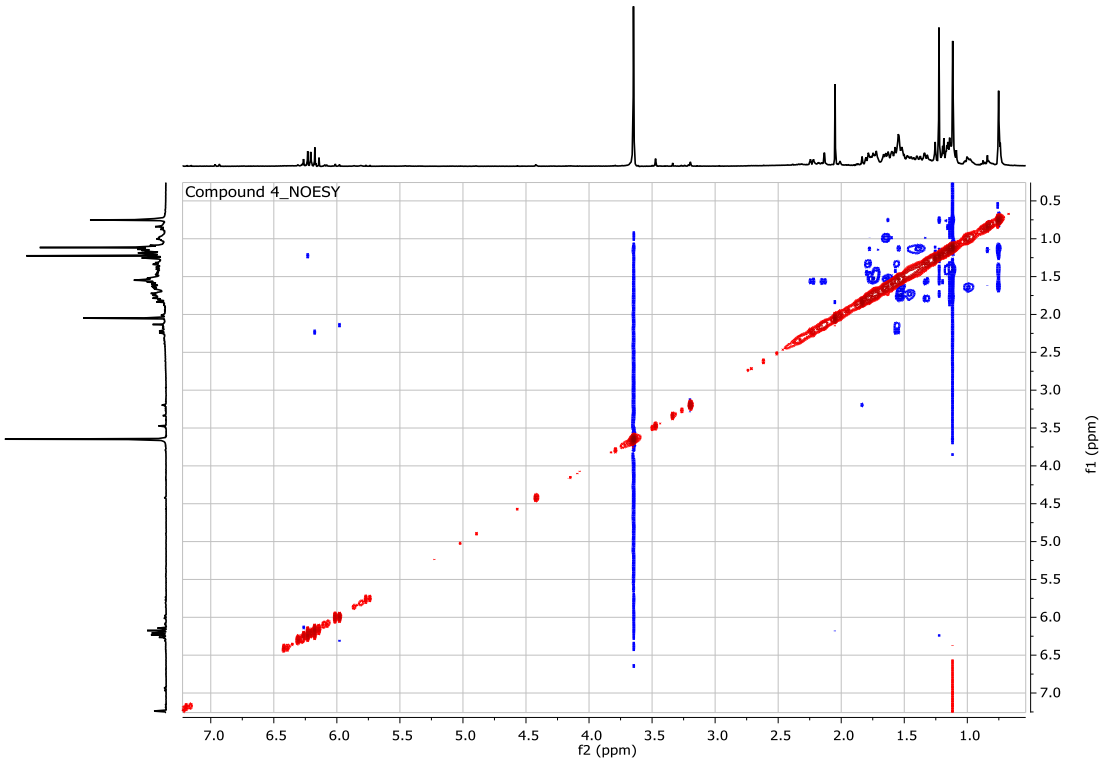


Figure S33. NOESY (500 MHz, $CDCl_3$) spectrum of compound **4**

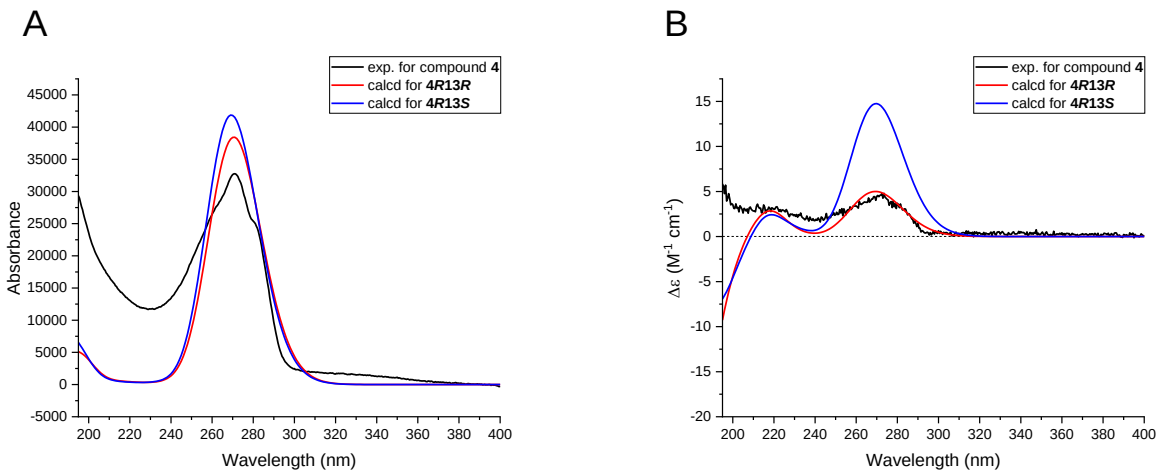


Figure S34. Comparison of experimental and computed UV (A) and ECD (B) (CH_3OH) spectra for compound **4,** where 4R stands for *4R5R8R9R10S*

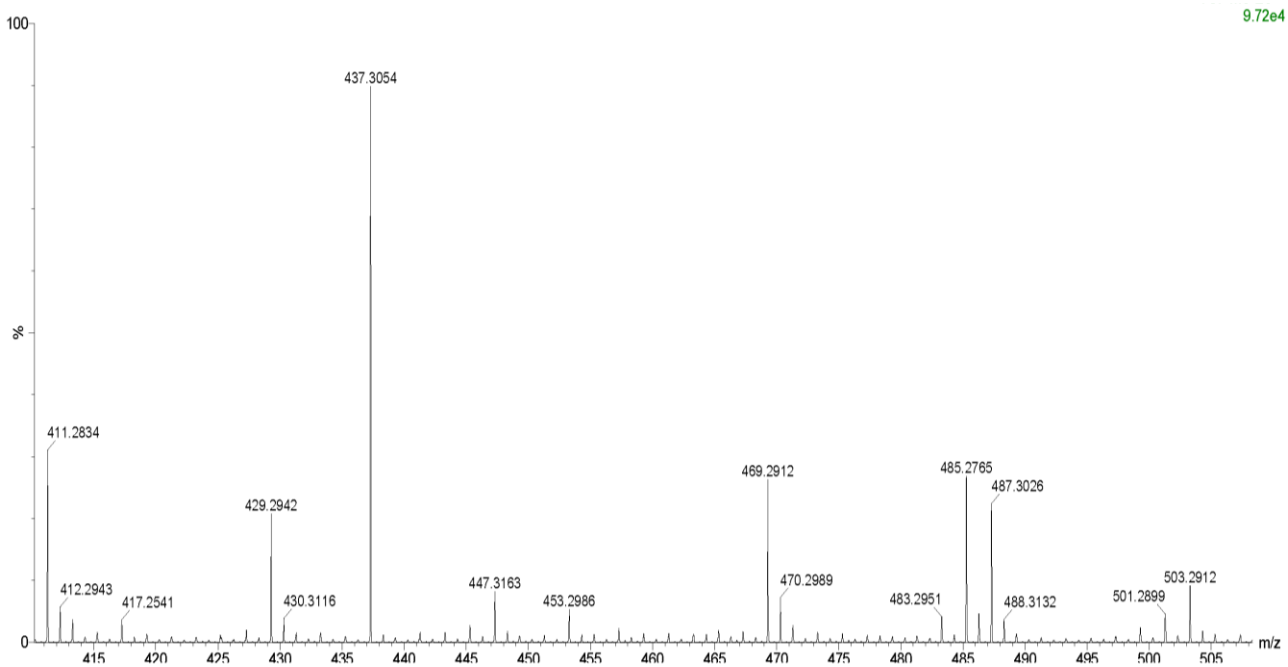


Figure S35. HRESIMS spectrum of compound **4**

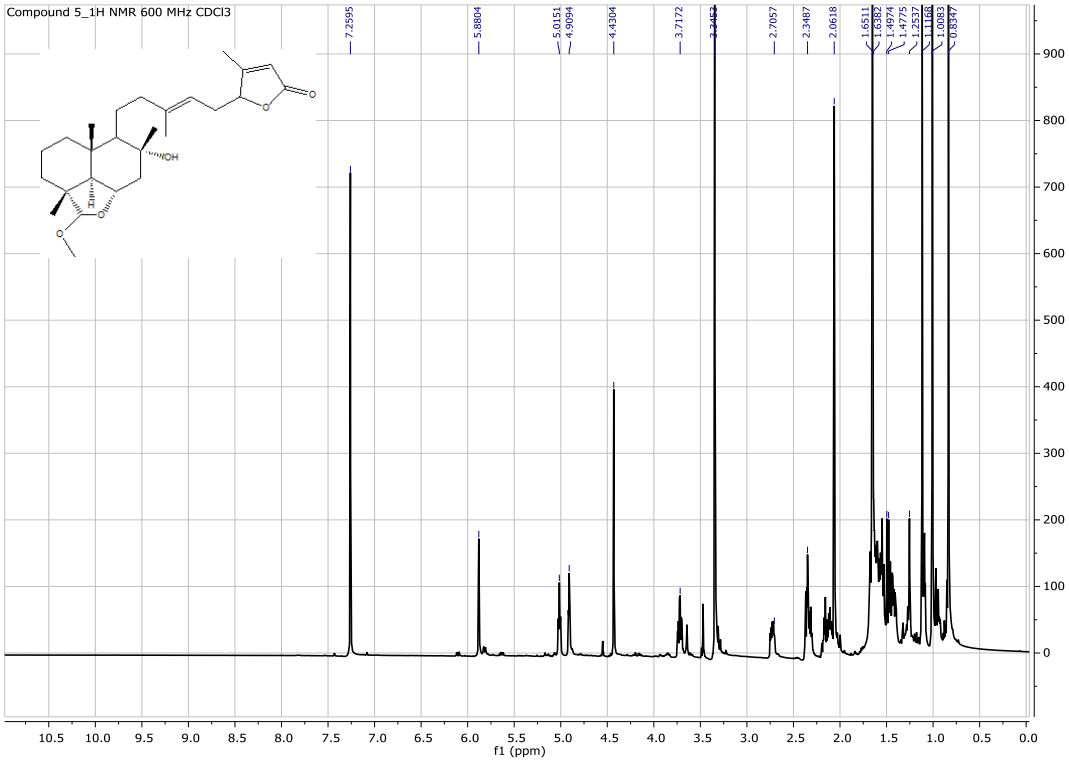


Figure S36. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of compound **5**

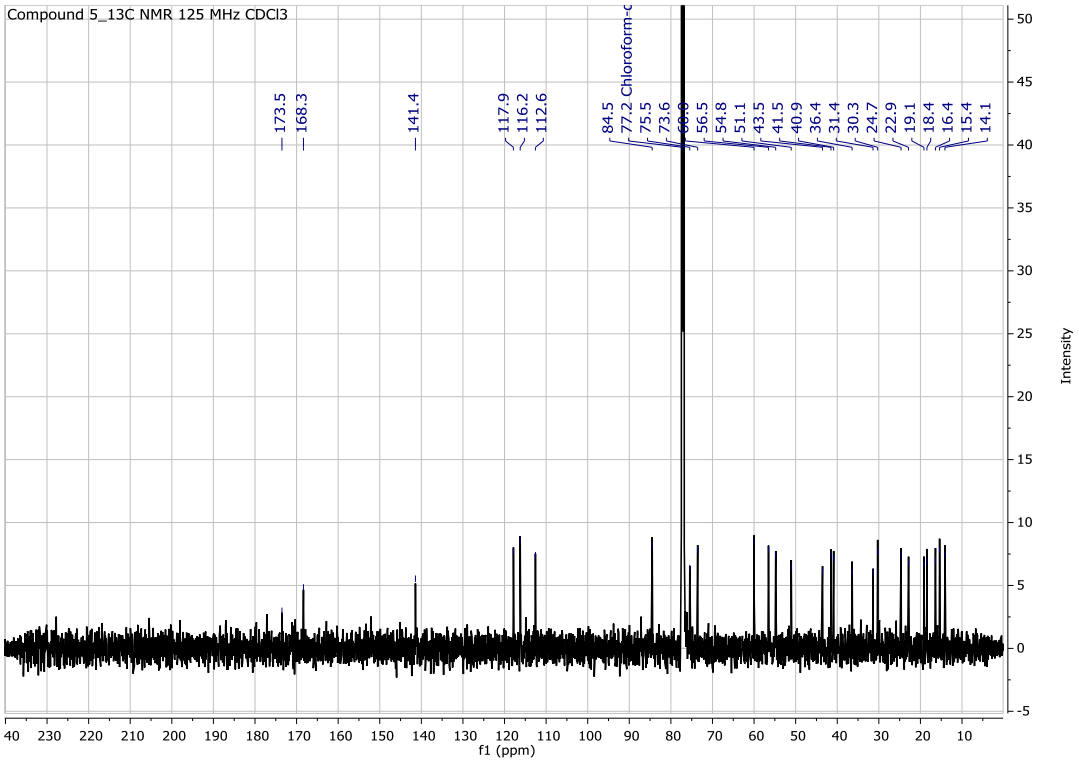


Figure S37. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **5**

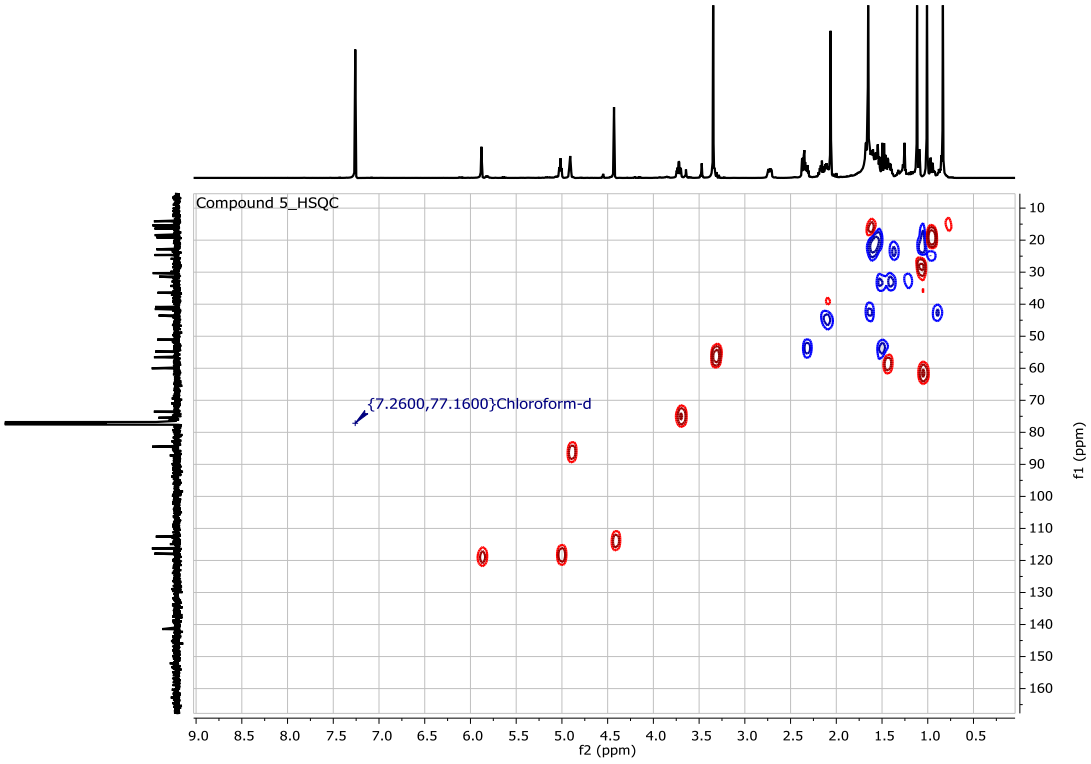


Figure S38. HSQC (600 MHz, $CDCl_3$) spectrum of compound **5**

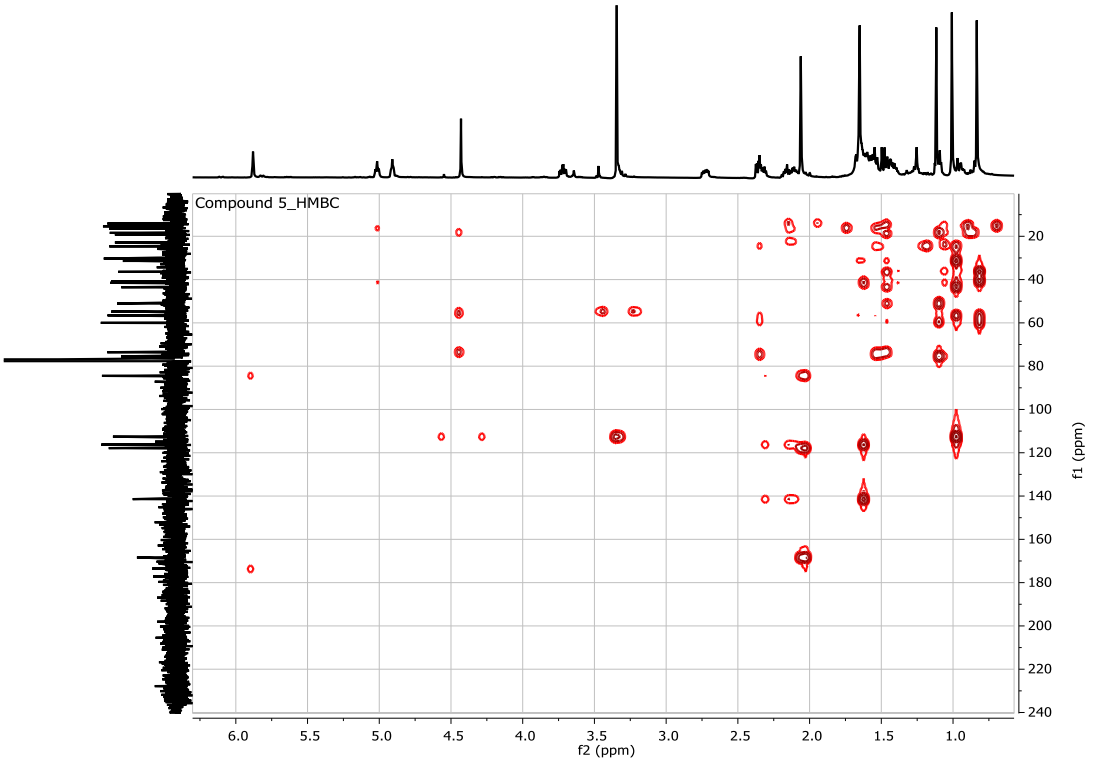


Figure S39. HMBC (600 MHz, $CDCl_3$) spectrum of compound **5**

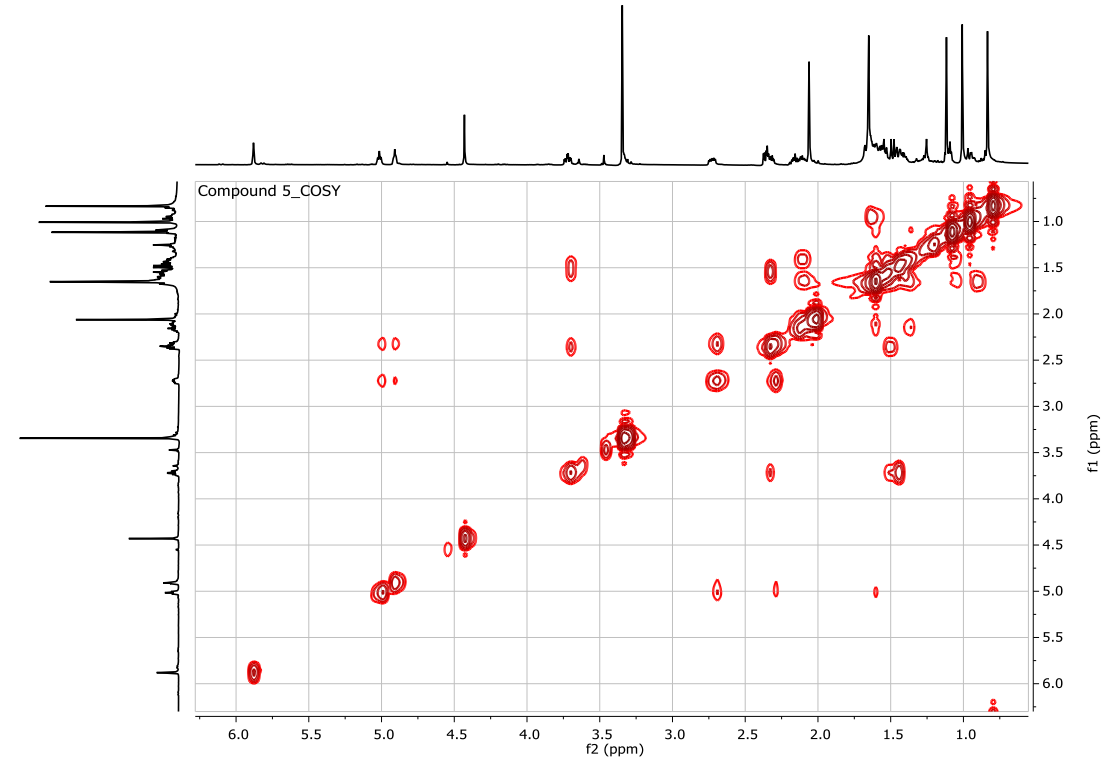


Figure S40. COSY (600 MHz, $CDCl_3$) spectrum of compound **5**

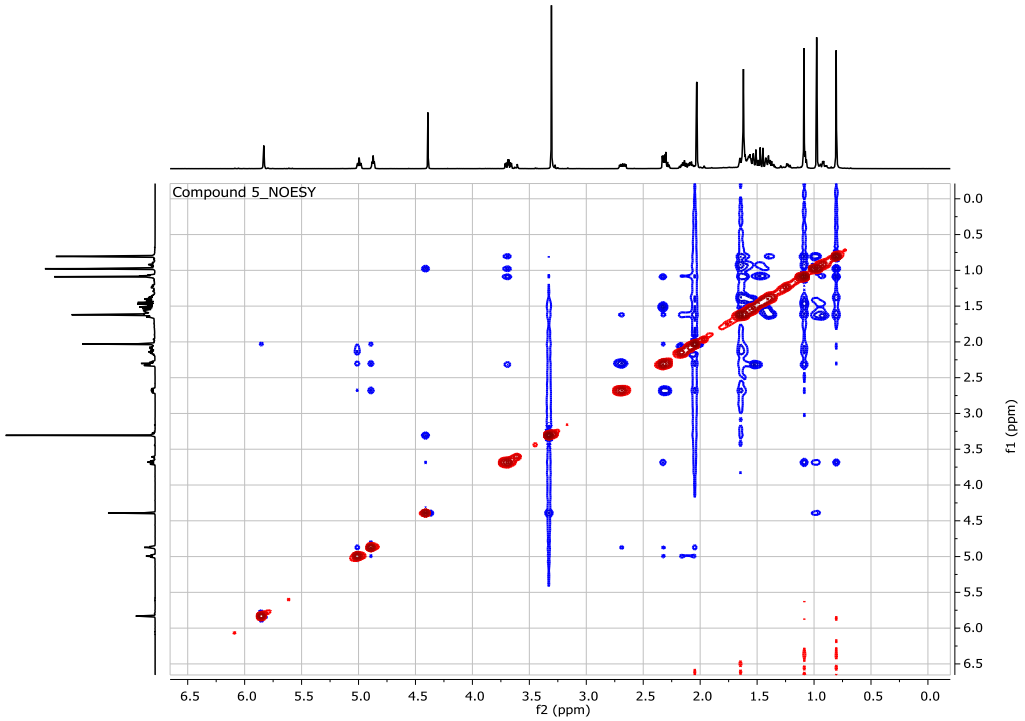


Figure S41. NOESY (500 MHz, $CDCl_3$) spectrum of compound **5**

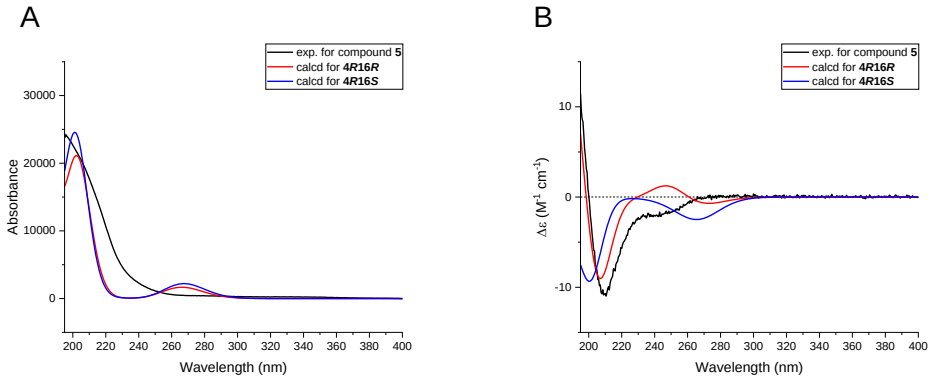


Figure S42. Comparison of experimental and computed UV (A) and ECD (B) (CH_3OH) spectra for compound **5**, where 4R stands for *4R5R6S8R9R10S23S*

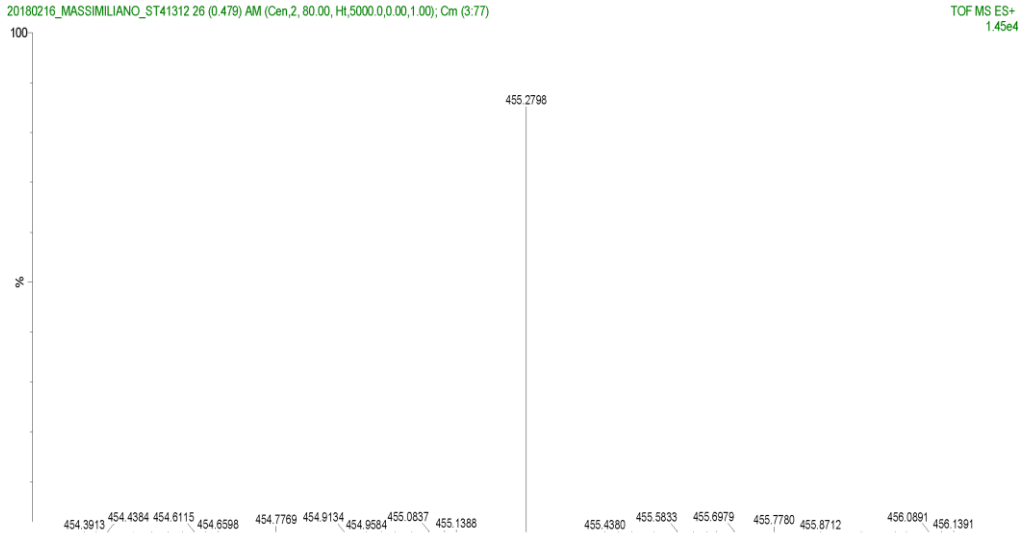


Figure S43. HRESIMS spectrum of compound **5**

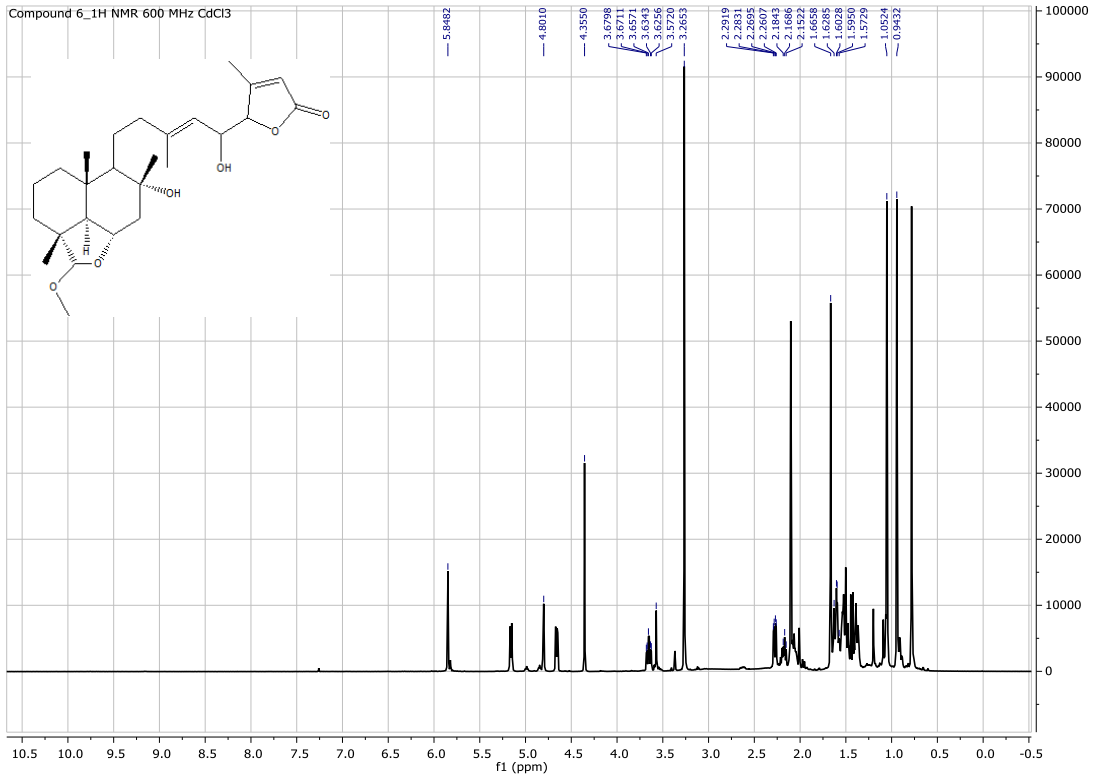


Figure S44. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of compound **6**

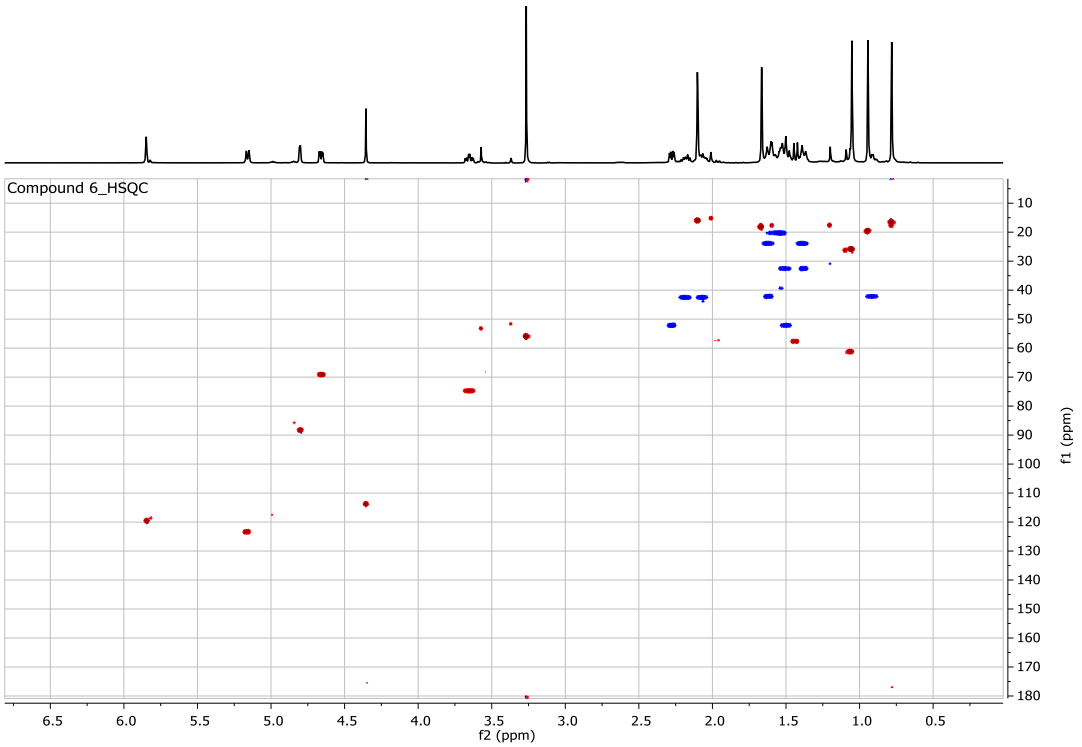


Figure S45. HSQC (600 MHz, $CDCl_3$) spectrum of compound **6**

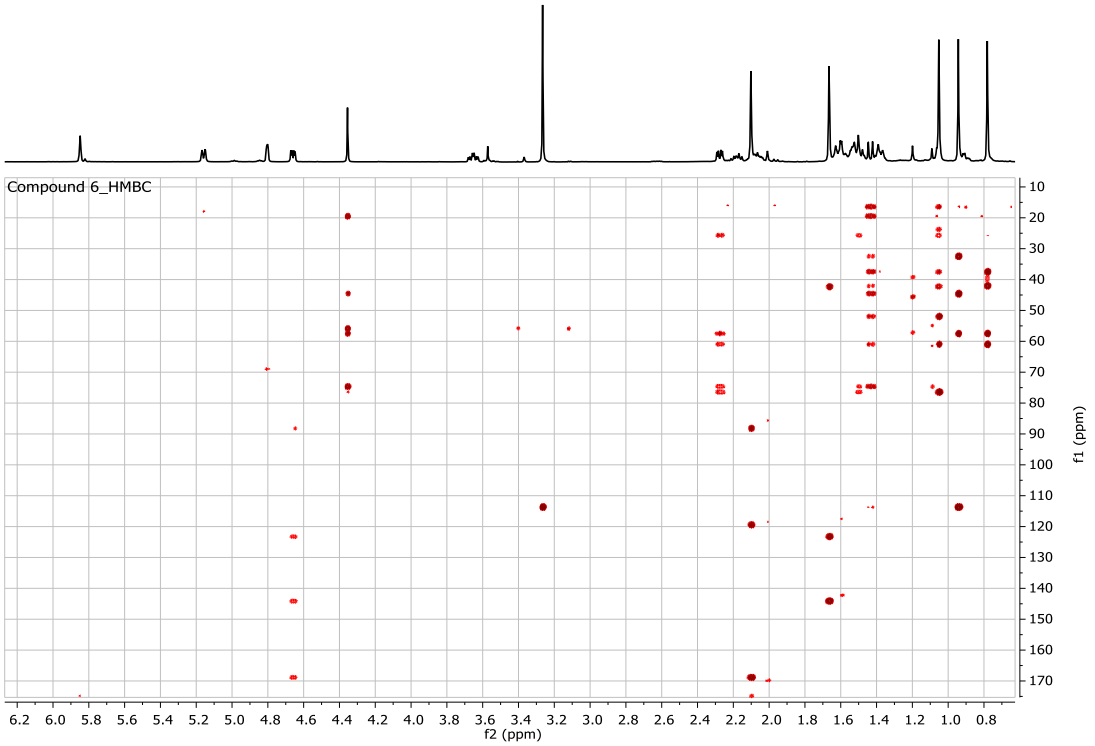


Figure S46. HMBC (600 MHz, $CDCl_3$) spectrum of compound **6**

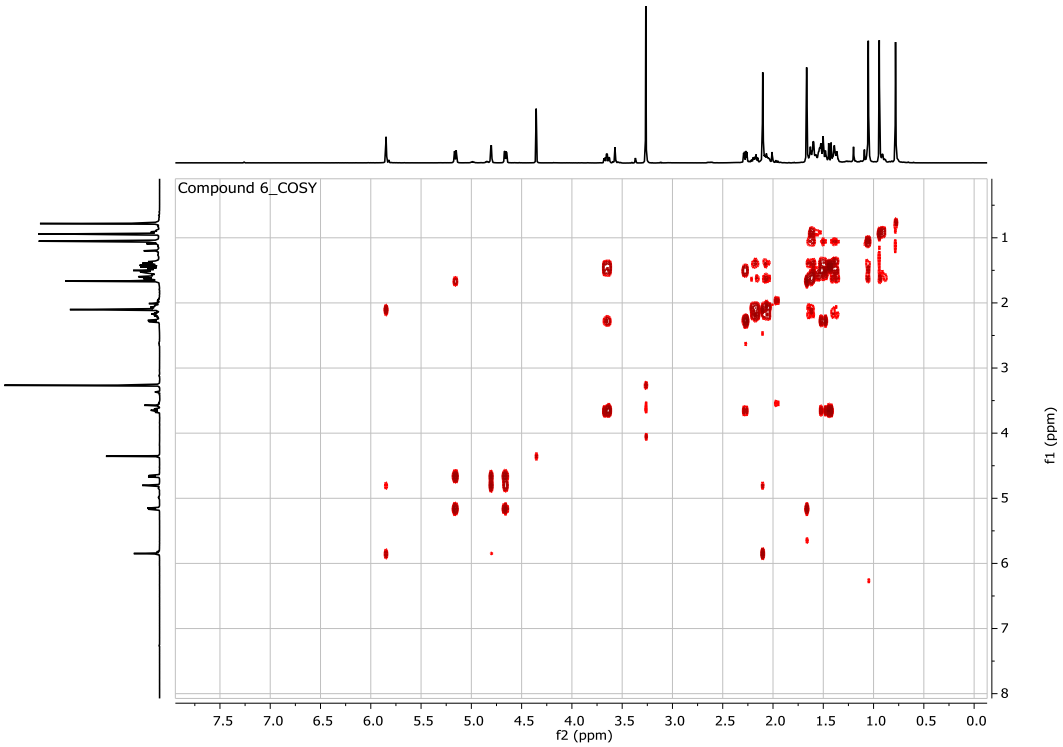


Figure S47. COSY (600 MHz, $CDCl_3$) spectrum of compound **6**

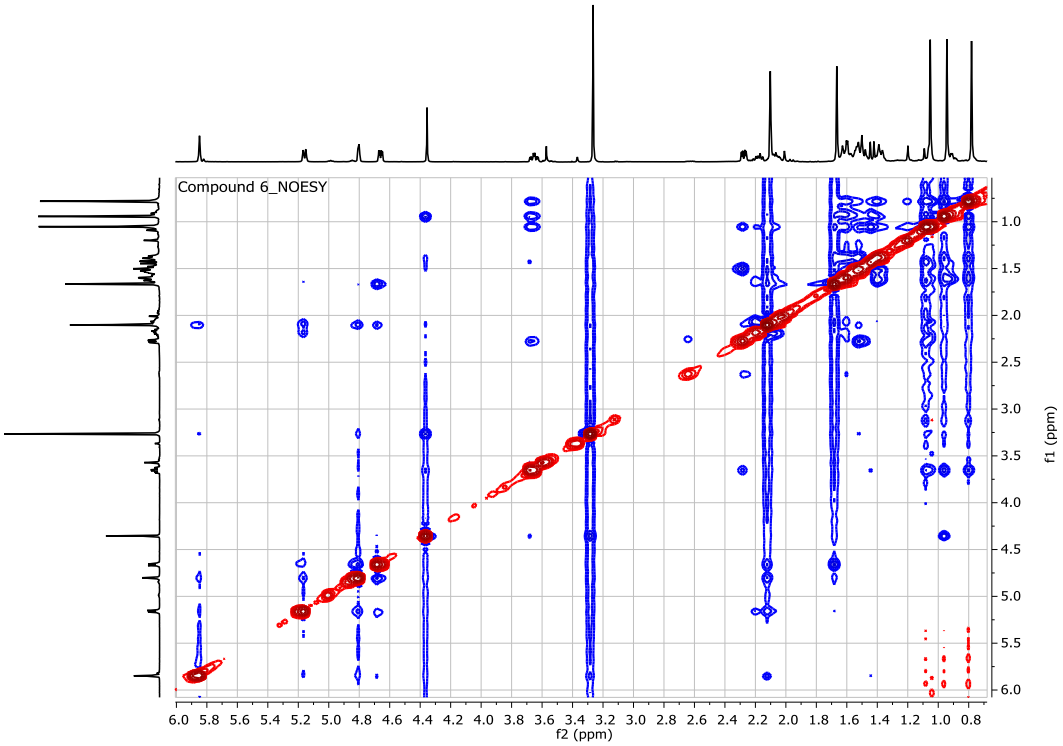


Figure S48. NOESY (500 MHz, $CDCl_3$) spectrum of compound **6**

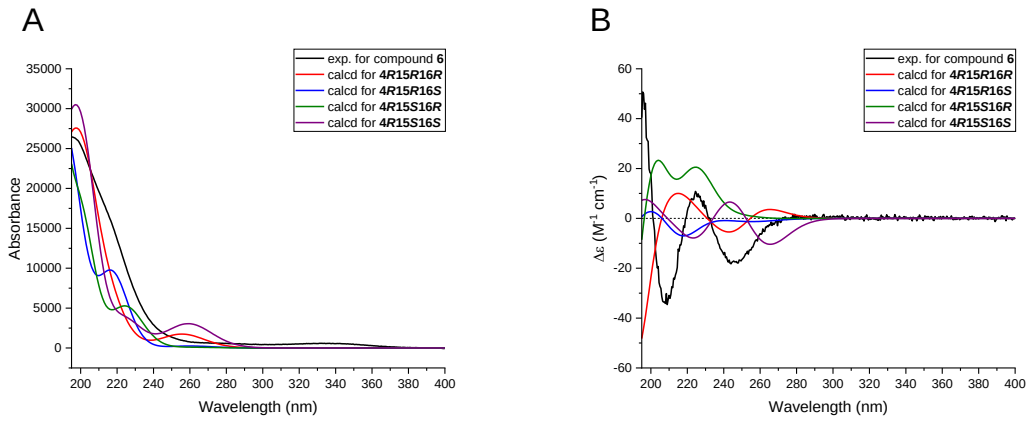


Figure S49. Comparison of experimental and computed UV (A) and ECD (B) (CH_3OH) spectra for compound **6**, where 4R stands for *4R5R6S8R9R10S23S*

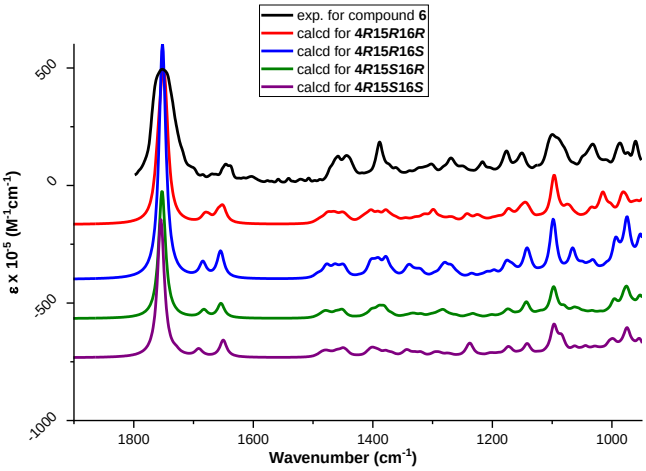


Figure S50. Comparison of experimental and computed IR ($CDCl_3$) spectra for compound **6**, where 4R stands for *4R5R6S8R9R10S23S*. The wavenumber scale factor 0.9820 was used to scale the computed spectra

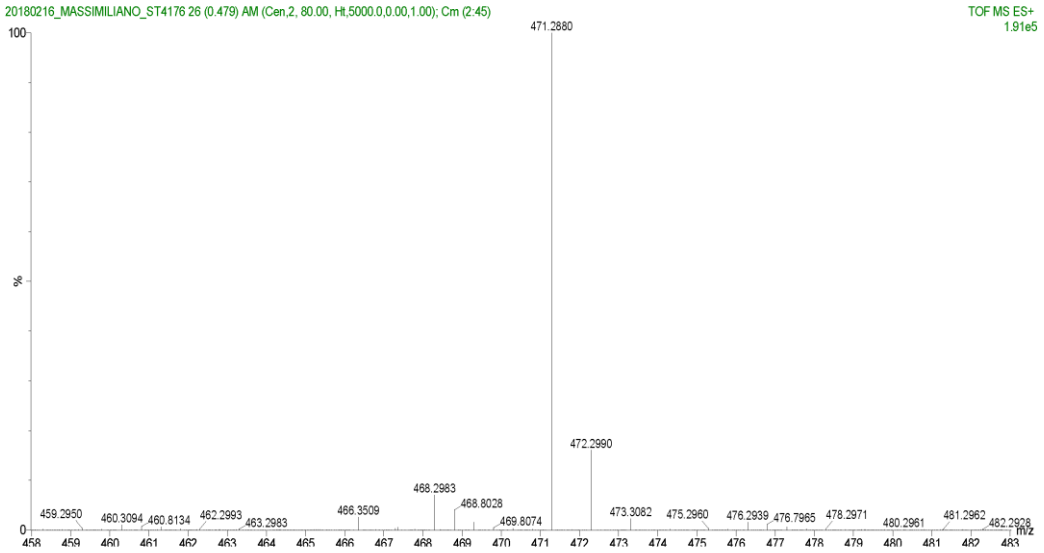


Figure S51. HRESIMS spectrum of compound **6**

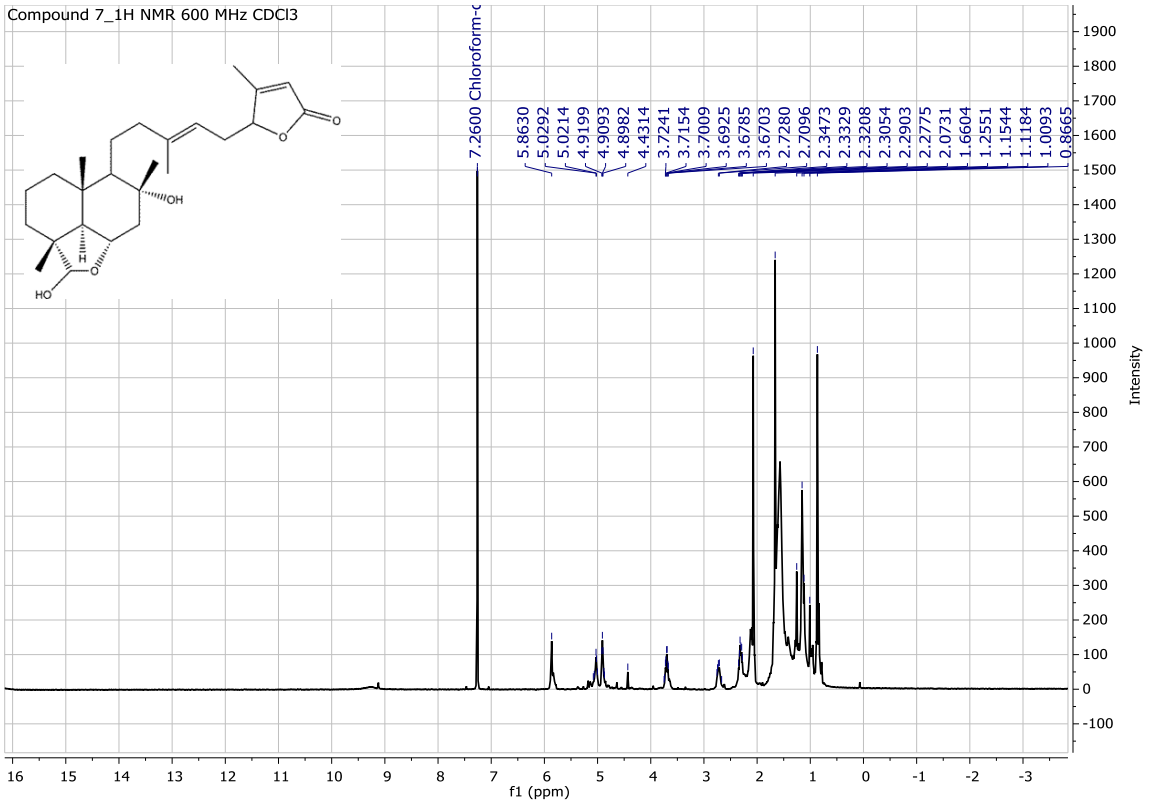


Figure S52. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of compound **7**

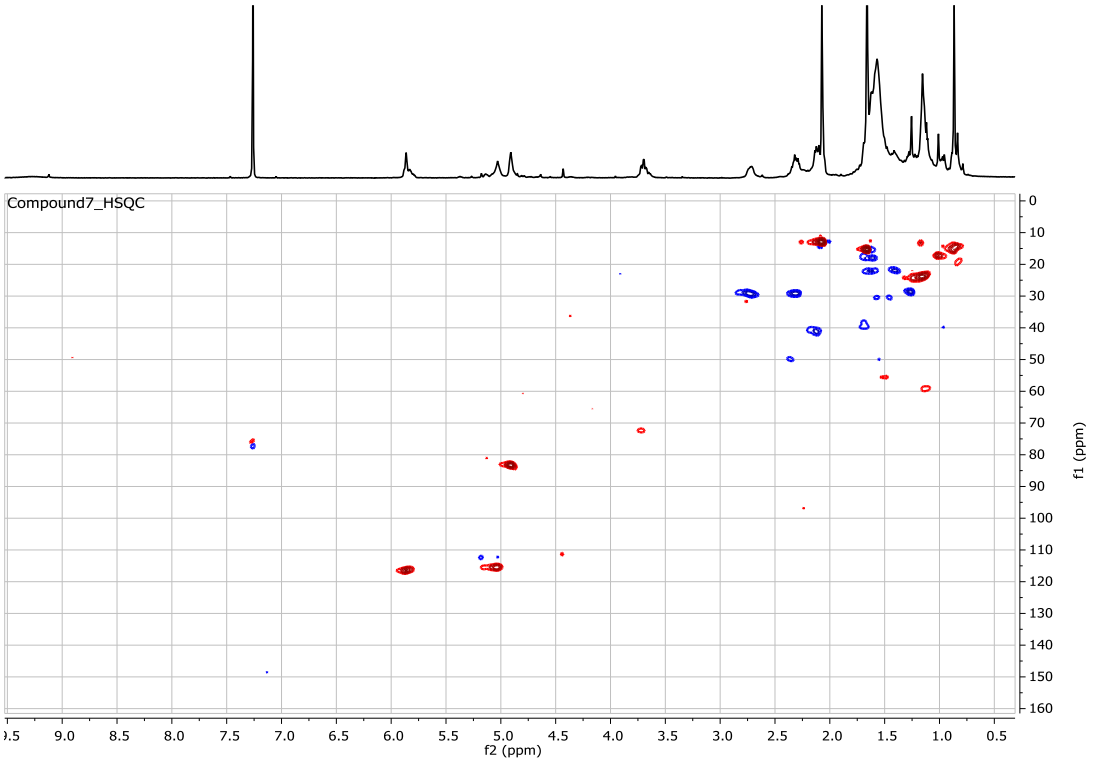


Figure S53. HSQC (600 MHz, $CDCl_3$) spectrum of compound **7**

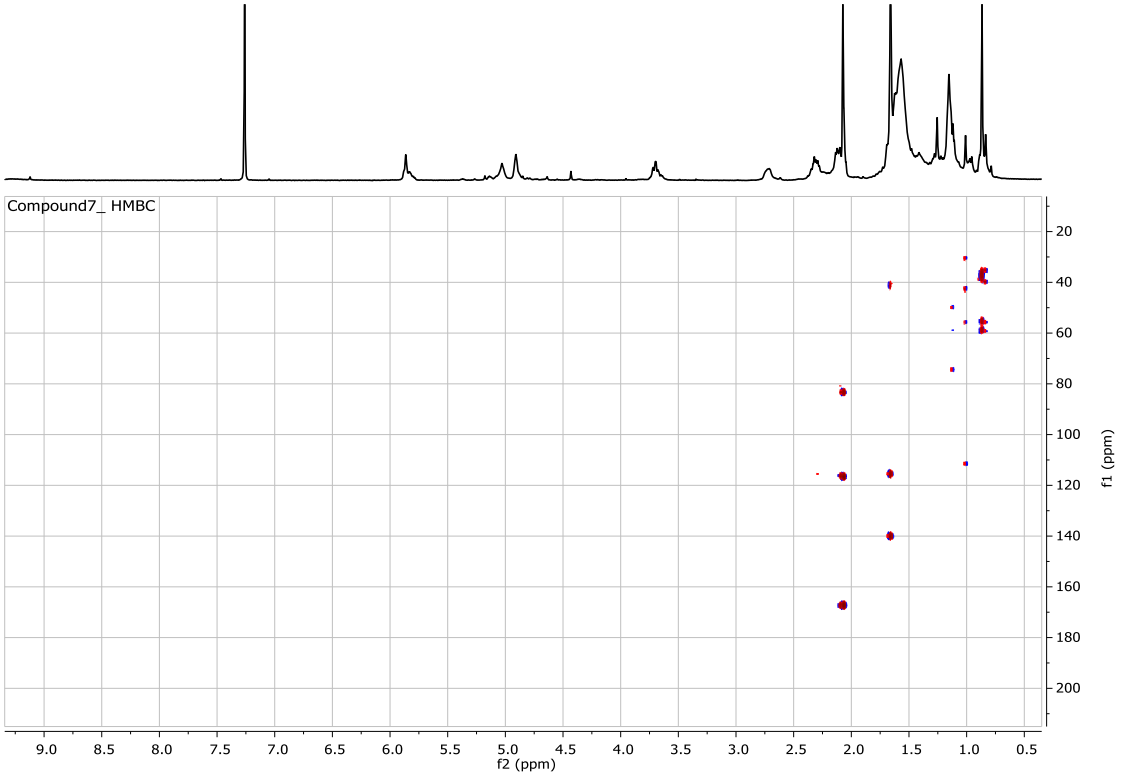


Figure S54. HMBC (600 MHz, $CDCl_3$) spectrum of compound **7**

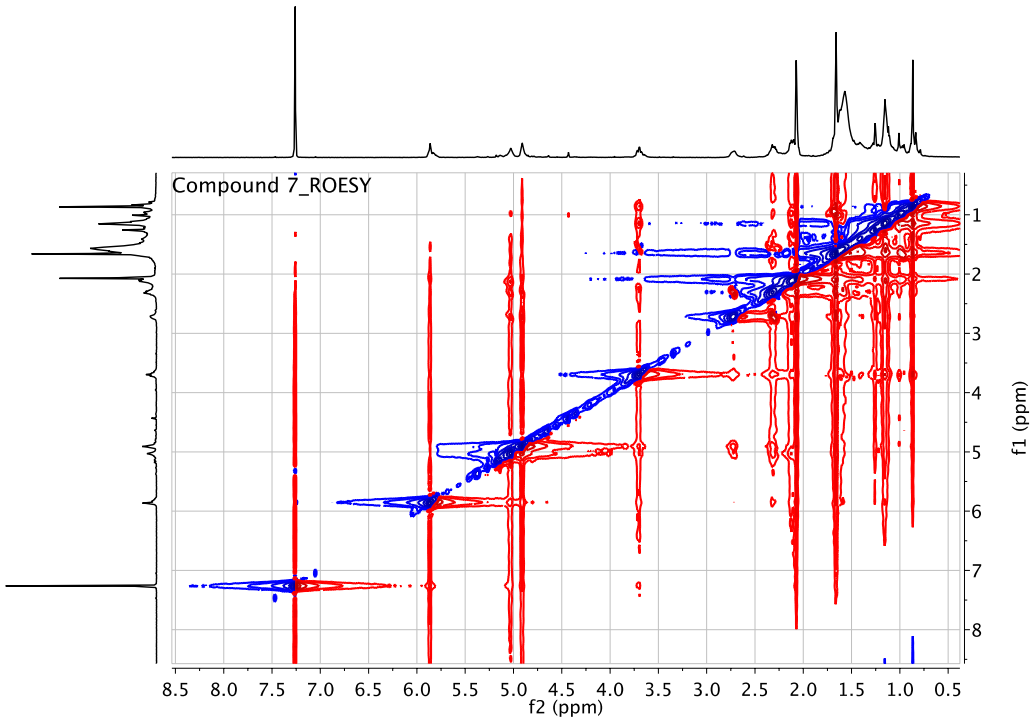


Figure S55. ROESY (600 MHz, $CDCl_3$) spectrum of compound **7**

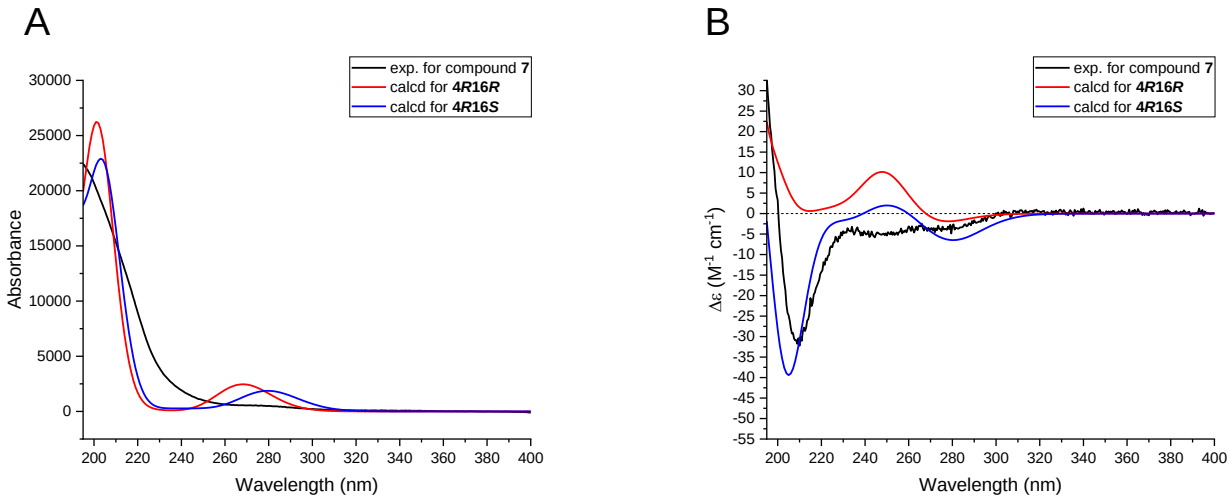


Figure S56. Comparison of experimental and computed UV (A) and ECD (B) (CH_3OH) spectra for compound **7,** where 4R stands for *4R5R6S8R9R10S23S*

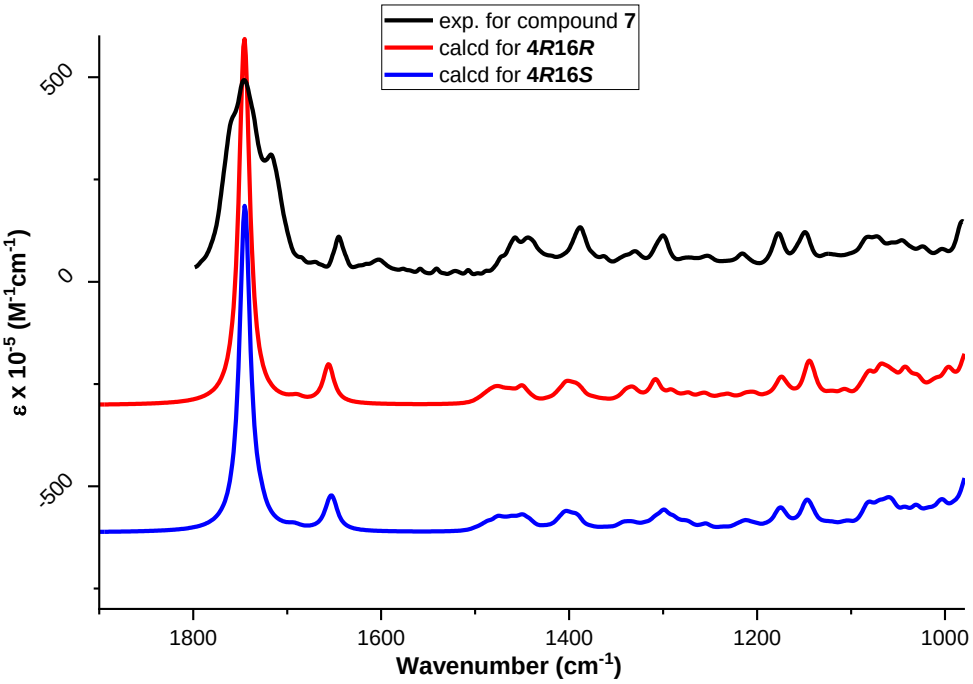


Figure S57. Comparison of experimental and computed IR ($CDCl_3$) spectra for compound **7**, where 4R stands for *4R5R6S8R9R10S23S*. The wavenumber scale factor 0.9820 was used to scale the computed spectra

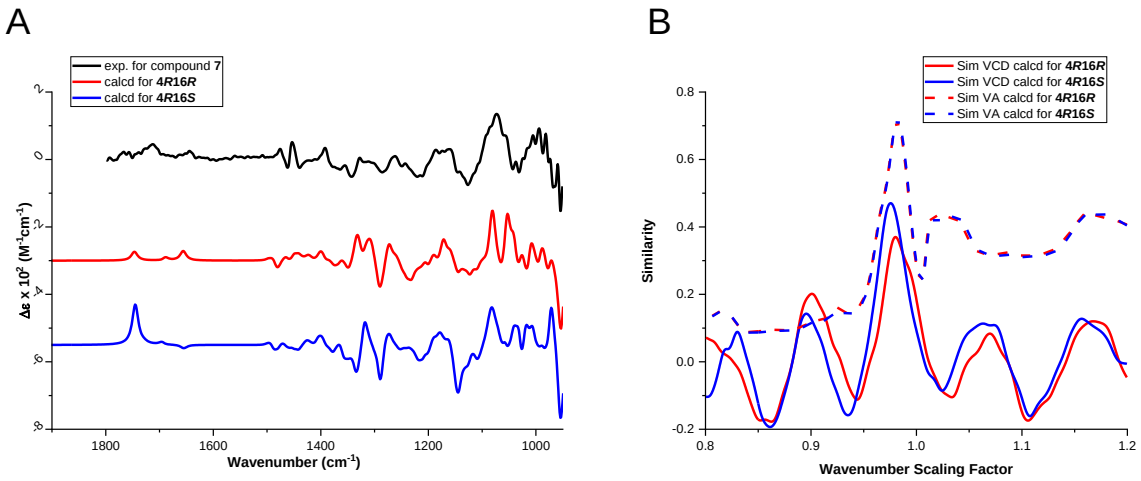


Figure S58. Comparison of experimental and computed VCD in CDCl3 spectra for compound **7** (A). Similarities (SimVA and SimVCD) between experimental and computed VA and VCD spectra of **7** were plotted as functions of wavenumber scale factor (B). 4R stands for *4R5R6S8R9R10S23S*. The wavenumber scale factor corresponding to the maximal SimVA value in B (0.9820) was used to scale the computed spectra in A

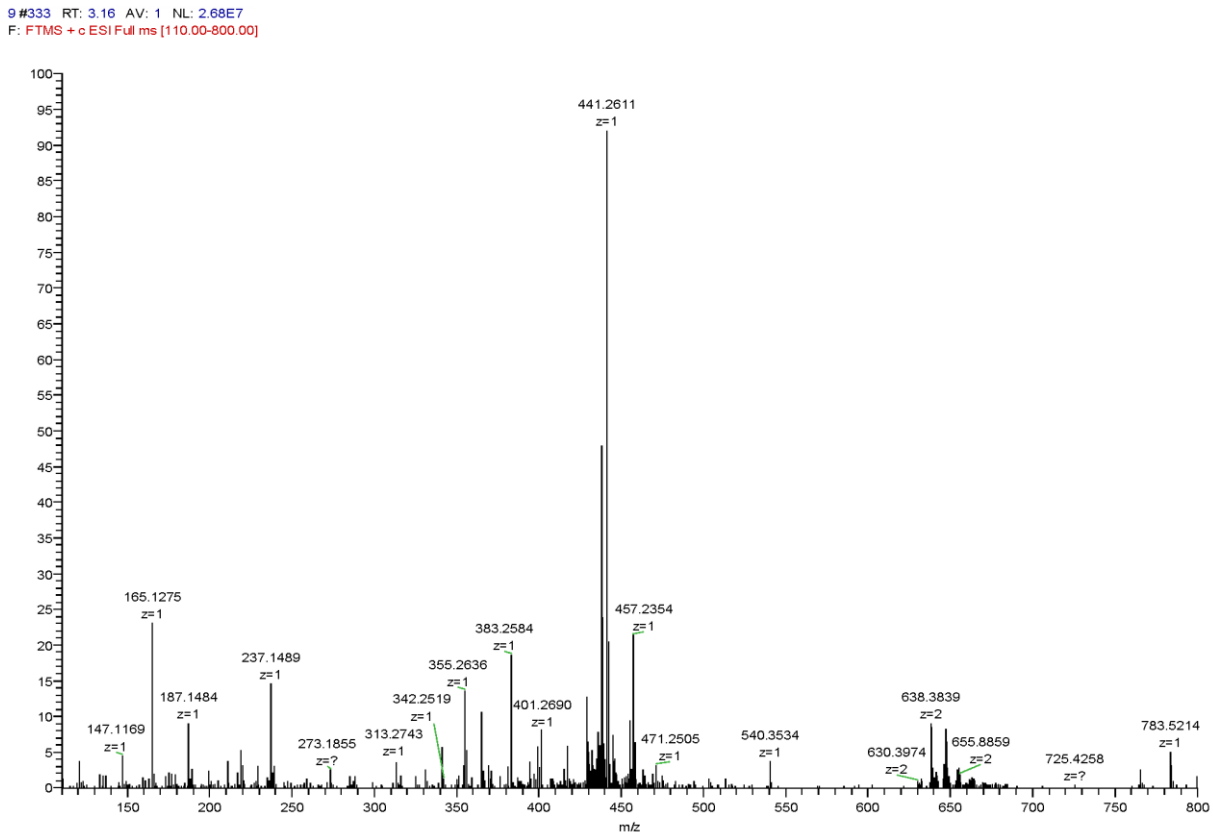


Figure S59. HRESIMS spectrum of compound **7**

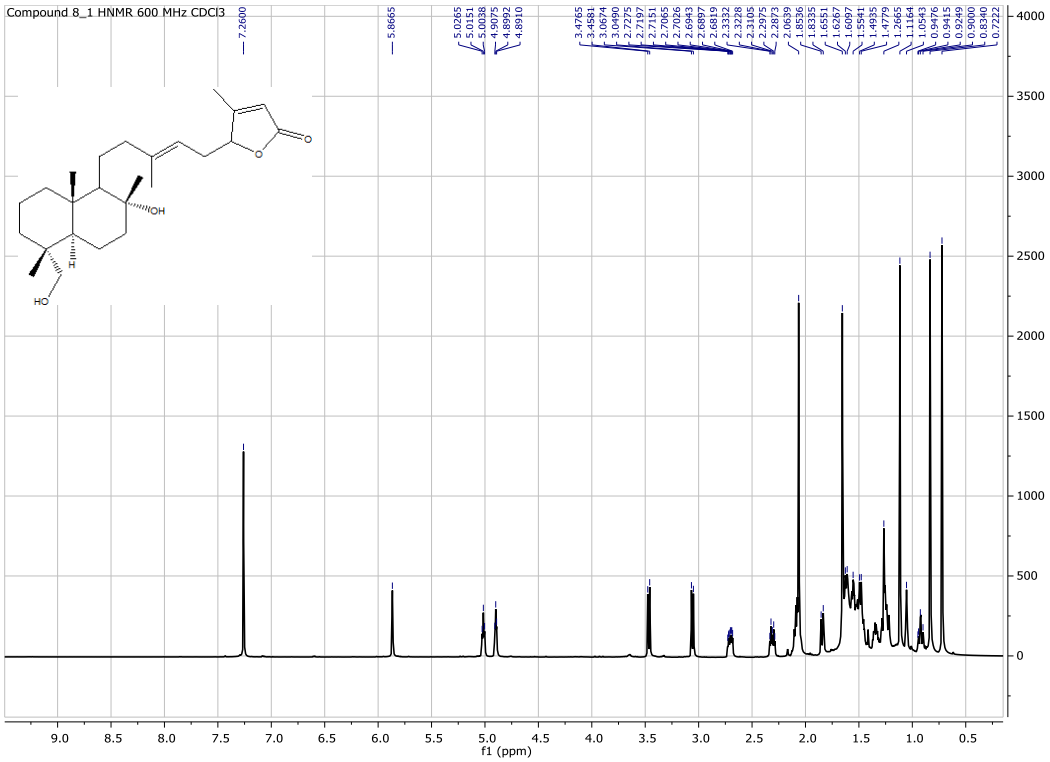


Figure S60. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of compound **8**

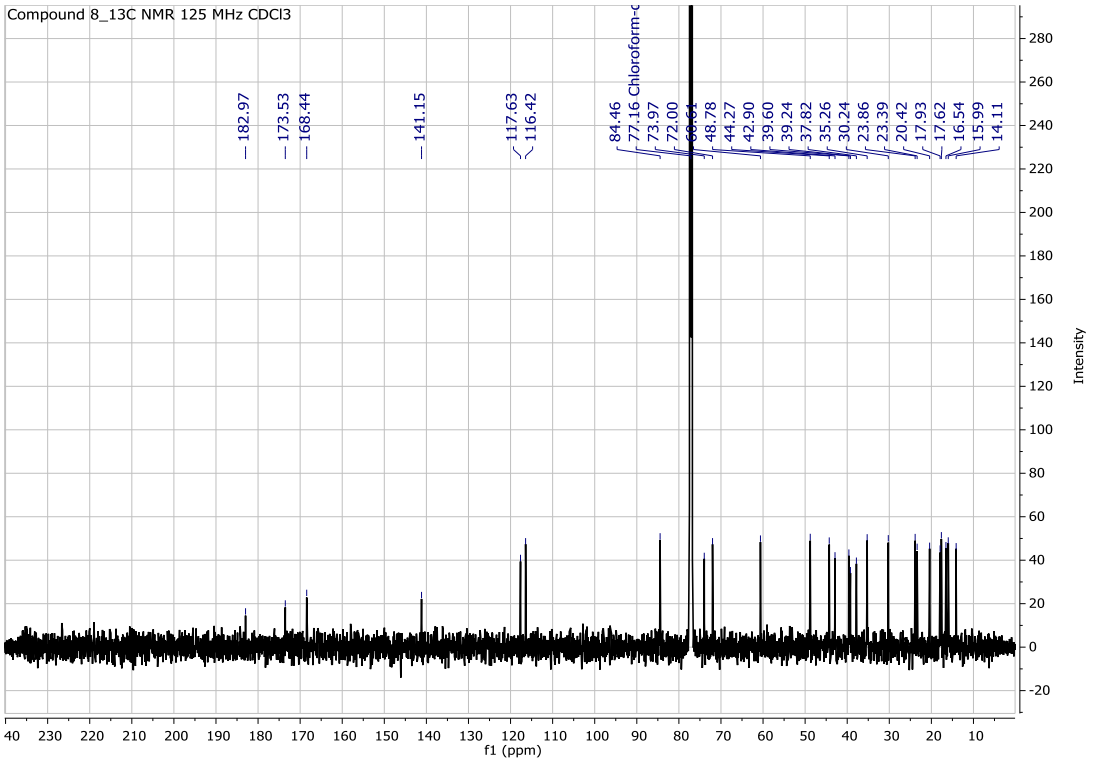


Figure S61. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **8**

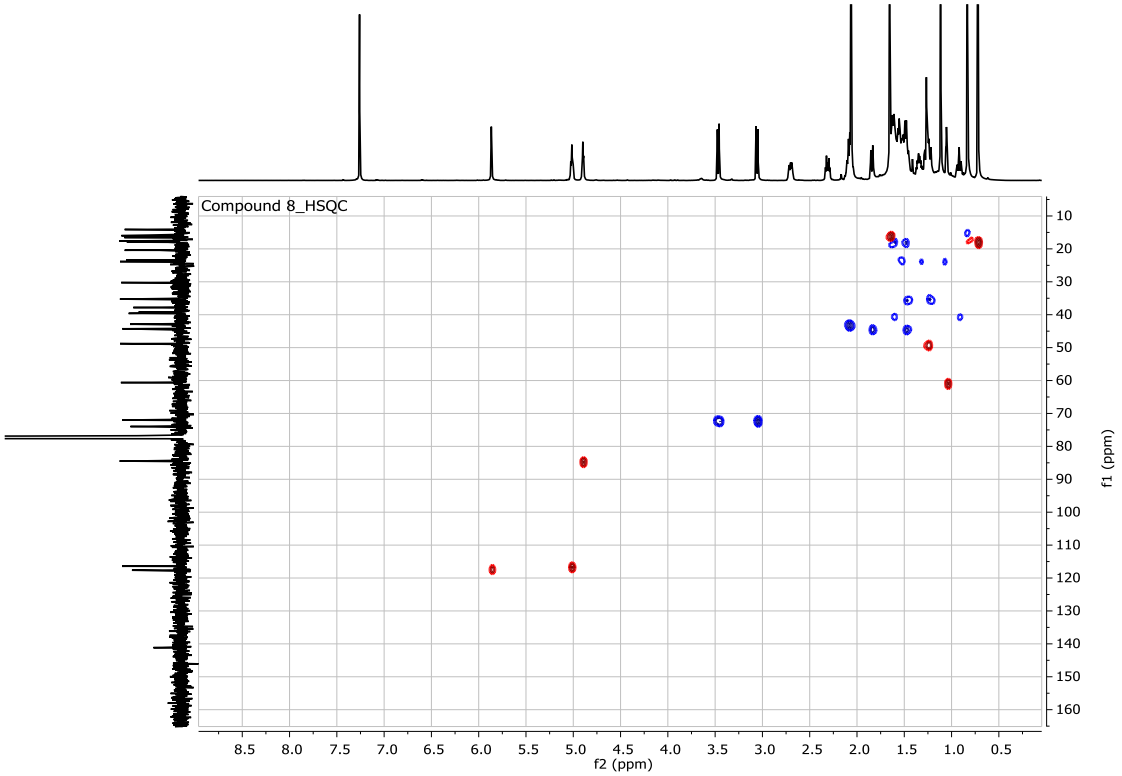


Figure S62. HSQC (600 MHz, $CDCl_3$) spectrum of compound **8**

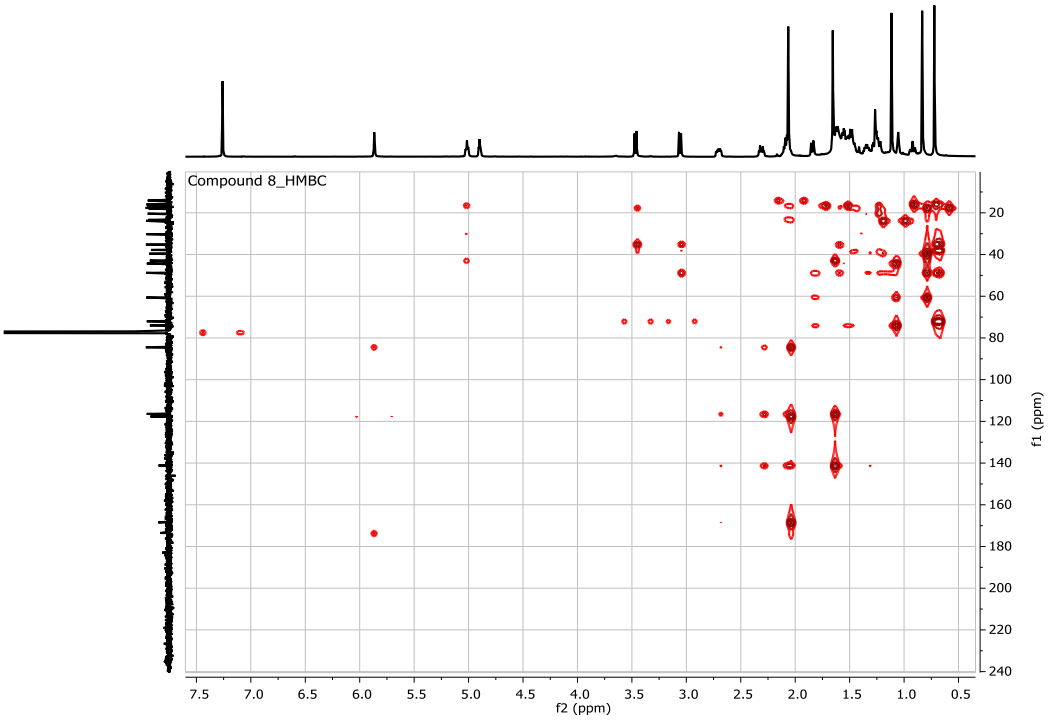


Figure S63. HMBC (600 MHz, $CDCl_3$) spectrum of compound **8**

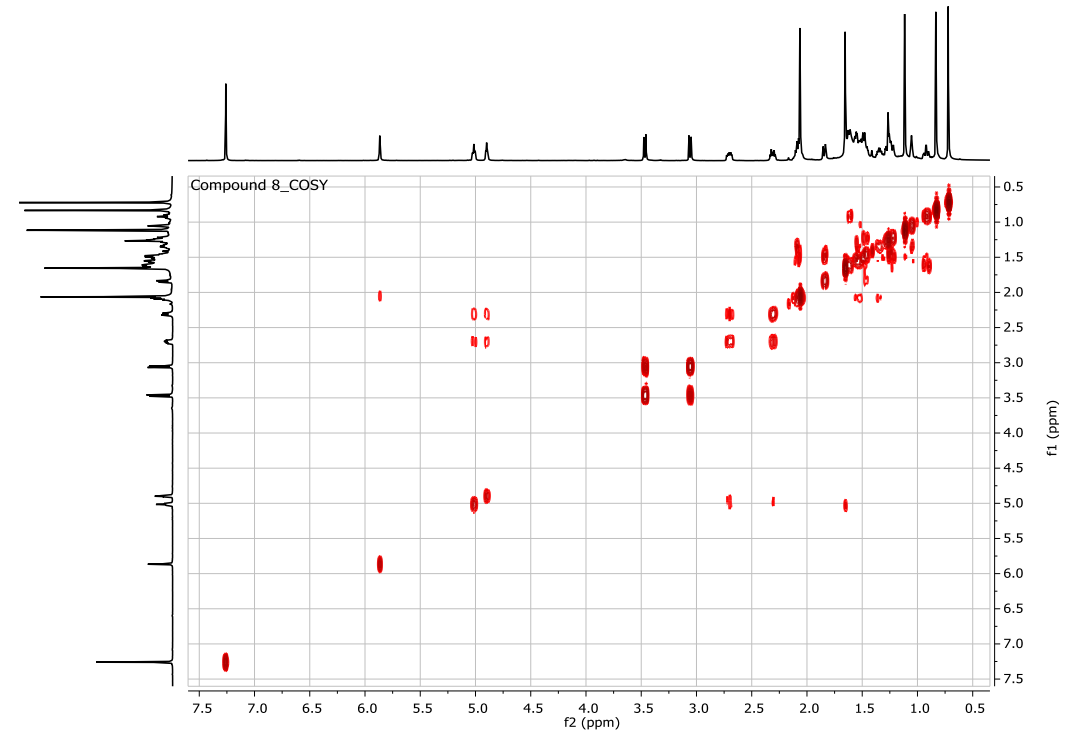


Figure S64. COSY (600 MHz, $CDCl_3$) spectrum of compound **8**

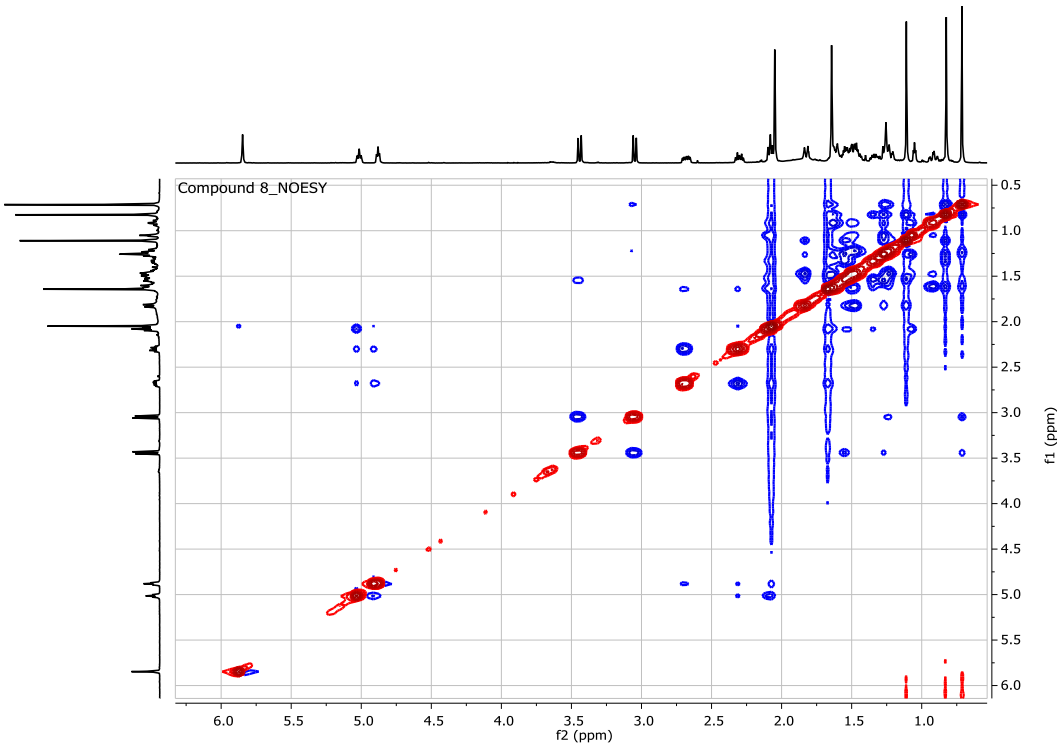


Figure S65. NOESY (500 MHz, $CDCl_3$) spectrum of compound **8**

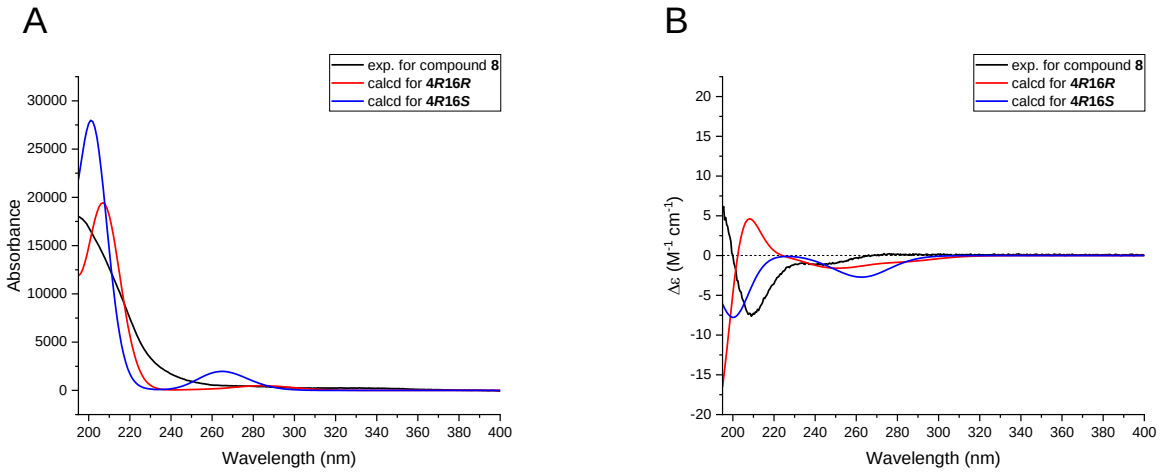


Figure S66. Comparison of experimental and computed UV (A) and ECD (B) (CH3OH) spectra for compound **8,** where 4R stands for *4R5R8R9R10S*

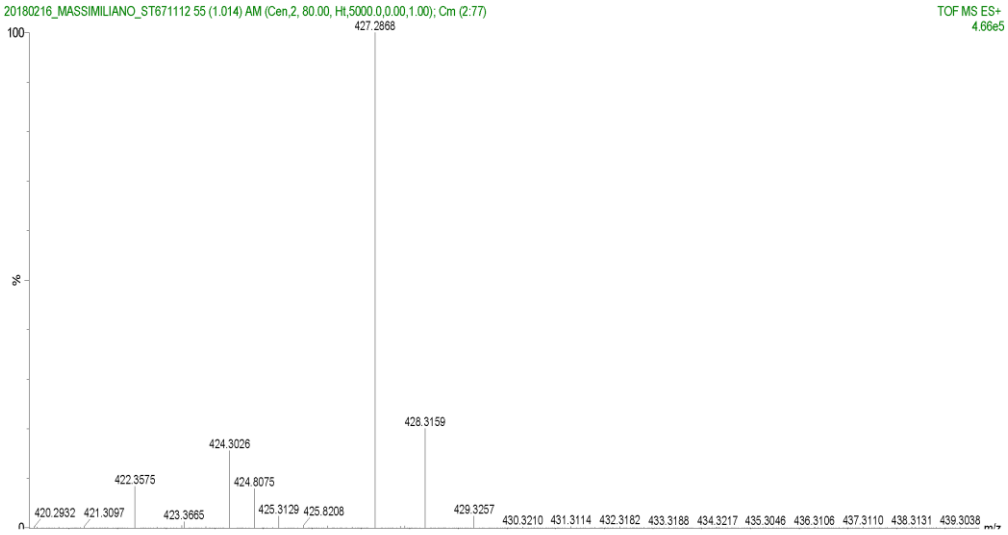


Figure S67. HRESIMS spectrum of compound **8**

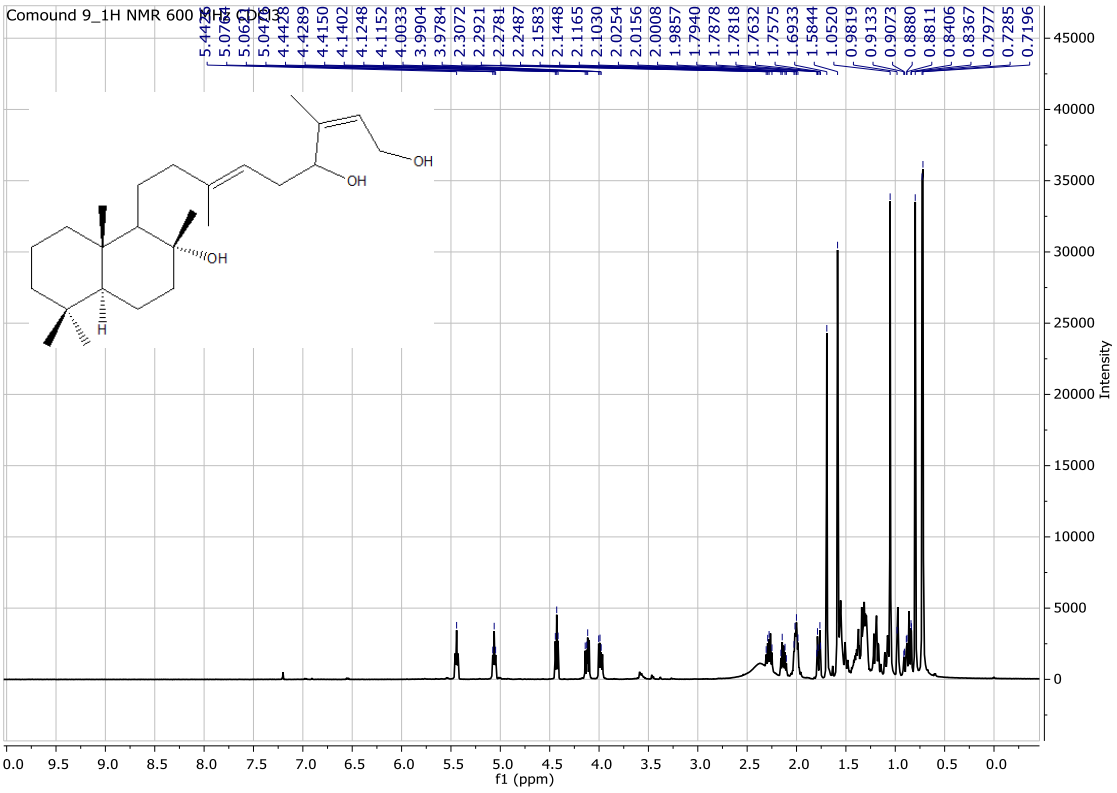


Figure S68. ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of compound **9**

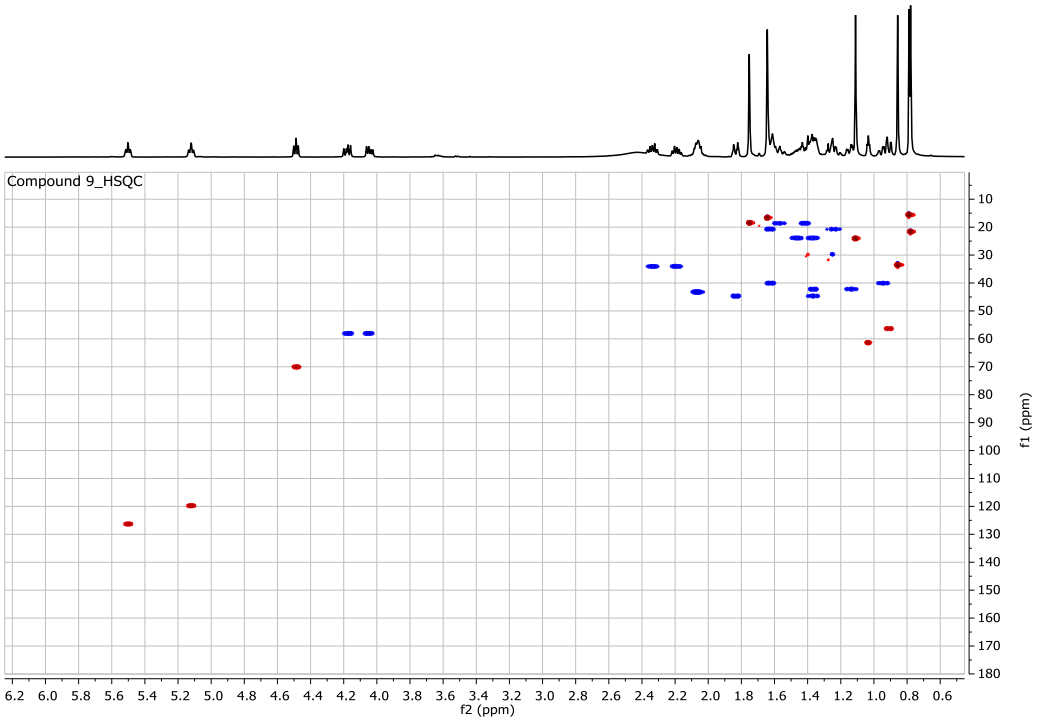


Figure S69. HSQC (600 MHz, $CDCl_3$) spectrum of compound **9**

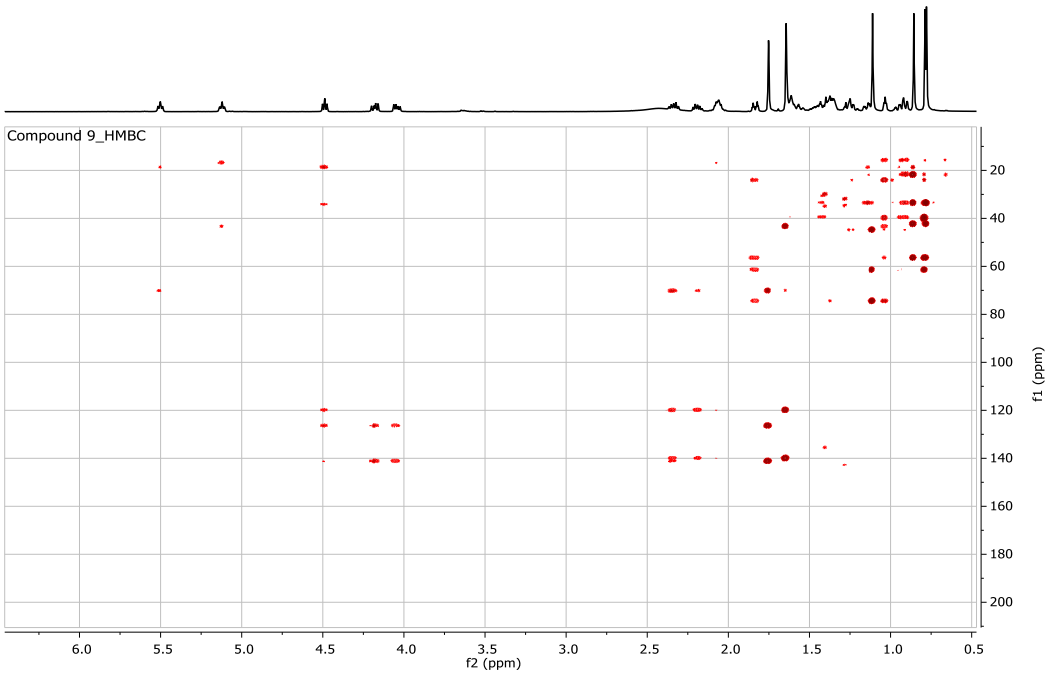


Figure S70. HMBC (600 MHz, $CDCl_3$) spectrum of compound **9**

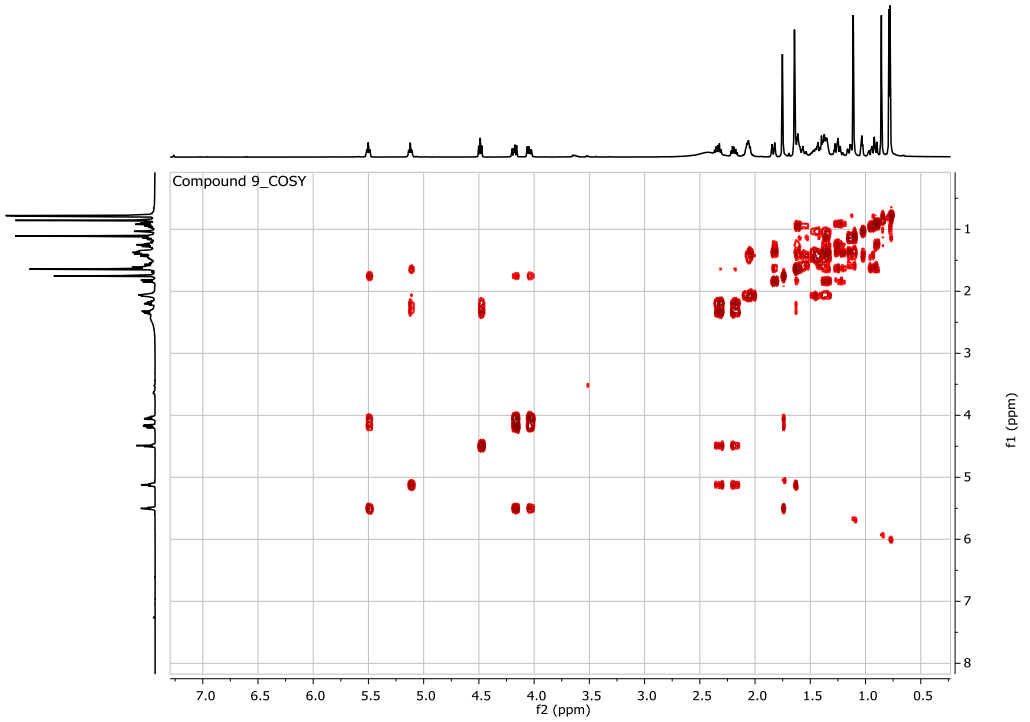


Figure S71. COSY (600 MHz, $CDCl_3$) spectrum of compound **9**

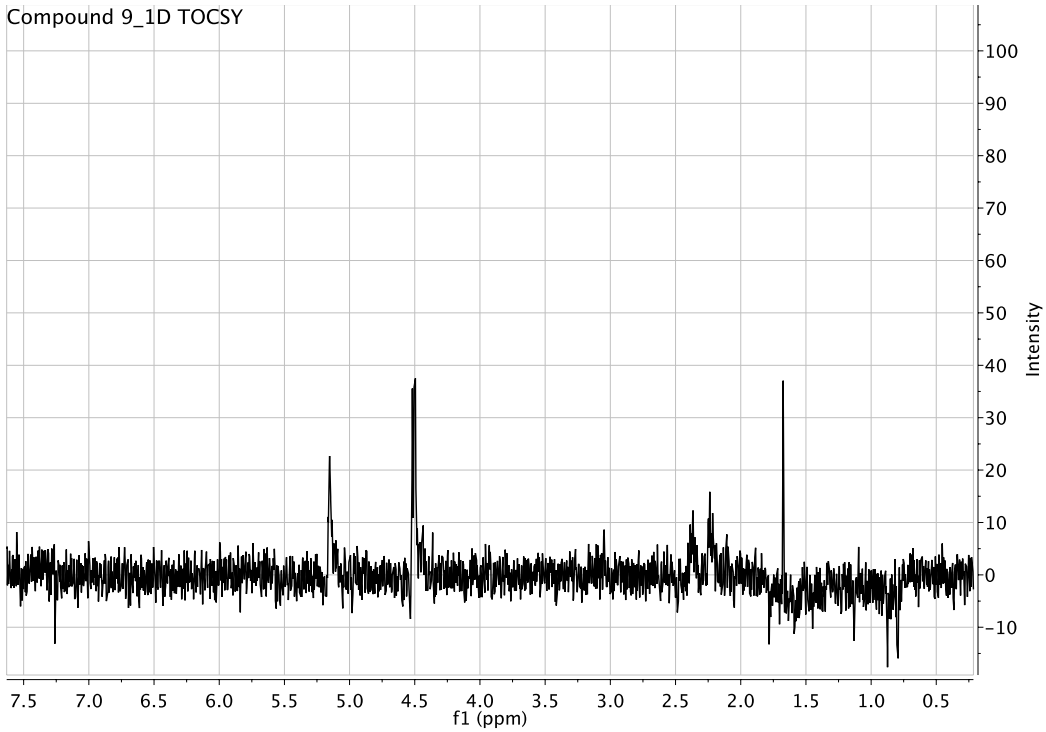


Figure S72. 1D TOCSY (600 MHz, $CDCl_3$) spectrum of compound **9**

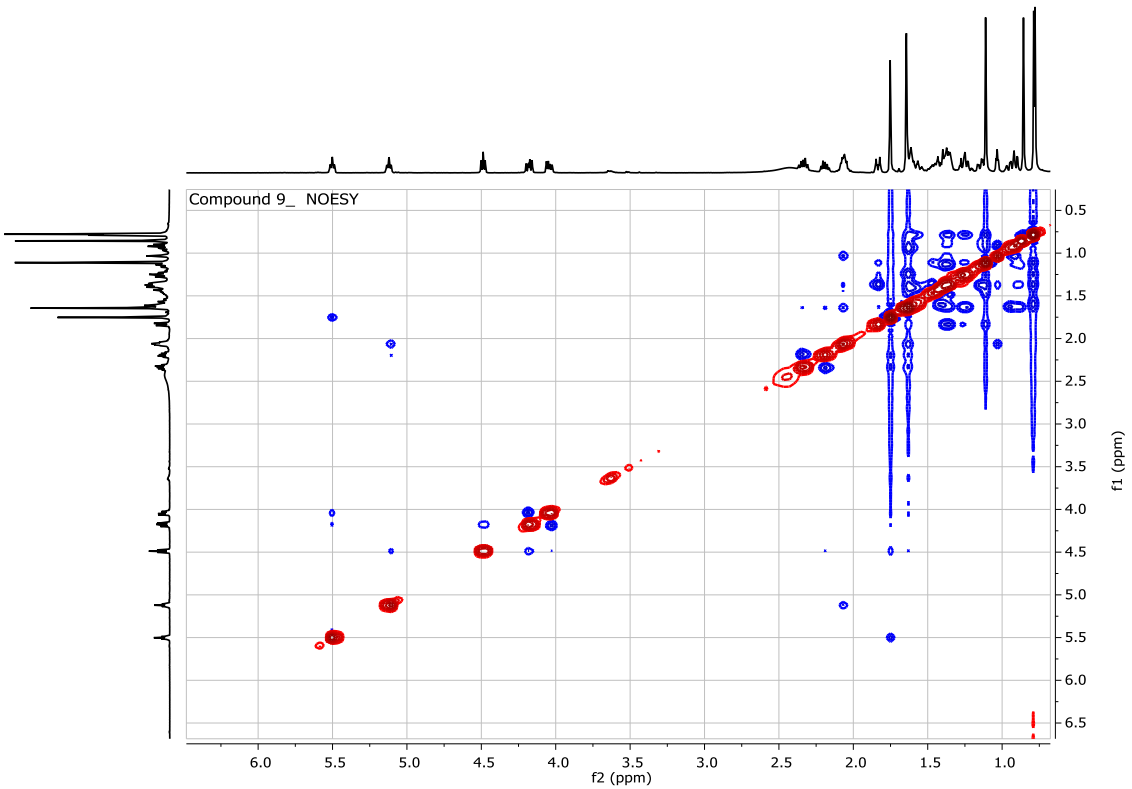


Figure S73. NOESY (500 MHz, $CDCl_3$) spectrum of compound **9**

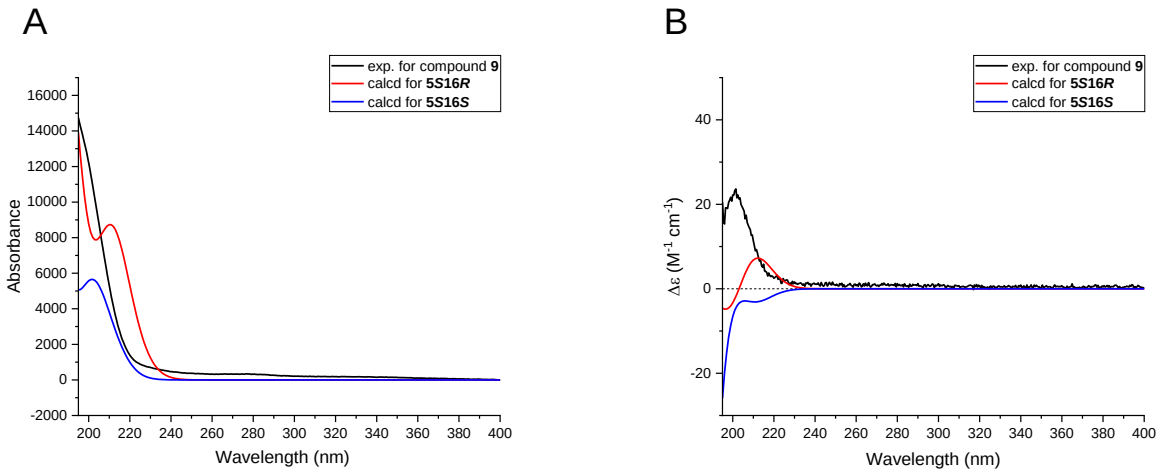


Figure S74. Comparison of experimental and computed UV (A) and ECD (B) (CH_3OH) spectra for compound **9**, where 5S stands for *5S8R9R10S*

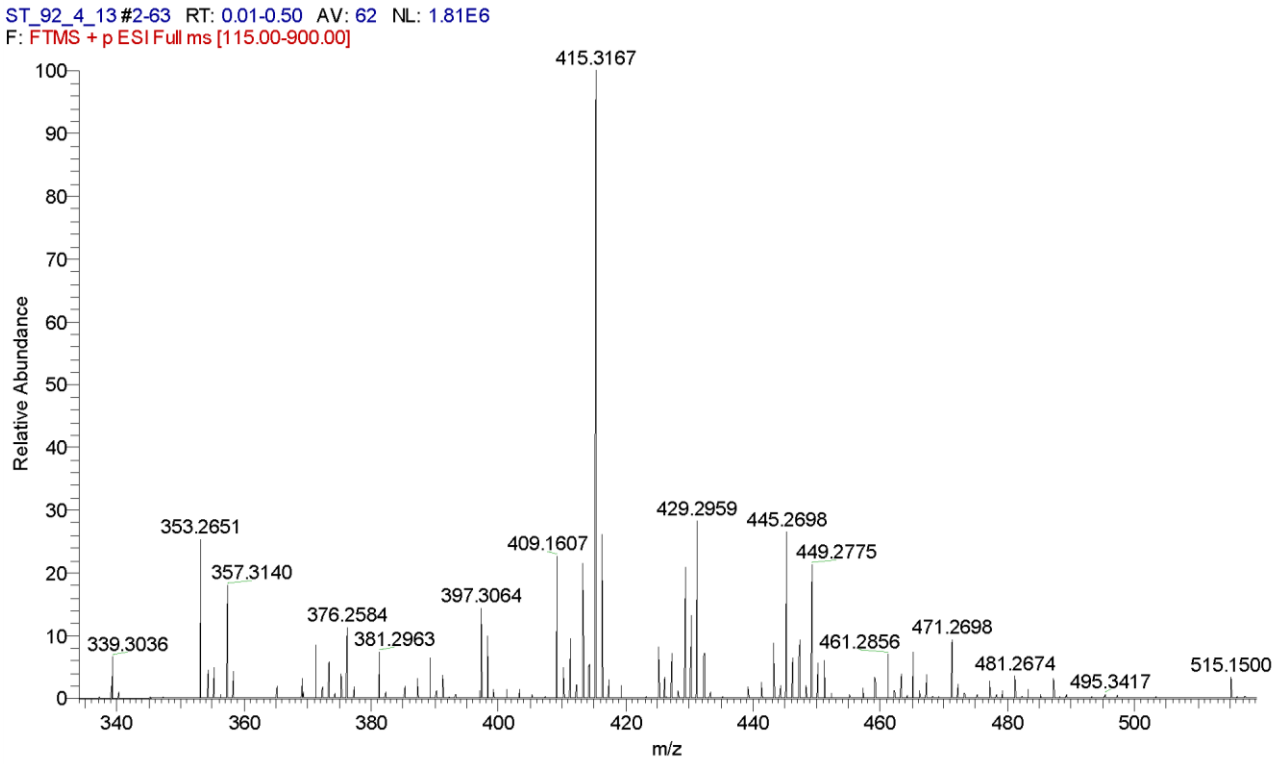


Figure S75. HRESIMS spectrum of compound **9**

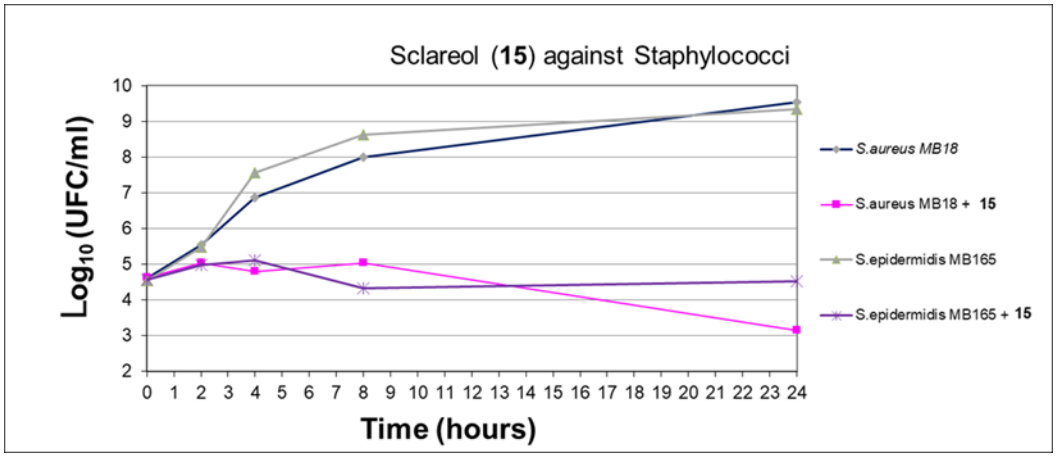


Figure S76. Effect of sclareol (**15**) on viable cell number of selected susceptible *Staphylococcus* strains. Time-kill curves were recorded in the absence or in the presence of 15 at a concentration of 4 × MIC.

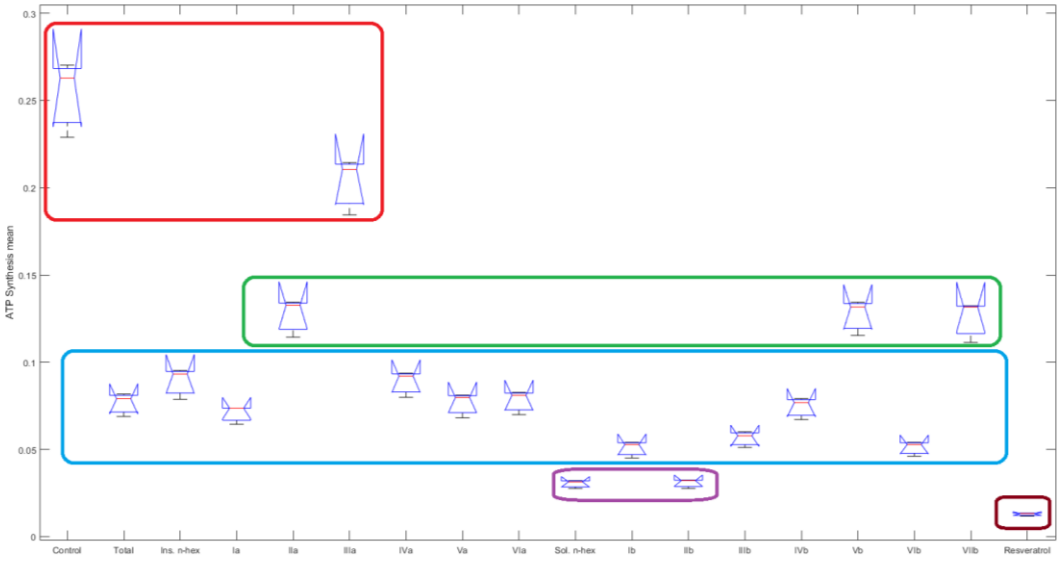


Figure S77. Effect of total extract, n-hexane insoluble and soluble fractions and relative sub-fractions (I_a-VI_a, I_b-VI_b) on ATP synthesis in rod Outer Segments (OS). ATP synthesis by OS (5µg) in the presence of total extract, n-hexane insoluble and soluble fractions and relative sub-fractions (I_a-VI_a, I_b-VI_b) (80 µg/mL). Activity is expressed as µmol ATP produced/min/mg of total protein. All data were tested with one-way ANOVA (using MATLAB 2019a statistical toolkit). Mean and standard deviation of each measure are presented according to the standards of MATLAB boxplot. The application of Bonferroni method defined 5 groups ($p < 0.05$) indicated by colored rectangles.

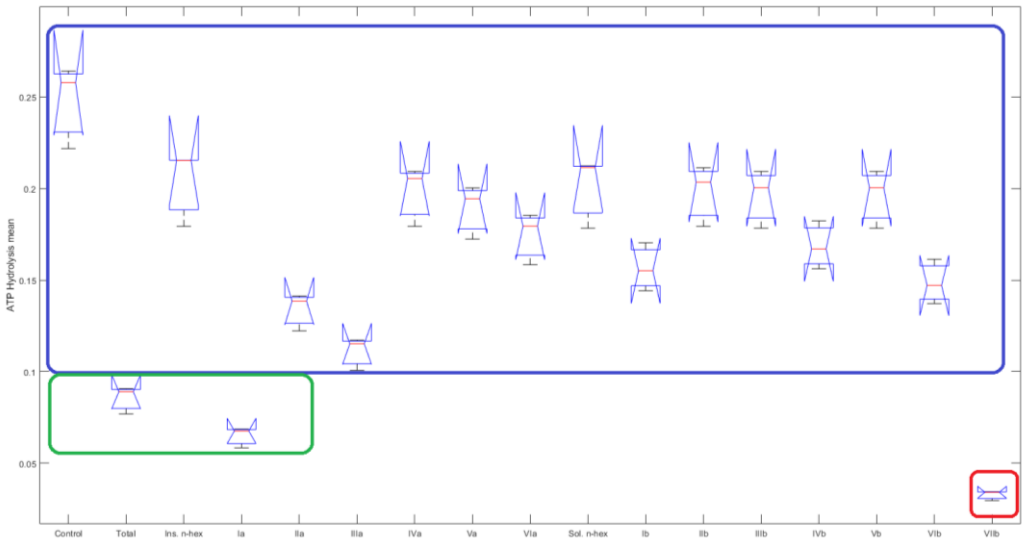


Figure S78. Effect of total extract, n-hexane insoluble and soluble fractions and relative sub-fractions (I_a-VI_a, I_b-VI_b) on ATP hydrolysis activity in rod Outer Segments (OS). ATP hydrolysis by OS (5 µg) in the presence of total extract, n-hexane insoluble and soluble fractions and relative sub-fractions (I_a-VI_a, I_b-VI_b) (80 µg/mL). Positive control: 30 µM resveratrol. Activity is expressed as µmol ATP hydrolyzed/min/mg of total protein. All data were tested with one-way ANOVA (using MATLAB 2019a statistical toolkit), Mean and standard deviation of each measure is presented according to the standards of MATLAB boxplot. The application of Bonferroni method defined 3 groups ($p < 0.05$) indicated by colored rectangles.

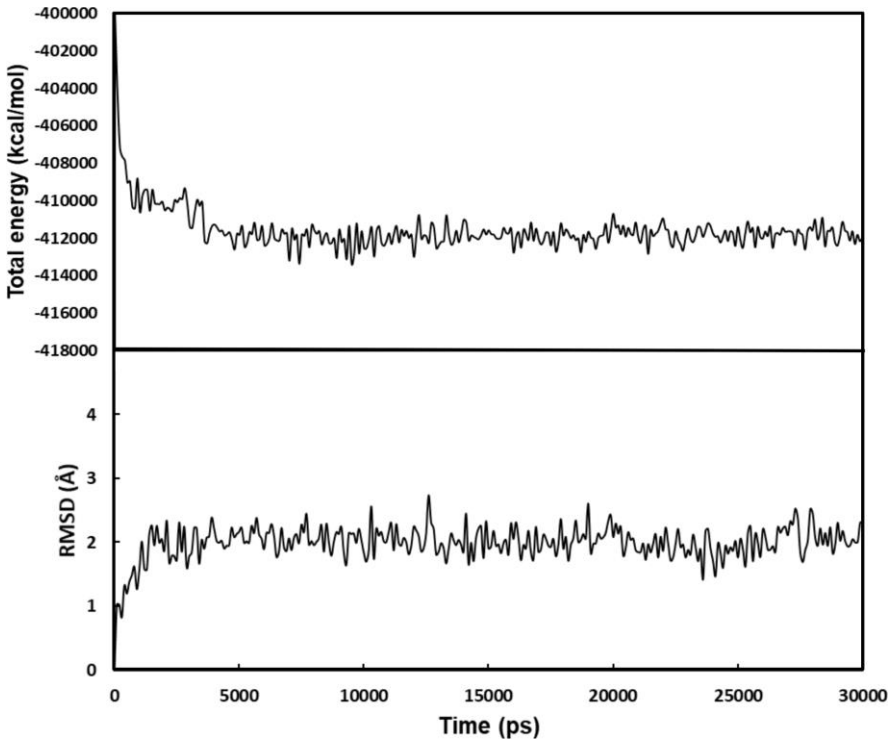


Figure S79. Analysis of the MD simulation of the reference complex (PDB code 2JJ2). In the first plot, the total energy of the system vs. time is reported; the second plot shows the RMSD of the ligand disposition from its crystallographic coordinates during the simulation.

Table S1. MIC values of total extract *n*-hexane insoluble and soluble fractions and relative sub-fractions against representative clinical strains

Microbial strains	**Total extract**	***n*-hexane Insol.**	**I_a**	**II_a**	**III_a**	**IV_a**	**V_a**	**VI_a**	**n-hexane Sol.**	**I_b**	**II_b**	**III_b**	**IV_b**	**V_b**	**VI_b**
E. faecalis MB 1 (VRE)	128	128	>128	>128	>128	>128	>128	>128	>128	>128	128	64	128	>128	>128
E. faecium MB 152 (VRE)	128	>128	>128	>128	>128	>128	>128	>128	128	>128	128	128	64	>128	>128
S. aureus MB 18 (MRSA)	128	128	64	>128	>128	128	128	64	128	>128	>128	128	64	64	>128
S. epidermidis MB 165 (MRSE)	>128	>128	32	64	64	128	64	32	64	>128	>128	128	128	128	>128
S. agalactiae MB 149	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
S. pneumoniae MB 35	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
Proteus mirabilis MB 14	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
E.coli MB123	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
Moraxella catarrhalis MB 15	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
Klebsiella pneumoniae MB 11	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
C. albicans MB796	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128
C. glabrata MB796	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128

MIC values, expressed in µg/mL of total extract, *n*-hexane insoluble and soluble fractions and relative sub-fractions (I_a-VI_a, I_b-VI_b). MRSA: Methicillin resistant *S. aureus*; MRSE: Methicillin resistant *S. epidermidis*; VRE: Vancomycin resistant Enterococcus

Table S2. MM-PBSA results for the three different ligand protein complexes of manool (**17**) bound to F_1-ATPase.

MM-PBSA Method					
	EEL	**VDW**	**ENPOLAR**	**EPB**	**ΔPBSA**
Pose 1	-5.12	-42.61	-4.16	42.75	-9.13
Pose 2	-9.27	-44.18	-4.04	45.37	-12.12
Pose 3	-11.42	-46.52	-3.81	40.36	-21.39

ΔPBSA is the sum of the electrostatic (EEL) and van der Waals (VDW), as well as polar (EPB) and non-polar (ENPOLAR) solvation free energy. Data are expressed as kcal/mol.

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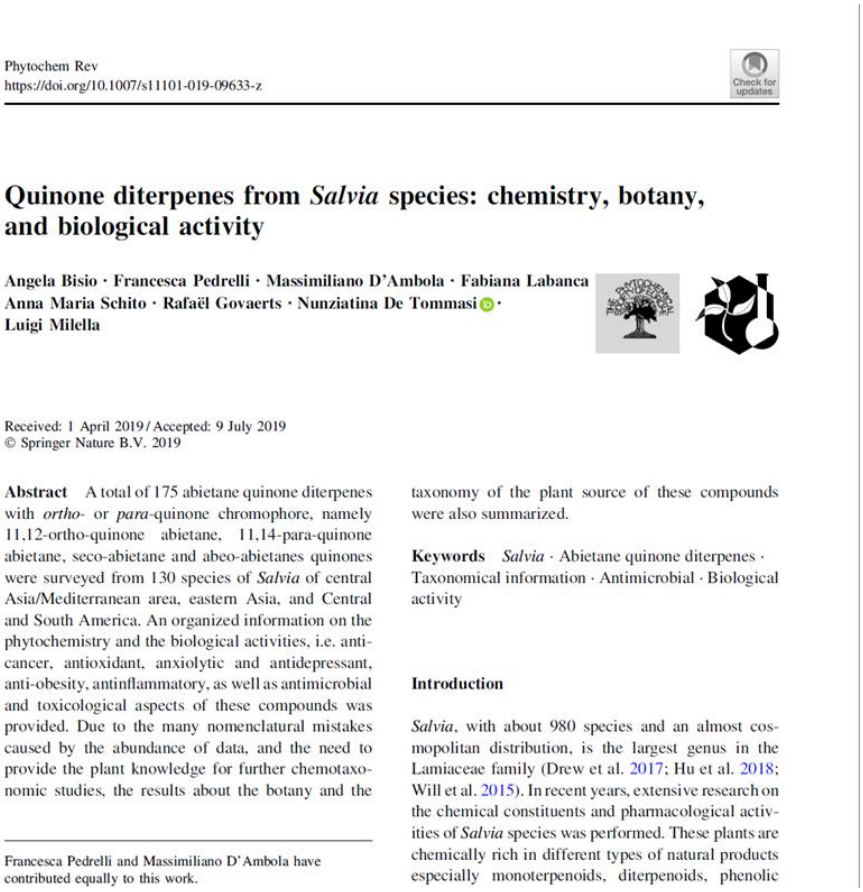

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Quinone diterpenes from *Salvia* species: chemistry, botany, and biological activity

Angela Bisio · Francesca Pedrelli · Massimiliano D'Ambola · Fabiana Labanca · Anna Maria Schito · Rafaël Govaerts · Nunziatina De Tommasi · Luigi Milella

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Abstract A total of 175 abietane quinone diterpenes with *ortho*- or *para*-quinone chromophore, namely 11,12-ortho-quinone abietane, 11,14-para-quinone abietane, seco-abietane and abeo-abietanes quinones were surveyed from 130 species of *Salvia* of central Asia/Mediterranean area, eastern Asia, and Central and South America. An organized information on the phytochemistry and the biological activities, i.e. anti-cancer, antioxidant, anxiolytic and antidepressant, anti-obesity, antinflammatory, as well as antimicrobial and toxicological aspects of these compounds was provided. Due to the many nomenclatural mistakes caused by the abundance of data, and the need to provide the plant knowledge for further chemotaxonomic studies, the results about the botany and the taxonomy of the plant source of these compounds were also summarized.

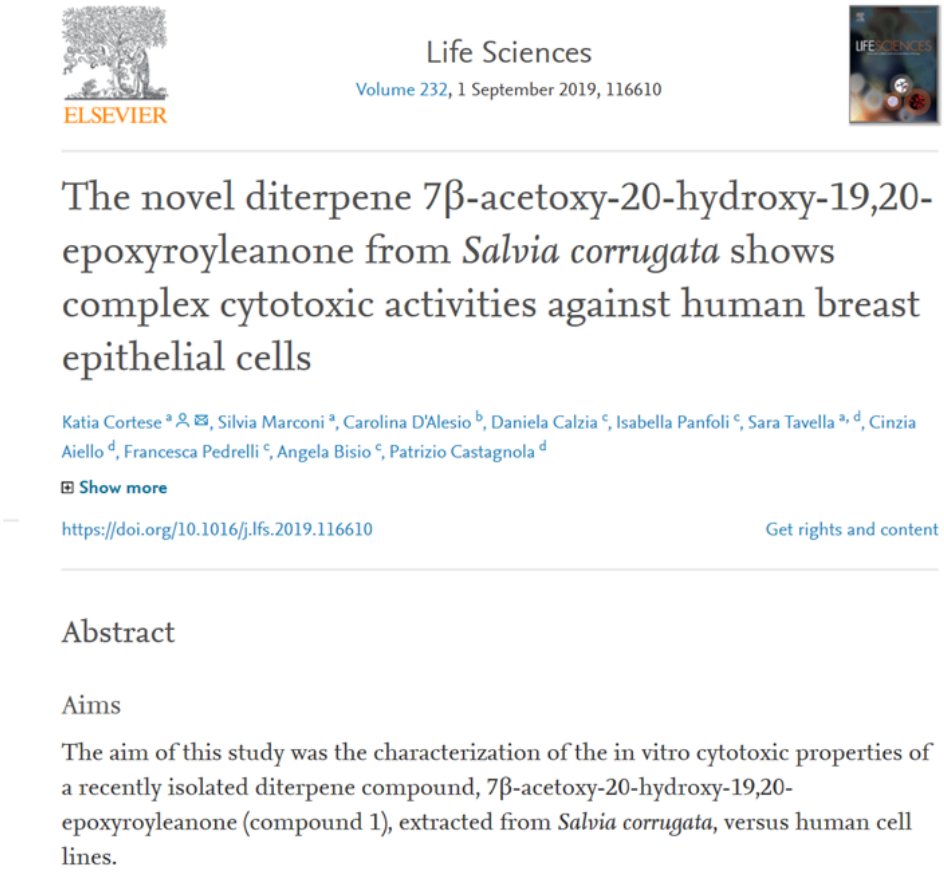
Keywords *Salvia* · Abietane quinone diterpenes · Taxonomical information · Antimicrobial · Biological activity

Francesca Pedrelli and Massimiliano D'Ambola have contributed equally to this work.

Introduction

Salvia, with about 980 species and an almost cosmopolitan distribution, is the largest genus in the Lamiaceae family (Drew et al. 2017; Hu et al. 2018; Will et al. 2015). In recent years, extensive research on the chemical constituents and pharmacological activities of *Salvia* species was performed. These plants are chemically rich in different types of natural products especially monoterpenoids, diterpenoids, phenolic

Fig.14. Work about Quinone diterpenes from *Salvia* species published in 2019 by Phytochemistry Review



Life Sciences
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The novel diterpene 7β-acetoxy-20-hydroxy-19,20-epoxyroyleanone from *Salvia corrugata* shows complex cytotoxic activities against human breast epithelial cells

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Abstract

Aims

The aim of this study was the characterization of the in vitro cytotoxic properties of a recently isolated diterpene compound, 7β-acetoxy-20-hydroxy-19,20-epoxyroyleanone (compound 1), extracted from *Salvia corrugata*, versus human cell lines.

Fig.15. Work about *Salvia corrugata* published in 2019 by Life Sciences