Cinnamic Acid Derivatives as Novel Antinociceptives for Acute Pain

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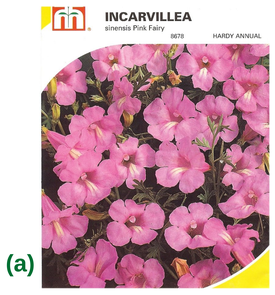
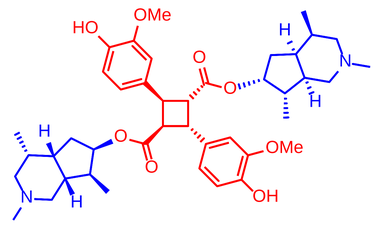
INTRODUCTION

- Chronic pain necessitates consistent use of medications or alternative therapies[1]
- Opioids, the most effective pain medication, are the most commonly abused and misused, and have many side effects including constipation, drowsiness, nausea, dependence and tolerance[2]
- Incarvillateine (INCA), found in *Incarvillea sinensis*, a plant in traditional Chinese medicine (Figure 1a) has been used to treat rheumatism and relieve pain, and known to act through adenosine receptor[3]
- Adenosine receptors (A_1, A_{2a}, A_{2b} and A_3) have proven to have antinociceptive effects in a mouse model[3]
- Chemical structure of INCA core (highlighted in red, Figure 1b) is identical to one of the products of photodimerization reaction of a trans-cinnamic acid (Figure 2)



(a)



(b)

Figure 1. (a) *Incarvillea sinensis*[4] and (b) incarvillateine

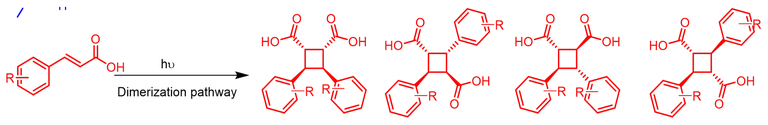
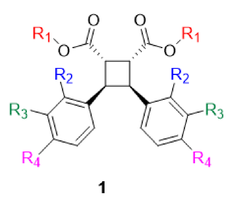


Figure 2. Photodimerization of *trans*-cinnamic acids (*t*-CA) affords cinnamic acid dimers (CADs), which are isomers of the INCA core



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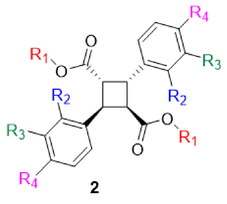
affix	R_1	R_2	R_3	R_4
a	-H	-H	$-OCH_3$	-OH
b	-H	-Cl	H	-H
c	-H	-H	$-CH_3$	-H
d	i-Pr	-H	H	-H
e	-H	-H	$-OCH_3$	-H
f	-iPr	-H	H	$-CH_3$



2

Figure 3. Structures of CAD and CAD-Ds screened for nociceptive studies

HYPOTHESIS

Derivatives of cinnamic acid dimers (CAD-Ds) show potent antinociceptivity through adenosine receptor action

MATERIALS AND METHODS

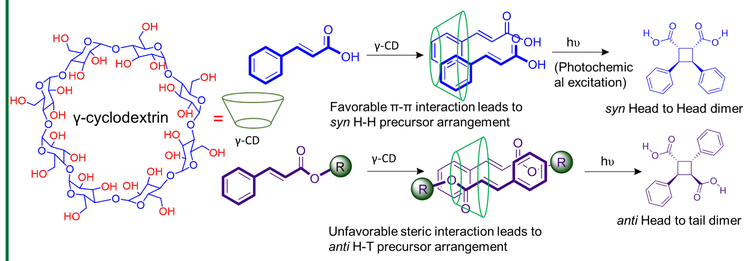


Figure 4. CAD and CAD-D synthesis using cavitand mediated photodimerization (CMP) method

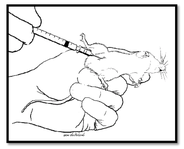


Figure 5. Intraperitoneal injection of test compounds (10 min before formalin)[5]

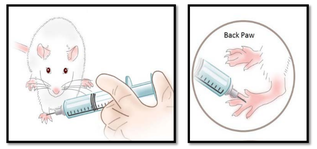


Figure 6. Subcutaneous injection of formalin (20 ml 1%) in left hind paw[5]

- Animals: Male CD1 mice (20-40 g)
- Time spent licking the paw:
  - Early (neurogenic) phase (0-5 min)
  - Late (inflammatory) phase (5-50 min)
- Computer modeling using docking software (AutoDock)

RESULTS

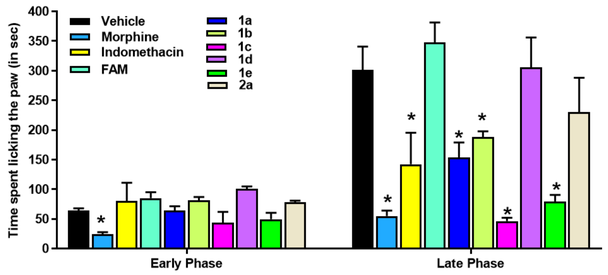


Figure 7. Acute pain response of test compounds (30 mg/kg) in male mice. * p < 0.05 vs. vehicle late phase control. (n=5 animals/group)

RESULTS

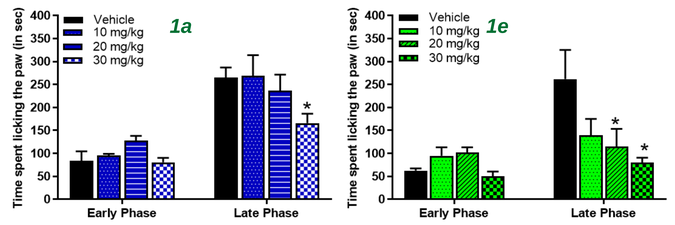


Figure 8. Antinociceptive dose response for compounds *1a* and *1e*. *p<0.05 vs. vehicle late phase control. (n=5 animals/group)

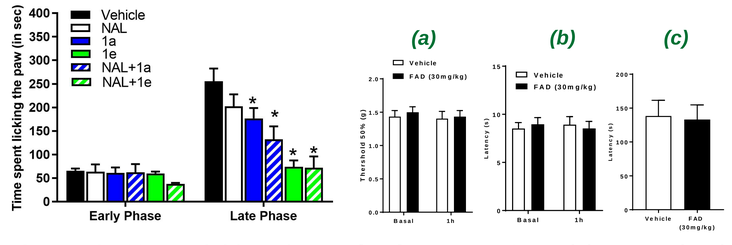


Figure 9. Non-opioid actions of compounds *1a* and *1e*. *p<0.05 vs. vehicle control. (n=5 animals/group)

Figure 10. (a) Mechanical allodynia, (b) thermal nociception, and (c) locomotor function tests in mice treated with compound *1a*.

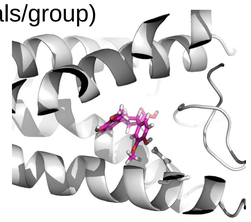


Figure 11. Compound *1a* (pink, tube model) with homology model of A_3 receptor (PDB code 1OEA)

CONCLUSION

CAD-Ds (compounds *1a* and *1e*) act through adenosine receptor as non-opioidergic antinociceptives

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REFERENCES

1. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. Washington (DC): National Academies Press (US); 2011.
2. American Society of Regional Anesthesia and Pain Medicine. Treatment options for chronic pain. (2017).
3. Wang, M.; Yu, G.; Yi, S.P.; Zhang, F.Y.; Wang, Z.T.; Huang, B.; Su, R.B.; Jia, Y.X.; Gong, Z.H. *Sci Rep*. 2015, *5*, Article Number 16107.
4. https://zh.wikipedia.org/wiki/File:Incarvillea_sinensis_var_przewalskii_01.jpg
5. https://www.clodrosome.com/animal-injection/