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# Identification of odorant molecules as novel CB1 receptor ligands through *in silico* approach

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## INTRODUCTION

✓ The CB1 endocannabinoid system is one of the main systems involved in the regulation of dietary intake<sup>1,2</sup>

Ligands of the CB1 receptor : **CB1 agonists** induce food intake  
**CB1 antagonists** decrease food intake and suppress appetite

✓ CB1 receptor expression: the CB1 receptor is expressed in the brain and in a number of peripheral tissues in mammals; a CB1-like receptor has also been localized in the olfactory epithelium of *Xenopus laevis* tadpoles<sup>3</sup>

✓ Aroma perception has recently been shown to be implicated in the process of satiety<sup>4</sup>

These findings led us to hypothesize that odorant molecules could have an impact on food intake through interactions with the endocannabinoid system

## Aims of the study

to identify odorant molecules that could interact with the CB1 receptor using *in silico* and *in vitro* approaches

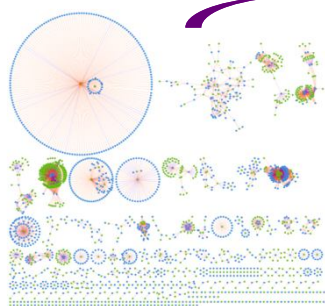
### Chemogenomic study

Using around 3000 odorant molecules described in the Flavor-Base (Leffingwell & Assoc. <http://www.leffingwell.com/>)

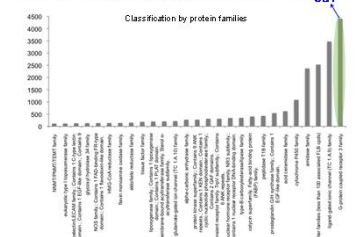
Network pharmacology

Mapping the odorant pharmacological space: odor-drug associations

- Structural fingerprints
- Similarity searches vs the ChemProt database<sup>5,6</sup>



### Protein target prediction for odorants



### 3D-QSAR pharmacophore approach

*In silico* screening

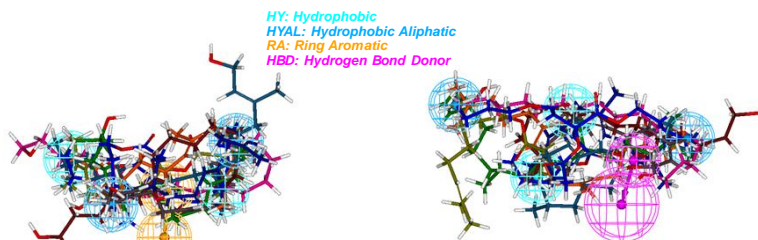
Mapping on agonist and antagonist Catalyst/HypGen (Accelrys) models obtained on the basis of literature data<sup>7,8</sup>

#### Agonist model

2 HY, 2 HYAL, 1 RA, correl.=0.99, cost=47, fixed cost=44.5, null cost=237, config=15

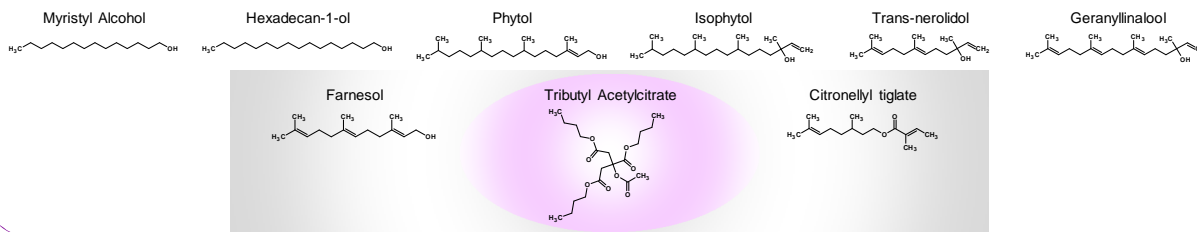
#### Antagonist model

2 HY, 2 HYAL, 1 HBD, correl.=0.98, cost=75, fixed cost=67, null cost=243, config=15

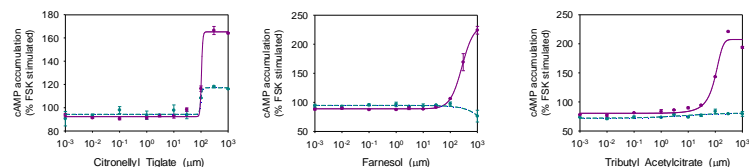


- small sphere corresponds to the center of Hydrogen Bond Donor
- large sphere is the projection sphere corresponding to a Hydrogen Bond Donor on the receptor site

### Chemical structures of molecules predicted to be CB1 ligands



### In vitro assays

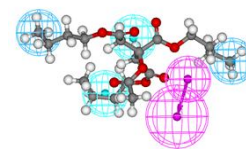


Human HEK293 cells were cotransfected with a plasmid encoding the mouse CB1 receptor cDNA and with a plasmid encoding an engineered cAMP sensitive luciferase (Promega). After incubation with the substrate of luciferase, forskolin (FSK, 1 μM), then the odorant molecules were injected and the luminescence was recorded for 30 min on a bioluminescence plate reader.

three molecules are inverse agonists of the CB1 receptor *in vitro*  
 best activity obtained with Tributyl Acetylacrylate

### Alignment of Tributyl Acetylacrylate on CB1 antagonist model

2 HY, 2 HYAL, 1 HBD, correl.=0.98, cost=75, fixed cost=67, null cost=243, config=15



## Conclusion and perspectives

- On the basis of these findings, interactions between the endocannabinoid system and odorant molecules could be proposed as a mechanism involved in the establishment of satiety
- Three odorant molecules act as CB1 inverse agonists *in vitro*, supporting the possible pharmacological relevance of the newly identified odorant-target relationships

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