

## Neoclerodane Diterpenes as Potential Drug Abuse Therapeutics

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**Purpose:** *Salvia divinorum* is gaining popularity as a legal recreational drug in the United States and Europe. The main active component of the hallucinogenic sage is salvinorin A, a neoclerodane diterpene that has been shown to be a selective and potent  $\kappa$ -opioid receptor agonist. Currently however, there is little research into the detailed pharmacokinetic and pharmacodynamic properties of *Salvia divinorum*, as well as both short and long-term effects of its use.  $\kappa$ -Opioid agonists have been shown to antagonize the effects of CNS stimulants by modulating the level of dopamine in the brain.  $\kappa$  Antagonists possess utility in the treatment of opioid dependence and have been shown to have anti-depressant activity as well as block stress-induced behavior responses. Salvinorin A thus represents not only a potential drug of abuse but also a possible route for the creation of novel therapeutics for stimulant and opioid dependence.

**Methods:** Initially, we set out to optimize the extraction of salvinorin A from *Salvia divinorum* leaves in order to synthesize and evaluate analogues of salvinorin A. For the isolation of salvinorin A, we have modified existing procedures and increased the bio-yield to approximately 7.5 g from 1.5 kg of dried leaves. Analogues were synthesized and tested for opioid receptor affinity using [<sup>125</sup>I]-IOXY and activity using the [<sup>35</sup>S]-GTP $\gamma$ S assay.

**Results:** We have prepared analogues with similar binding affinity at  $\kappa$ -opioid receptors and also prepared a non-nitrogenous ligand possessing  $\mu$ -opioid receptor affinity. In addition, we synthesized a deuterated analogue that allows for LC-MS detection of salvinorin A and its metabolites in biological fluids.

**Conclusions:** The ability to detect salvinorin A in body fluids will allow for the future determination of a metabolic pathway. In addition, analogues with high affinity and selectivity will be further optimized as potential therapeutics.

