DUAL AFFINITY TO OPIOID RECEPTORS

From potent hallucinogenic salvinorin A to promising analgesic AK-1401

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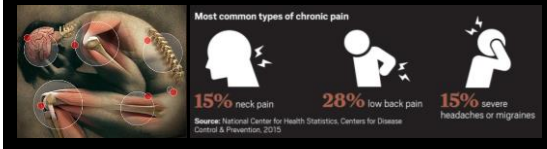
Participants in the Neuroscience Research Program (NRP) Workshop 'Opiate Receptor Mechanisms' in Boston, MA, USA on 19-21 May 1974.
The workshop was proposed by Frederic Worden, NRP Director.

Solomon H. Snyder and Gavril W. Pasternak. *Trends Pharmacol. Sci*., **2003**, *24 (4)*, 198-205

Some statistics about pain



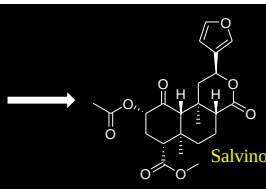
- Approx. 1.5 billion people suffer from pain globally, 100 million in USA
- Approximately 77% suffering people report feeling depressed, 70% report trouble concentrating, 59% report an impact on the enjoyment of life
- Estimated cost of the impact of chronic pain in the US considering health care, lost wages and productivity is approx. $560-635 billion annually.

Sources: Institute of Medicine National Academies, 2011, American Pain Foundation, 2006 and Global Industry Analysts Inc., 2011

Friderich Sertörner (1783-1841)

- 1805 - isolated pure crystalline morphine from opium
- tested his compound on mice, dogs and his friends
- results were not conclusive and confusing, due to the overdose of the drug

Salvia divinorum (Labiatae)

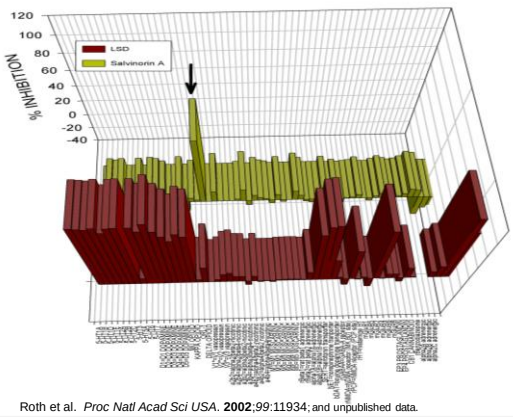


Salvinorin A

Major active metabolite of *Salvia divinorum* (av. 0.2%)

- neoclerodane diterpenoid
- most potent natural dissociative hallucinogen
- selective, high affinity KOP receptor agonist

- Effective dose 200 μg (when smoked) similar in potency to LSD
- Still not regulated federally in the United States, illegal in 31 states.
- Currently banned in 21 countries.



Roth et al. *Proc Natl Acad Sci USA*. **2002**;*99*:11934; and unpublished data.

Therapeutic potential of KOP receptor ligands:

KOP receptor agonists:
- non-addictive analgesics
- drug abuse (reduce some effects of cocaine)
- bipolar disorders
- mania

KOP receptor antagonists:
- treatment of depression (anhedonia, dysphoria and despair)
- potential anxiolytics

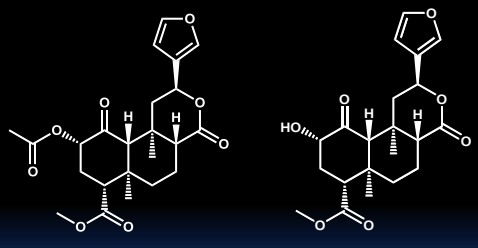
Biological activity of salvinorin A:

- antinociceptive
- antipruritic
- antidiarrheal
- anxiolytic
- anti-addiction (cocaine)
- antidepressive
- neuroprotective against brain damage
- sedative and dysphoric

Current status of salvinorin A research

- Over 500 papers and patents published
- Several hundreds of derivatives and analogs described
- Most of all functional groups were modified

Nature's Structure-Activity Relationship



salvinorin A

active

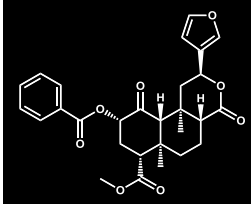
K_i = 2.3 nM

salvinorin B

inactive

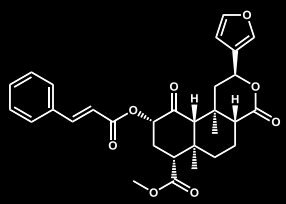
K_i = >10,000 nM

A number of compounds with modified side chain at C2 were obtained



Herkinorin

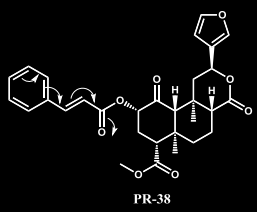
KOP K_i = 90 nM [salv A 1.7 nM]
MOP K_i= 12 nM
DOP K_i= 1170 nM



PR-38

KOP K_i = 9.6 nM [salv A 1.7 nM]
MOP K_i= 52 nM
DOP K_i= 700 nM

Advantage of extended conjugation



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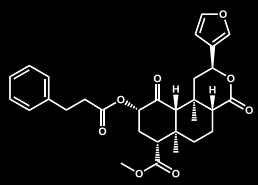
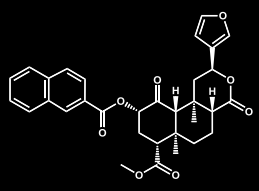
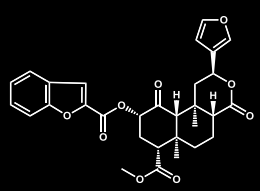


KOP K_i = 180 nM [salv A 1.9 nM]
MOP K_i = 280 nM
DOP K_i = 9330 nM

Conjugated bond as a part of aromatic or heteroaromatic ring

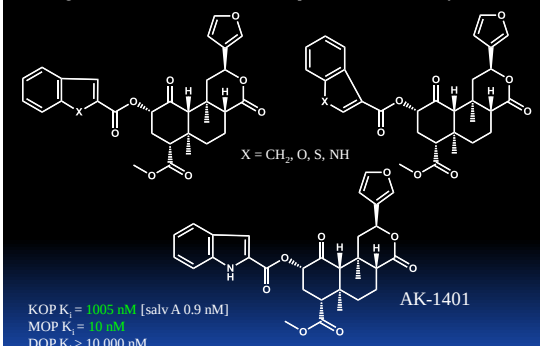


KOP K_i = 5490 nM [salv A 1.9 nM]
MOP K_i = 180 nM
DOP K_i > 10,000 nM



KOP K_i = 70 nM [salv A 1.9 nM]
MOP K_i = 10 nM
DOP K_i = 580 nM

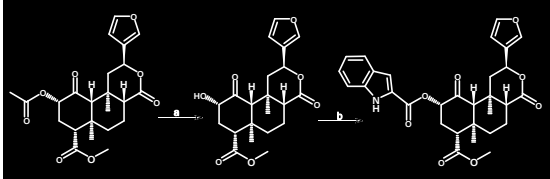
All eight aromatic and heteroaromatic compounds with fused 6,5-system were made



AK-1401

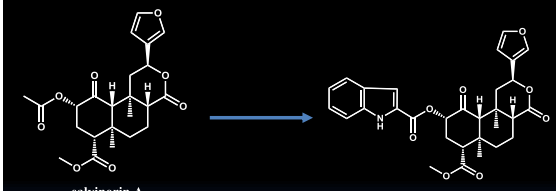
KOP K_i = 1005 nM [salv A 0.9 nM]
MOP K_i = 10 nM
DOP K_i > 10,000 nM

In summary plant-derived salvinorin A was converted to AK-1401 in two steps



Salvinorin A **Salvinorin B** **AK-1401**

What has changed ?



salvinorin A

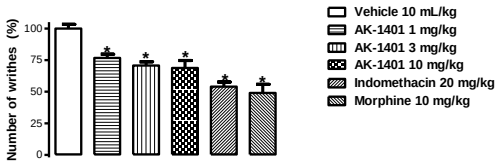
AK-1401

KOP K_i = 0.9 nM

KOP K_i = 1005 nM
MOP K_i = 10 nM
DOP K_i > 10,000 nM

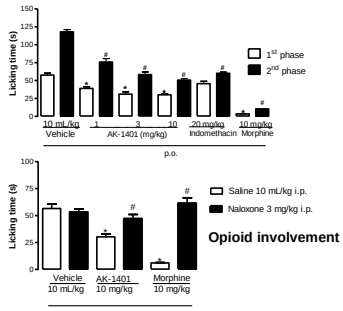
KOP has emerged as an alternative molecular target for the creation of safer analgesics (Roth, 2016)

Acetic acid-induced abdominal writhing test[1]



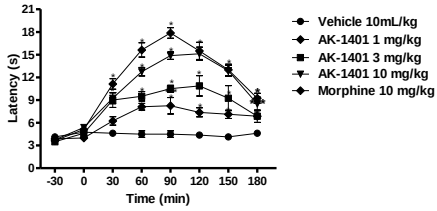
1. Koster, R., Anderson, M. and De Beer, E.J. (1959) Acetic Acid for Analgesic Screening. Federation Proceedings, 18, 412-417.

Formalin paw test[2]



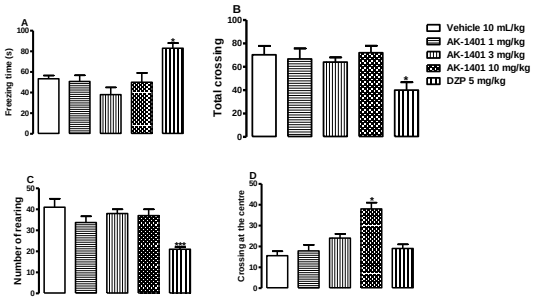
2. Wheeler-Aceto H, Porreca F, Cowan A. The rat paw formalin test: comparison of noxious agents. Pain. 1990 Feb;40(2):229-38.

Hot plate test[3]



3. Le Bars D1, Gozariu M, Cadden SW. Animal models of nociception. Pharmacol Rev. 2001 Dec;53(4):597-652.

Open field test[4]



4. Gould T.D., Dao D.T., Kovacsics C.E. (2009) The Open Field Test. In: Gould T. (eds) Mood and Anxiety Related Phenotypes in Mice. Neuromethods, vol 42. Humana Press, Totowa, NJ

Summary of key results

- AK-1401
  - Showed dual affinity towards KOP and MOP receptors with 100-fold MOP preference
  - Showed good oral bioavailability
  - Elicits antinociceptive effect in mice
  - Did not induce locomotion incoordination

Conclusion and implications

- ❑ By chemical modification we were able to modulate the pharmacological profile from salvinorin A, a highly selective KOP receptor agonist, to AK-1401, a new dual affinity KOP/MOP ligand with significant antinociceptive effects.
- ❑ Development of promising analgesic drug candidate that could:
- Translate to effective pain relief
- Proffer solution to opioid crisis emanating from pain management