



## Minireview

Psychopharmacology of the hallucinogenic sage *Salvia divinorum*

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## Abstract

At present, the Mexican mint *Salvia divinorum* is an unregulated hallucinogen. This has resulted in various on-line botanical companies advertising and selling *S. divinorum* as a legal alternative to other regulated plant hallucinogens. It is predictable that its misuse will increase rapidly. The active ingredient in *S. divinorum* is the neoclerodane diterpene, salvinorin A (**1a**), which has been shown to be a  $\kappa$  agonist both in vitro and in vivo. This review will cover the current state of research into the psychopharmacology of *S. divinorum*.

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## Introduction

Of the almost 1000 species of *Salvia* in the world, none has fired the imagination as much as *Salvia divinorum* Epling and Játiva-M (Reisfield, 1993). *S. divinorum* is a plant from the Sage family that has been used in traditional spiritual and ethnopharmacological practices by the Mazatec Indians of Oaxaca, Mexico to produce “mystical” or hallucinogenic experiences (Váldes III et al., 1983). The western world first learned of this species in 1962 when Epling and Játiva-M described the plant from specimens collected by Hofmann and Wasson (Hofmann, 1980). The plant was named *S. divinorum* after its use in divination by the Mazatec Indians. Other native uses for the plant include

the treatment of diarrhea, headache, and rheumatism. In addition, the plant is used to treat a semi-magical disease known as panzón de barrego, or swollen belly, which is caused by a curse from an evil sorcerer (Váldes III et al., 1983). *S. divinorum* leaves or fortified extracts, have recently become increasingly available in the United States through numerous internet suppliers. The DEA has recently placed it on the list of drugs of concern (National, 2003). Young adults have begun to smoke the leaves and leaf extracts of the plants recreationally to induce powerful hallucinations (Hazelden, 2004). Currently, *S. divinorum* is unregulated in most countries and available throughout the world over the internet. It is, however, listed as a controlled substance in Denmark, Australia, and Italy. To date, U.S. laws for controlled substances do not ban the use of *S. divinorum* or its active components. This has resulted in many internet companies advertising and selling *S. divinorum*-derived products as legal hallucinogens.

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The active constituent in *S. divinorum* is the neoclerodane diterpene salvinorin A (**1a**) (Fig. 1) (Siebert, 1994; Váldes, 1994). A smoked dose of 200 to 500  $\mu\text{g}$  in humans produces profound hallucinations lasting approximately 1 h (Siebert, 1994; Váldes III et al., 2001). Thus, it has a potency in humans that is similar to the highly active synthetic hallucinogen LSD (Sheffler and Roth, 2003).

Curiously, **1a** does not act at the presumed molecular target responsible for the actions of classical hallucinogens, the serotonin 5-HT<sub>2A</sub> receptor (Egan et al., 1998; Glennon et al., 1984; Nichols, 2004). An initial pharmacological screen using a NovaScreen™ protocol was unsuccessful in identifying the molecular target for the hallucinogenic activity of **1a** (Siebert, 1994). A more recent screening protocol identified the molecular target of **1a** to be the  $\kappa$  opioid receptor (Roth et al., 2002). Additional studies have shown **1a** to be a potent and selective and highly efficacious  $\kappa$  agonist in vitro and in vivo (Butelman et al., 2004; Chavkin et al., 2004; Roth et al., 2002).

### Chemistry

*S. divinorum* is a relatively rare plant and few chemical studies have characterized its components. The first compounds isolated from *S. divinorum* were the neoclerodane diterpenes salvinorin A (**1a**) and salvinorin B (**1b**) (Ortega et al., 1982; Váldes et al., 1984). Prior to this report, Valdés III was working on the isolation and characterization of the psychoactive substance from *S. divinorum* (Váldes III, 1983). Infusions of the plant had been shown to possess psychotropic activity (Váldes III et al., 1983) but the component responsible for this activity and its mechanism of action were not known.

Having ascertained the active component to be a terpenoid, efforts were initiated by Valdés III to identify the molecular target of this compound. These efforts were largely unsuccessful. A manuscript describing the isolation of the psychotropic terpenoid, divinorin A and its congener divinorin B, was then submitted to the *Journal of Organic Chemistry*. Comparison of the structures of divinorin A and divinorin B with **1a** and **1b** isolated by Ortega et al. found these compounds to be identical. Therefore, divinorin A and B are now called salvinorin A and B, respectively. Later work by Valdés isolated another neoclerodane diterpene salvinorin C (**2**). However, it has been suggested that **2** has no psychotropic activity (Siebert, 2004). Additional neoclerodane diterpenes, salvinorin D–F (**3–5**) and divinorins A–C (**6–8**) have been isolated (Bigham et al., 2003; Munro and Rizzacasa, 2003). Further phytochemical investigations in the author's laboratory have identified salvinicin A (**9**) and B (**10**) (Harding et al., 2005, in press). Furthermore, various neoclerodanes have been prepared semi-synthetically (Beguin et al., 2005; Harding et al., 2005; Munro et al., 2005).

Currently, there are no radioligands or pharmacological tools of the salvinorin A chemotype. However, a deuterium labeled analog of salvinorin A (**1c**) and its utility as an internal standard for the detection of **1a** and its metabolites in biological fluids by LC-MS has been described (Tidgewell et al., 2004).

### Pharmacology

As mentioned earlier, **1a** was found to be a potent  $\kappa$  agonist in vitro (Roth et al., 2002). Using a screen of 50 receptors, transporters, and ion channels, **1a** showed a distinctive profile

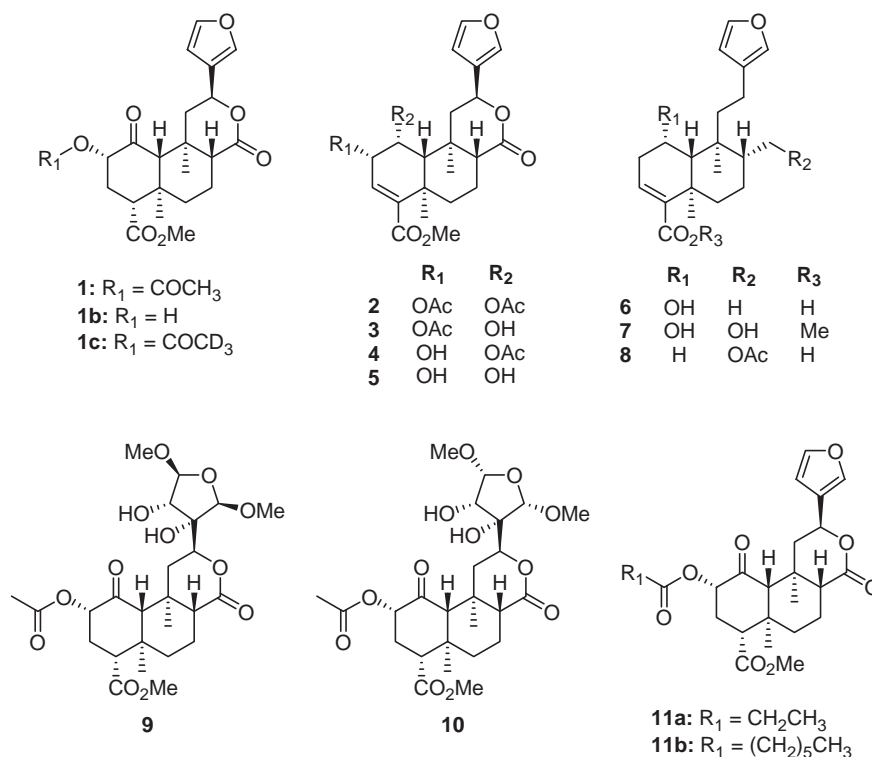


Fig. 1. Structures of salvinorin A (**1a**), salvinorin B (**1b**) and related analogues **2–11**.

that was different than the classical hallucinogen, lysergic acid diethylamide (LSD). Functional studies also demonstrated that **1a** is a potent and selective  $\kappa$  opioid agonist at both cloned  $\kappa$  opioid receptors expressed in human embryonic kidney-293 cells and native  $\kappa$  opioid receptors expressed in guinea pig brain.

There has been only one report of behavioral testing of **1a** in nonhuman primates (Butelman et al., 2004). All subjects ( $n=3$ ) dose-dependently exhibited over  $\geq 90\%$  U69,593-appropriate responding after subcutaneous injection of **1a** (0.001–0.032 mg/kg). Quadazocine (0.32 mg/kg), a  $\kappa$  selective opioid antagonist, blocked the effects of **1a**. However,  $\kappa$  selective antagonist GNTI (1 mg/kg; 24 h pretreatment) did not cause significant antagonism of the effects of **1a** (GNTI, under these conditions, was only effective as an antagonist in two of three monkeys). Therefore, **1a** produces discriminative stimulus effects similar to those of a high efficacy  $\kappa$  agonist. Interestingly, ketamine (0.1–3.2 mg/kg) was not generalized by any subject. This work indicates that not all compounds that produce hallucinogenic or psychotomimetic effects in humans are generalized by subjects trained to discriminate U69,593.

Presently, few studies have been initiated to more fully understand the remarkable selectivity of **1a** for  $\kappa$  opioid receptors. This is the first example of a nonnitrogenous opioid selective ligand. Given its unique structure, its mode of interaction with the  $\kappa$  opioid receptor is not clear. A recent report explored the role of the 2-acetyl group of **1a** on affinity

and selectivity for  $\kappa$  opioid receptors (Chavkin et al., 2004). Structural modification of this position resulted in a change in activity from a full agonism to partial agonism for inhibition of forskolin-stimulated cAMP production. In particular, **1a** was found to be a full agonist while propionate **11a** and heptanoate **11b** were found to be partial agonists in this assay (Chavkin et al., 2004). Surprisingly, **1a** was found to be more efficacious than the selective  $\kappa$  agonist U50,488 and similar in efficacy to the naturally occurring peptide ligand for  $\kappa$  receptors, dynorphin A.

Recently, several analogues of **1a** were evaluated for affinity at  $\kappa$  opioid receptors (Harding et al., in press–a,b; Munro et al., 2005). Salvinorin C (**2**) was found to have 250-fold lower affinity compared to **1a** ( $K_i=1022$  nM vs.  $K_i=4$  nM) whereas **3** and **4** were found to have no affinity for  $\kappa$  receptors ( $K_i>10,000$  nM) (Munro et al., 2005). Additional work found that reduction of the furan ring (**12**) (Fig. 2) reduced affinity for  $\kappa$  receptors compared to **1a** ( $K_i=156$  nM vs.  $K_i=4$  nM). Removal of the lactone carbonyl (**13**) was found to have little effect on binding compared to **1a** ( $K_i=6$  nM vs.  $K_i=4$  nM). Reduction of the ketone to an  $\alpha$ -alcohol (**14**) reduced affinity over 250-fold compared to **1a** ( $K_i=1125$  nM vs.  $K_i=4$  nM). Removal of the ketone (**15**) resulted in a 5-fold loss of affinity compared to **1a** ( $K_i=18$  nM vs.  $K_i=4$  nM). Finally, the C-8 epimer of **1a** (**16**) was found to have 41-fold lower affinity for  $\kappa$  receptors compared to **1a** ( $K_i=163$  nM vs.  $K_i=4$  nM). Interestingly, benzoyl derivative **17** was found to

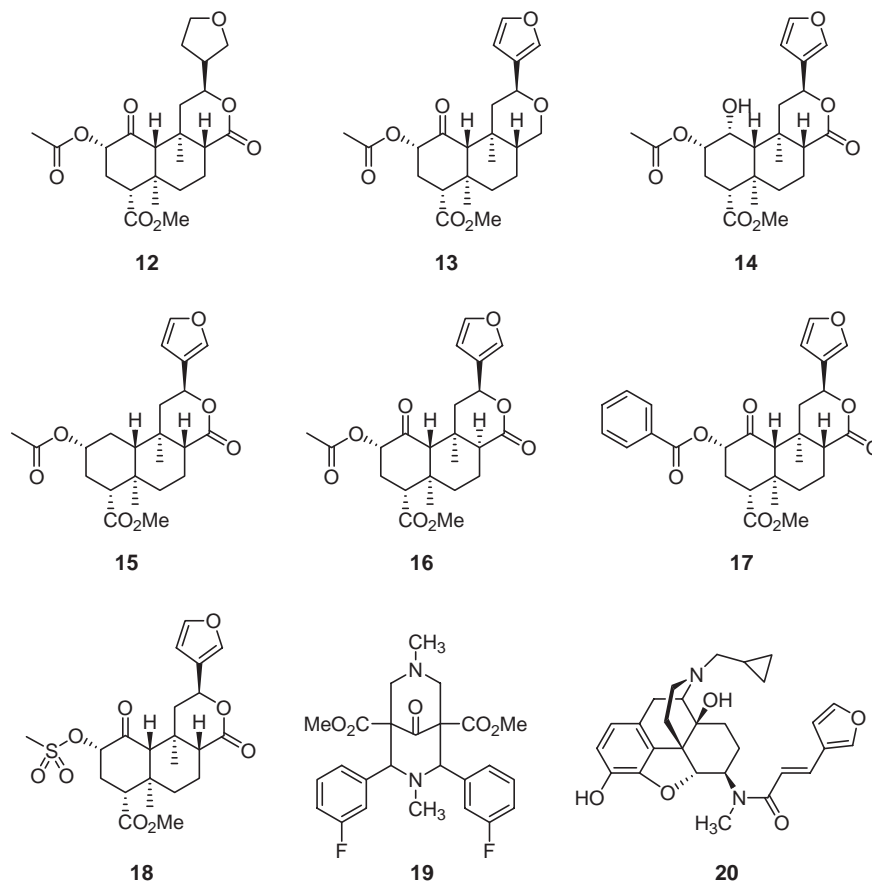


Fig. 2. Structures of salvinorin A analogues (**12–18**) and 3FLB (**19**), and TRK-820 (**20**).

be the first example of a nonnitrogenous  $\mu$  opioid receptor agonist (Harding et al., in press–a,b). In addition, mesylate **18** was found to be more potent as an agonist at  $\kappa$  receptors compared to **1a**.

The pharmacological activity of **1a** was compared to two other structurally distinct  $\kappa$  ligands, 3FLB (**18**) and TRK-820 (**19**) (Wang et al., 2005). Binding affinities using [<sup>3</sup>H]diprenorphine at  $\kappa$  receptors were in the order of **19** ( $K_i=75$  pM) > **1a** ( $K_i=7.9$  nM) > ( $K_i=248$  nM). All compounds were found to be full agonists in the [<sup>35</sup>S]GTP- $\gamma$ -S binding assay in the order of **19** ( $EC_{50}=25$  pM) >> **1a** ( $EC_{50}=2.2$  nM) > **18** ( $EC_{50}=73.6$  nM). Interestingly, **1a** was found to be 40-fold less potent in promoting internalization of the hKOR compared to U50,488 and showed little anti-scratching activity and no antinociception in mice (Wang et al., 2005). It has been speculated that the divergence between the in vivo and in vitro effects of **1a** may be due to in vivo metabolism of **1a** to metabolites that are inactive at the  $\kappa$  opioid receptor (Wang et al., 2005). Another possibility for the discrepancies is that **1a** may be interacting with additional receptors, ion channels, and/or transporters.

Recently, systemic administration of **1a** has been found to elevate intracranial self-stimulation levels (ICSS) in rats (Todtenkopf et al., 2004). This depressive-like effect was found to be qualitatively similar to the systemic administration of U69,593. Pretreatment with the selective  $\kappa$  opioid antagonist ANTI (5<sup>l</sup>-acetylamidinoethylnaltrindole) dose dependently blocked elevations in ICSS threshold effects. This finding then suggests that stimulation of  $\kappa$  receptors in rats triggers depressive-like signs in a behavioral model.

### Toxicology

The potential toxicity and metabolism of **1a** has not been fully investigated in laboratory animals or humans. An initial study examined the potential toxicity of **1a** in rodents (Mowry et al., 2003). This study showed that little to no toxicity associated with high doses of **1a** in mice. However, the study was carried out for only two weeks. No significant histologic differences between the control mice and the ones treated with doses of **1a** were found. However, this does not mean that potential toxicities do not exist.

Presently, the identity of the metabolites of **1a** are not definitely known. It was suggested that **1b** is a metabolite of **1a** (Roth et al., 2004; Valdés et al., 2001). However, there are few analytical methods to study the routes of metabolism of **1a** in vitro or in vivo. One method for determining the concentration of **1a** in human and rhesus monkey plasma, rhesus monkey cerebrospinal fluid, and human urine by negative ion LC-MS/APCI has recently been described (Schmidt et al., 2005a). The fully validated method had a lower limit of detection using FDA guidelines of 2 ng/mL for 0.5 mL plasma samples; the linear range was from 2–1000 ng/mL. Several derivatives in the salvinorin family can also be analyzed by this method. The method has been used to establish that **1b** is the principal metabolite of **1a** ex vivo. However, **1b** was not found in significant amounts in plasma of nonhuman primates. A

preliminary study indicated that the elimination half-life of **1a** in nonhuman primates was found to be  $56.6 \pm 24.8$  min for all subjects tested (Schmidt et al., 2005b).

### Conclusion

*S. divinorum* is an unregulated hallucinogenic plant whose use is increasing. The active component of *S. divinorum* is the neoclerodane diterpene salvinorin A (**1a**). In vitro pharmacological studies have found **1a** to be a potent and selective  $\kappa$  agonist in vitro. In vivo studies indicate that **1a** produces discriminative stimulus effects similar to those of a high efficacy  $\kappa$  agonist. However, there are discrepancies between the in vitro and in vivo effects of **1a**. Preliminary structure activity relationship data has suggested that the 2-position is critical for  $\kappa$  opioid receptor binding and activation. Toxicological studies have not identified significant differences in histology between the control mice and the ones treated with doses of **1a**. However, this does not rule out the possibility that toxicities do exist. Currently, the metabolites of **1a** are not definitively known, however, the half-life of **1a** in nonhuman primates is  $56.6 \pm 24.8$  min. The body of knowledge of *S. divinorum* continues to grow and has the potential to identify novel opioid receptor modulators and give greater insight into opioid receptor mediated phenomena.

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