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# Natural products from the hallucinogenic sage

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**ABSTRACT**

*The isolation, structures and biological activity of the neoclerodane and other natural products obtained from the Mexican hallucinogenic sage,* Salvia divinorum *are reviewed.*

**Keywords**: *Salvia divinorum*, salviarins, opioid receptors, clerodanes, diterpenoids

Many of the herbs that are known as 'sages' belong to the genus *Salvia* which are in turn members of the large *Lamiaceae*. (*Labiatae*) family of plants. There are over 900 species of *Salvia* which are found in countries as widespread as China, Brazil, and Mexico as well as in many European countries particularly those around the Mediterannean. The common garden sage, *Salvia officinalis*, is used today as a culinary herb. However it and its relatives have a long history as medicinal plants[1,2]. There are reports in herbals from the sixteenth century of its use as a tonic and for the treatment of various infections. There is an old saying 'He that would live for aye, must eat Sage in May'. The Roman writer, Pliny used the Latin name *Salvia* derived from salvere, to heal, to describe these beneficial plants. Indeed the word 'sage' may have arisen as a corruption of this. *Salvias*, along with other members of the *Lamiaceae*, are noted for the terpenoid natural products which they contain. The volatile monoterpenoid essential oils are responsible for their use as aromatic herbs and some of their monoterpenoids may also contribute to the beneficial properties of the plants. In other cases, it is their diterpenoid content which is of value. A number of members of this genus have attracted attention. Thus the roots of the Chinese species, *S. miltiorrhiza*, are the source of the Chinese traditional medicine, Tan-shen. This contains a series of biologically-active diterpenoid quinones. A recent study[3] of Turkish *Salvia*

species has also revealed the presence of antibacterial diterpenoids some of which also possess cardiovascular activity. The Clary Sage, *S. sclarea*, has medicinal properties and also produces the diterpenoid, sclareol, which is used in the perfumery industry. A number of *Salvia* species are grown as ornamental plants. These include the delicate blue, *S. farinacea* and the bright red *S. splendens* beloved of the Parks and Gardens Departments of many local authorities. Examination of these plants has revealed the presence of diterpenoids amongst their natural product constituents.

*Salvia* species are particularly well-represented in Mexico where over 270 species have been recorded. In recent years, a relatively rare Mexican member of this genus, *S. divinorum*, has attracted interest because a biologically-active diterpenoid component binds selectively to the κ-opioid receptors in the brain[4]. The constituents of this species are the subject of this review. Unlike other *Salvia* species, *S. divinorum*, which grows in the Oaxaca region of Mexico, is used as a hallucinogenic plant[5]. It is known to the Mazatec people by the folk names of 'hojas or ska de la Pastora' or 'hojas de la Maria Pastora'. It may also be the plant known to the Aztecs as 'pipiltzintzintli'. As the name 'hojas' suggests the activity resides in the leaves. These are chewed or the dried leaves are smoked to induce hallucinations and a trance-like state. The effect has a relatively short time scale, reportedly up to an hour, but this was sufficiently long for the plant to be used in ritual divinations. In the last 10 to 15 years, this plant has begun to enter the so-called 'drug culture' as a recreational drug and substance of abuse. Its use is now illegal in some parts of the world.

Successful investigations into the structures of the bio-active components of the plant were first reported in 1982[6]. A diterpenoid neoclerodane structure was assigned to salvinorin A **1** on the basis of X-ray crystallographic and spectroscopic measurements. Its absolute stereochemistry was established in 1990[7]. An independent study of the plant was also reported in 1984[8] and in which the major components were described as divinorin A and B. These compounds were shown to be the same as salvinorins A and B and hence the divinorin name for them was dropped.

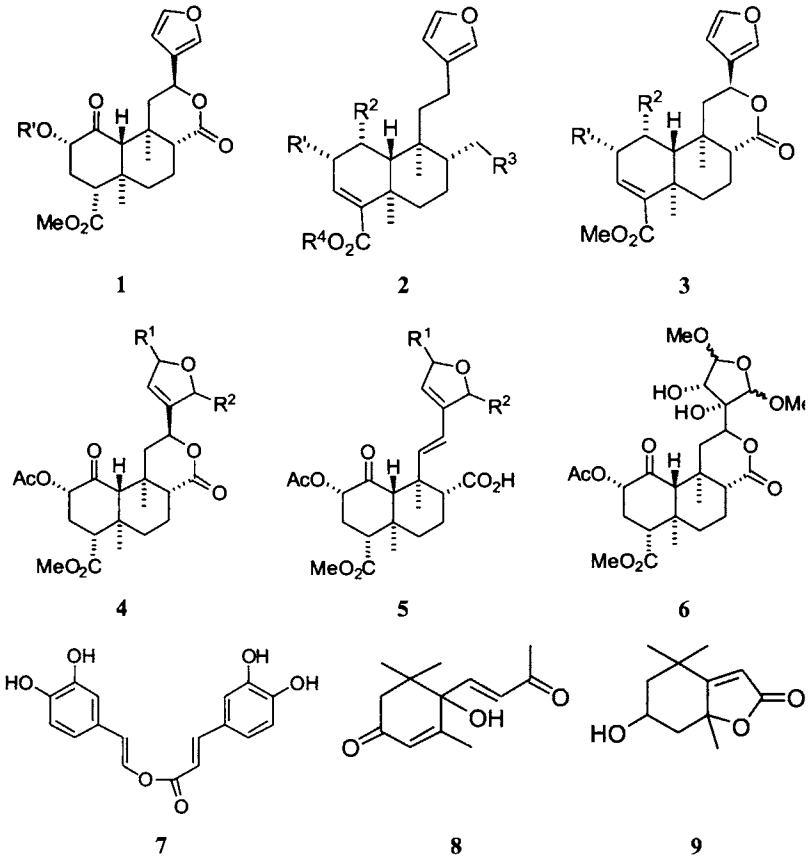
Natural products with the neoclerodane carbon skeleton are quite common constituents of *Salvia* species[9]. They belong to a much bigger group of natural products known as the diterpenoids which are niosynthesized from four $C_5$-isoprene units. The clerodane carbon skeleton is derived by a rearrangement of a bicarbocyclic group of diterpenoids known as the labdanes. The clerodane carbon skeleton of natural product was proposed for the first time in 1956[10]

for columbin, a bitter principle from the Colombo root (*Jatorrhiza palmata*). However, the name for this class of compound is derived from clerodin, a bitter principle obtained from the bark of the Indian Bhat tree, *Clerodendron infortunatum*. The structure of this compound was established in 1961 as a result of a combination of chemical degradation, spectroscopic measurements and X-ray crystallography[11,12]. Although these studies led to the correct relative stereochemistry of clerodin, the absolute stereochemistry was subsequently changed[13] because an analogy which was used in the original study, proved to be unreliable. The term neoclerodane was introduced to denote those natural products whose carbon skeleton has the same absolute stereochemistry as that assigned to clerodin in this 1979 revision. Those with the opposite absolute stereochemistry are known as 'ent-neoclerodanes'.

Over the last 50 years approximately a thousand natural products have been isolated with the neoclerodane carbon skeleton. They have been found in many families of plants including the *Lamiaceae*, the *Verbenaceae*, the *Euphorbiaceae* and the *Compositae* (*Asteraceae*). Neoclerodanes occur with either a *trans*- or a *cis*-A/B ring junction. A number, particularly from *Ajuga* and *Teucrium* species[14] have been studied because they possess insect anti-feedant activity. Structure : activity studies have been carried out in this context. However, *S. divinorum* remains the sole source of neoclerodanes with hallucinogenic activity. It is interesting to note that the Mazatec people only select those leaves which are free from insect damage to use in divinations.

The first clerodane to be isolated from a *Salvia* species was obtained in 1973 from a South American sage, *S. rubescens*[15] although its stereochemistry was not established at the time. The structure and stereochemistry of salviarin[16] and splendidin[17] from *S. splendens* were established in 1978 and 1979 respectively.

A comparison between the strategies used in the elucidation of the structure of clerodin in 1961 with those used in the study of salvinorin A in 1982 and the salvidins in 2006[18] reveals the impact of nuclear magnetic resonance spectroscopy on structural studies. In 1961 the application of NMR to structure determination was in its infancy. The main structural conclusions concerning clerodin were drawn from chemical degradation which was supportd by the $^{1}$H NMR evidence and confirmed by X-ray crystallography. In 1982, $^{13}$C and $^{1}$H NMR methods were used to identify particular carbon atoms and their substituents. The overall structure was again established by X-ray crystallography. In contrast in 2006 $^{13}$C and $^{1}$H NMR data were used to not only identify particular functiona-




1 2 3

4 5 6

7 8 9

lized carbon atoms but two-dimensional methods were also used to establish connectivities between several atoms and thus to establish substantial part structures.

The biological activity of salvinorin A has led to a very thorough investigation into the constituents of *S. divinorum*. Over 20 compounds with the neoclerodane carbon skeleton have been isolated[18–23]. Their structures are shown in Table 1. The simplest is hardwickiic acid. They can be divided into the salvinorins which possess the 17 →12 δ-lactone ring, the divinatorins which lack this ring, the salvidivins in which the furan ring is oxidized to a γ-hydroxybutenolide and the salvinicins in which this ring is oxidized to a dihydroxydimethoxy-tetrahydrofuran. In examining these structures, it is possible to see a biosynthetic sequence from hardwickiic acid through the divinatorins to the salvinorins and then to the salvidivins and salvinicins with hydroxylation at C-1 preceding that

***Table 1*** *Natural products from* Salvia divinorum

| Compound | Structure | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|---|
| Salvinorin A | 1 | Ac | | | |
| Salvinorin B | 1 | H | | | |
| Hardwickiic acid | 2 | H | H | H | H |
| Divinatorin A | 2 | H | OH | H | H |
| Divinatorin B | 2 | H | OH | OH | Me |
| Divinatorin C | 2 | H | H | OAc | H |
| Divinatorin D | 2 | H | OH | OAc | Me |
| Divinatorin E | 2 | H | OH | =O | Me |
| Divinatorin F | 2 | OH | OH | OH | Me |
| Salvinorin C | 3 | OAc | OAc | | |
| Salvinorin D | 3 | OH | OAc | | |
| Salvinorin E | 3 | OAc | OH | | |
| Salvinorin F | 3 | H | OH | | |
| Salvinorin G | 3 | =O | OAc | | |
| Salvinorin H | 3 | OH | OH | | |
| Salvinorin 1 | 3 | OH | OH | (δ-lactol in place of lactone) | |
| Salvidivin A | 4 | =O | OH | | |
| Salvidivin B | 4 | OH | =O | | |
| Salvidivin C | 5 | =O | OH | | |
| Salvidivin D | 5 | OH | =O | | |
| Salvinicin A | 6 | β-OMe | β-OMe | | |
| Salvinicin B | 6 | α-OMe | α-OMe | | |
| Nepetoidin B | 7 | | | | |
| Dehydrovomifoliol | 8 | | | | |
| Loliolide | 9 | | | | |

at C-17. Hydroxylation at C-2 and acetylation appears to take place at both the divinorin and salvinorin level. Oxidation of the furan ring is a final step. The lactols dimethylethers which replace the furan ring of the salvinorins may arise by the addition of oxygen to the furan followed by fragmentation or reduction of the adduct. In a sequence of this kind, there are some missing links and it is likely that a few more clerodanes of this type will be found in *S. divinorum*. Although not unique, the clerodanes from *S. divinorum* differ from many other *Salvia* clerodanes by having a C-18 methyl ester rather than an 18 → 19 γ-lactone ring.

Amongst the other natural products that have been isolated is nepetoidin B[18,24]. This is the caffeic acid ester of the enol of 3,4-dihydroxyphenyl-acetaldehyde. It is a powerful anti-oxidant and its hydrolysis and degradation products have also been detected. It is a characteristic metabolite of some subfamilies of the *Lamiaceae* and may have taxonomic significance. The lactones, loliolide and isololiolide[25] which have ant-repellant activity have also been

isolated along with dehydrovomifoliol, methyl caffeate and 3,4-dihydroxybenzaldehyde.

Simplified chromatographic methods have been described[20] for the isolation of salvinorin A from *S. divinorum*. Because of the use of this substance as a drug of abuse, chromatographic and mass spectroscopic methods for its detection in biological fluids have also been described[26].

Salvinorin A is a very powerful hallucinogenic substance. It has been estimated that a human response is observed with between 200 μg and 1 mg of material. A major stimulus to the work on salvinorin A came from the demonstration that it selectively binds to the κ-opioid receptor in the brain[4]. The major activities of the opioids (drugs with a morphine-like action on the central nervous system) are mediated by four families of receptor in the central nervous system. These are denoted as the μ, κ, σ and δ receptors and are distinguished from each other by the drugs which bind to them and the responses which they produce. Salvinorin A has a completely different structure to the other opioids. It does not contain nitrogen and has a different carbon skeleton and functionality. Consequently in the search for novel non-addictive analgesics, it has provided the starting point for structure: activity studies. Over the last 10 years, work in this area has burgeoned.

Modifications of salvinorin A for structure : activity studies have concentrated on variations of the chemically accessible functional groups. Recently, this work has been thoroughly reviewed[27]. Several hundred analogues have been examined. Various aspects of the chemistry of salvinorin A have been explored in this context[28–35] including the hydrolysis of the esters, epimerization of C-8 and the autoxidation of ring A to a diosphenol and its cleavage to a dicarboxylic acid. The oxidation, reduction and removal of the furan ring has also been examined. The modifications of ring A have concentrated on the 2α-acetoxy-1-ketone and the C-4 carbomethoxy group. Other changes have involved the δ-lactone ring attached to ring B and the furan ring. Whilst a number of these changes are tolerated and do not destroy the activity in terms of binding to and the response of the κ-opioid receptor, relatively few enhance the activity compared to the natural product. An interesting change was the replacement of the 2α-acetate with a 2α-benzoate to give a compound called herkinorin. This analogue had a decreased affinity for the κ-opioid receptor and an increased affinity for the μ-opioid receptor. Another interesting variation involved replacement of the 2α-acetate with a methoxymethyl group which led to an enhanced affinity for the κ-opioid receptor[34].

The 2α-stereochemistry was important for activity. Removal of the C-1 carbonyl group led to a reduction in activity. Reduction of the C-4 ester to an alcohol and hydrolysis to the acid also led to a loss of activity. Although changes at C-17 had little effect on binding they appeared to reduce the activity. On the whole, replacement of the furan ring[30,35] had a negative effect on the affinity. These studies have not only made use of the neoclerodanes obtained from *S. divinorum* but also of compounds that have been obtained by the modification of ring A of the neoclerodanes isolated from *S. farinacea*[36] and *S. splendens*[37,38]. However, none of these compounds showed any binding affinity for the κ-opioid receptor possibly because of the presence of the C-18 →C-19 lactone ring and the fact that the furan ring has a different configuration compared to the rest of the structure. The outcome of these structure:activity studies was to reveal the importance of the furan ring, the 2α-acetoxyl group and the C-4 carbomethoxy group of salvinorin A for binding and activity. Isotopically labelled samples of salvinorin A have been prepared[39].

Several studies on the mode of binding of salvinorin A to the κ-opioid receptor have been reported[40,41]. These implicate hydrophobic and hydrogen bonding interactions with specific amino acids rather than the salt-like binding associated with the nitrogen of the morphine series. These involve interactions between key tyrosine side chains and the acetoxyl and furan residues and between the methyl ester and specific isoleucine and glutamic acid side chains.

A consequence of the interest in the biological activity of salvinorin A has been its total synthesis[42,43]. The structure with its multiplicity of adjacent chiral centres represents a serious challenge. In one asymmetric synthesis, the creation of the tricyclic core of salvinorin A was achieved by a transannular Michael reaction of a macrocyclic bisenone. A number of approaches to the carbon skeleton have also been reported. Studies on the biosynthesis of salvinorin A have also commenced. There are two main pathways leading to the biosynthesis of the isoprene unit of the terpenoids. The best known of these utilizes mevalonic acid and has been found in animals, fungi and some plants. More recently another pathway based on 1-deoxyxylulose has been identified in higher plants. It has been shown[44] that the isoprene units of salvinorin A are formed by this pathway.

In conclusion, salvinorin A joins a growing list of biologically interesting diterpenoid natural products. This list includes compounds such as vitamin A, the gibberellin plant hormones, tumour inhibitory substances such as Taxol® and aphidicolin, the

anti-AIDS compound prostatin, the cardioactive forskolin and many others. It suggests that this family of natural products are worthy of more thorough evaluation.

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