

Strategies for Forecasting Evolution of New Drugs and Drug Classes

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On the Origin of 'New' Psychoactive Substances

The most fruitful basis for the discovery of a new drug is to start with an old drug.

James Black (1924-2010)

Nobel Prize in Physiology or Medicine, 1988

propranolol & cimetidine

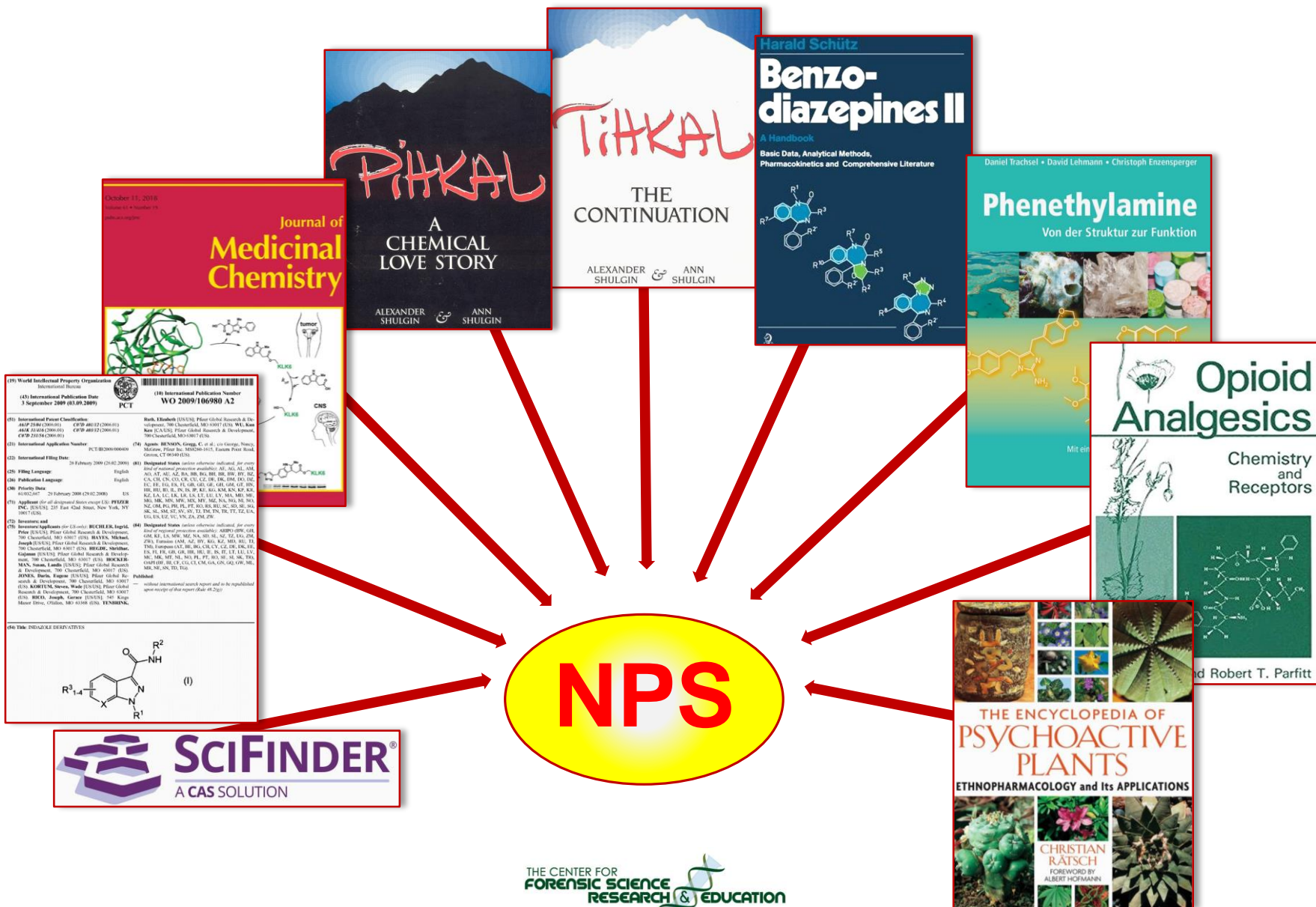
cited by Raju (2000) Lancet 355, 1022

Increase:

- ☘ **efficacy**
- ☘ **selectivity** (therapeutic index or safety margin)

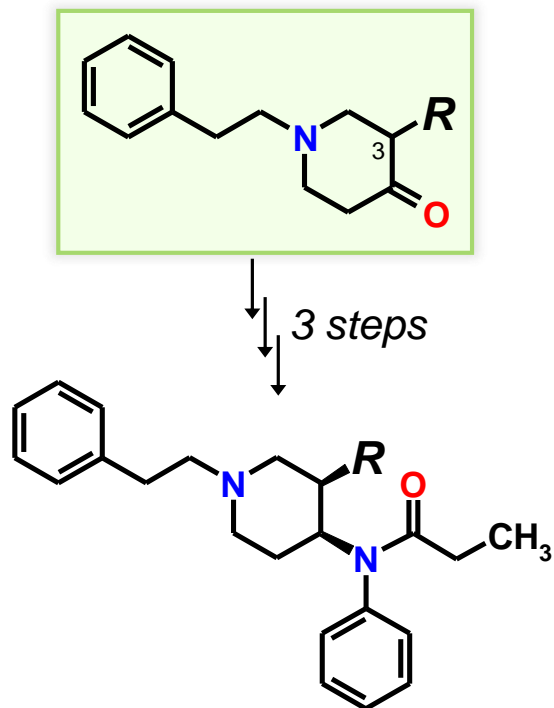
Unknown or problematic for most NPS 😞

Diverse & readily accessible sources of NPS



Fentanyl homologues: *methyl, ethyl, ... futile*

*But: may be prepared from **uncontrolled precursors***

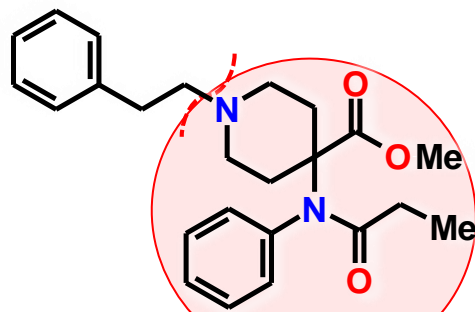


(±)-cis-3-R group	Antinociception rat, tail withdrawal ED₅₀ (mg/kg)	Potency relative to fentanyl
H (fentanyl)	0.0104	1
Methyl	0.0013	8
Ethyl	0.0068	1.49
Butyl	0.162	0.064

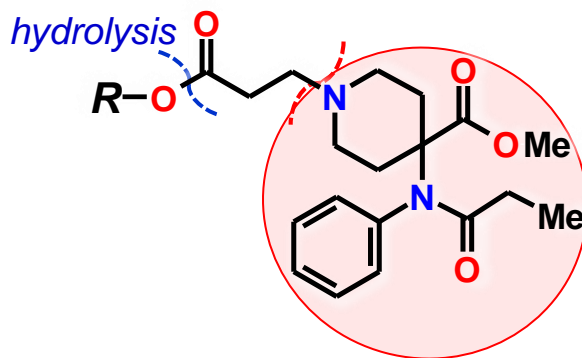
Ivanovic et al (2004) *J Serb Chem Soc* **69**, 511

The hydrolysis rate of remifentanil(s) is tunable

ester (*R*) homologues are **uncontrolled opioids**



Carfentanil



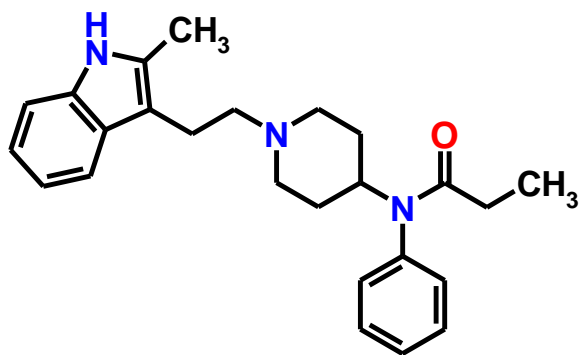
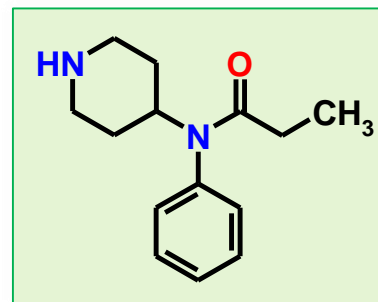
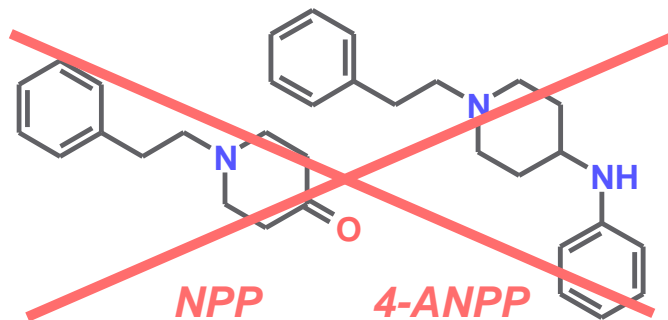
Compound or <i>R</i> group	Antinociception ED ₅₀ (μg/kg)	Duration in vivo (min)
Fentanyl	4.6	60
Carfentanil	0.52	45
Me (remifentanil)	4.4	15
Ethyl	1.7	10
tert-Butyl	0.021	85

Carfentanil & remifentanil(s) share a common dealkylated (nor) metabolite!

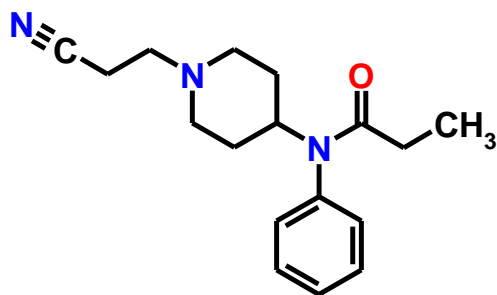
Feldman et al (1991) *J Med Chem* **34**, 2202

Move over NPP and 4-ANPP!

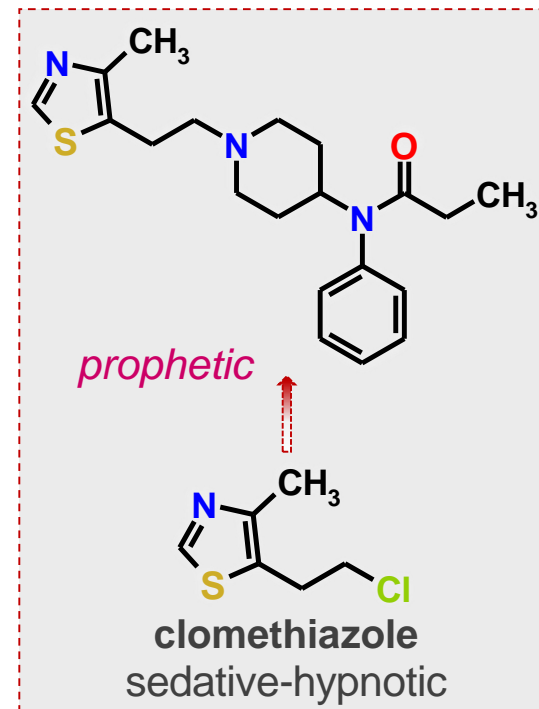
syntheses of new fentanils rely on **uncontrolled precursor**



Archibald, 1975

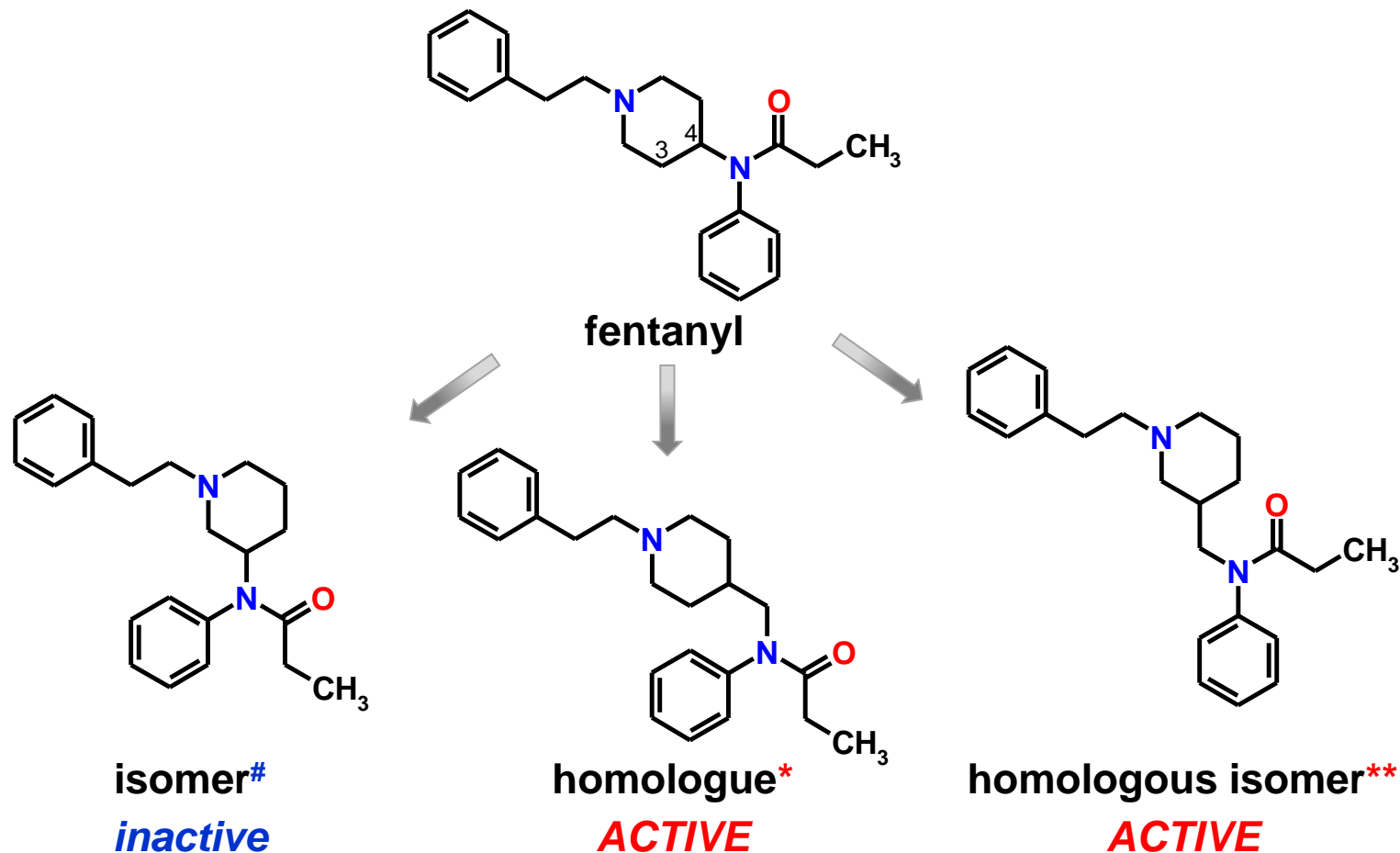


Gupta et al, 2013
+ related amides



Aminomethyl-piperidines are active

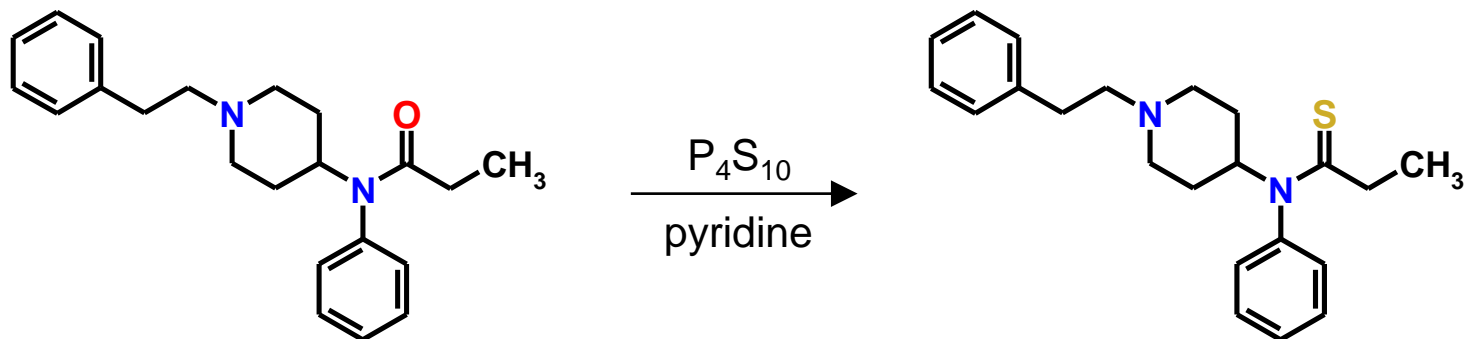
nipecotic acid-based fentanils



#Lobbezoo *et al* (1981) *J Med Chem* **24**, 777; *Peters *et al* (2010) US Patent 2010/0234427;

**Cuny *et al* (2003) US Patent 6,645,980

Fentanyl thioamide is antinociceptive in mice



fentanyl

VÚFB-13757
NIH 10483

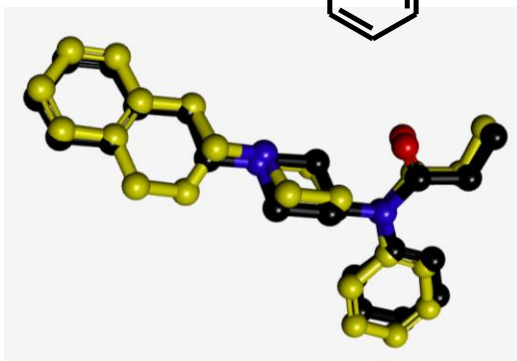
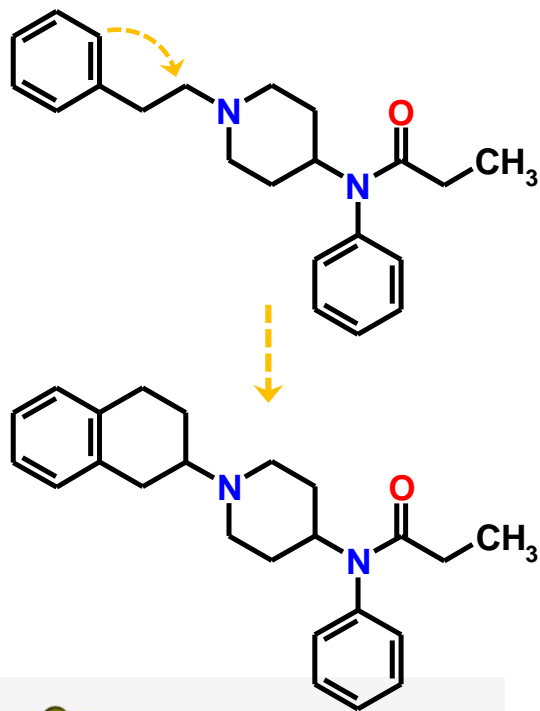
ED₅₀ = 0.18 mg/kg; fentanyl: 0.06 mg/kg
Haffner's test, mouse, sc administration

LD₅₀ = 20 mg/kg; fentanyl: 11 mg/kg
mouse, iv administration

NIDA Res Monogr (1988) **81**, 577; Jílek *et al* (1990) *Collect Czech Chem Commun* **55**, 1828

Conformationally constrained fentanils are active

phenethylamine → *aminotetralin*



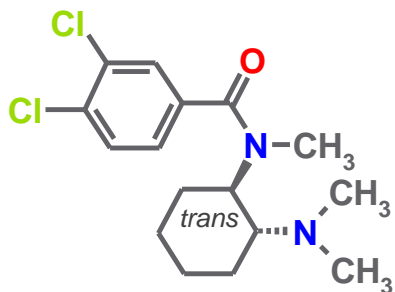
Compound	Antinociception ED ₅₀ (mg/kg) mouse, sc	Toxicity LD ₅₀ (mg/kg) mouse, ip
Fentanil citrate	0.010	109
Tetralino-F·HCl	0.012	44.8

Fifer *et al* (1984) *Eur J Med Chem* **19**, 519

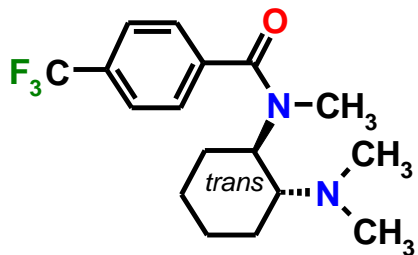
NO
U
TURN

series: structural & pharmacological diversity

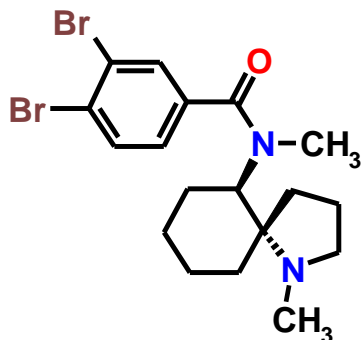
analgesic, antidepressant, anticonvulsant



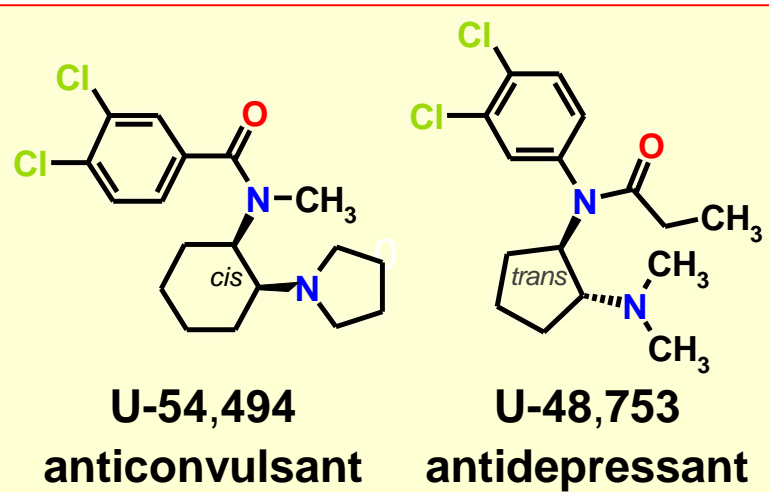
U-47,700
ED₅₀ = 0.2 mg/kg (sc)
opioid analgesic



ED₅₀ = 0.4 mg/kg (sc)
analgesic



ED₅₀ = 0.21 mg/kg (sc)
analgesic
U-77,891 (not Upjohn)
offered on the internet



U-54,494
anticonvulsant

U-48,753
antidepressant

Colour Index™: **TiO₂ Pigment White 6 CI 77891**

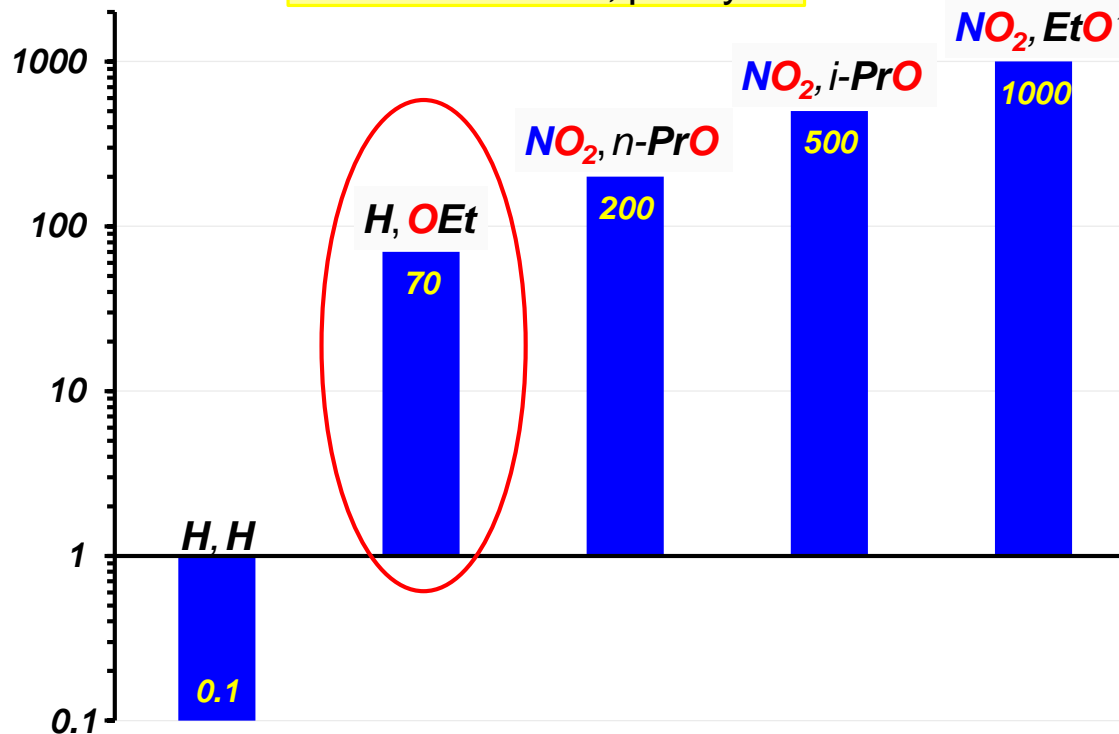
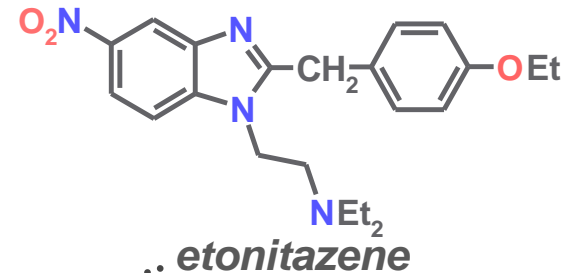
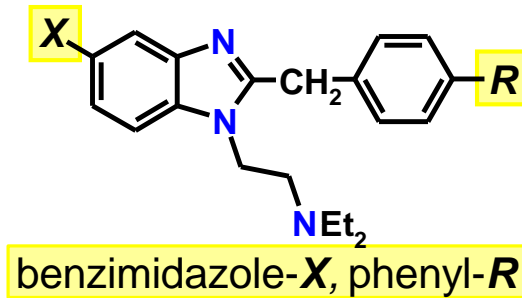


Solimini *et al* (2018) *Front Pharmacol* **9**, art.654; Cheney *et al* (1985) *J Med Chem* **28**, 1853;
VonVoigtlander (1983) *Drug Dev Res* **3**, 545; Fujimoto *et al* (1989) *J Med Chem* **32**, 1259

Waiting for etonitazene analogues...

Antinociception
mouse, tail-flick, sc

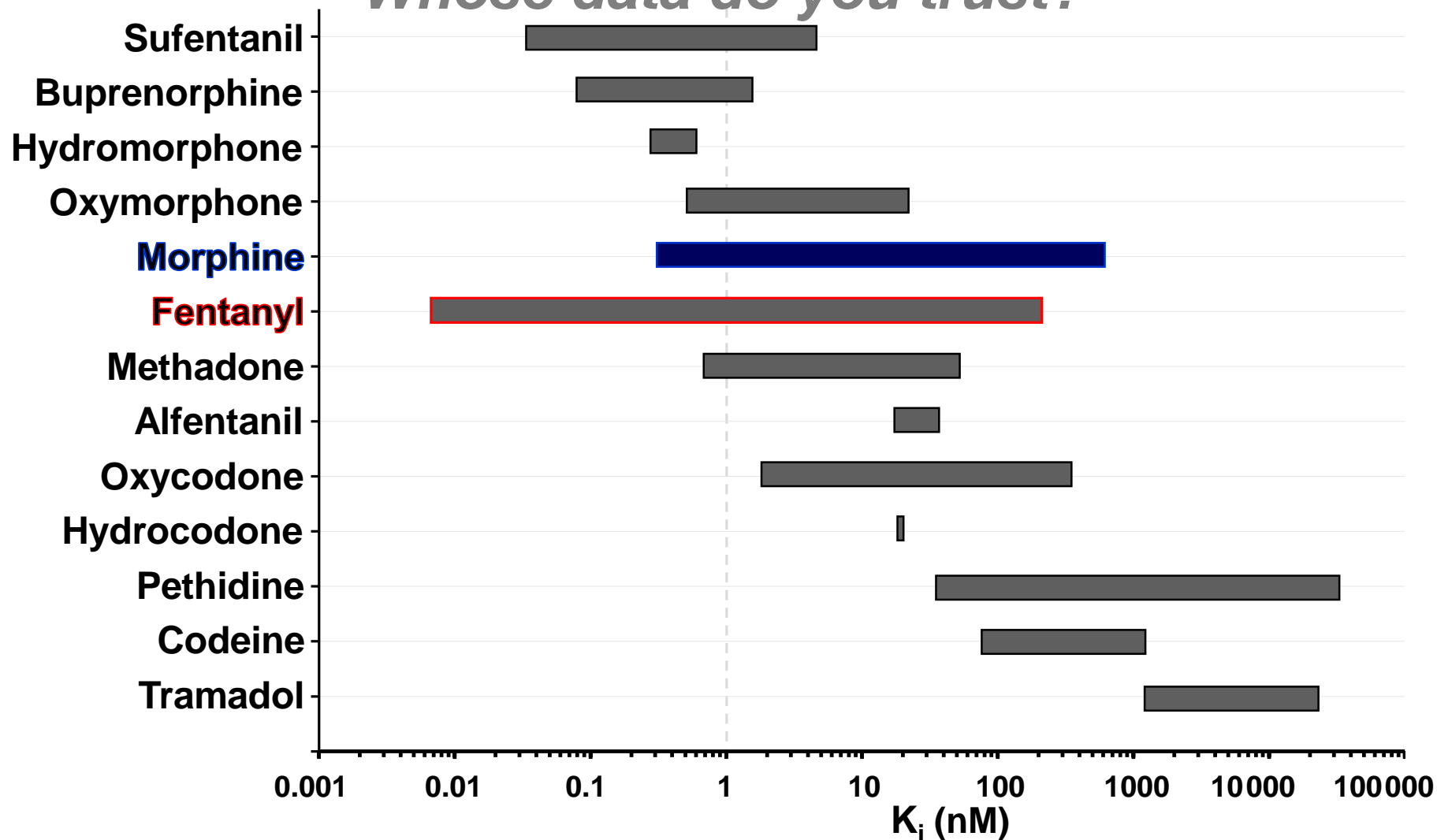
Morphine = 1



Hunger *et al* (1960) *Helv Chim Acta* **43**, 800 & 1032; also Zernig *et al* (1995) *Life Sci* **57**, 2113

Large variations in literature MOP affinity K_i values!

Whose data do you trust?



Volpe et al (2011) *Regul Toxicol Pharmacol* 59, 385

Exercise caution when assessing (*predicting?*) data!

In experimental data we trust

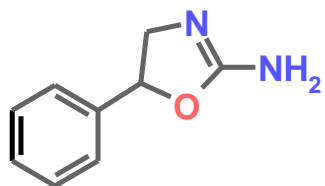
Receptor binding; antinociception, toxicity & safety margin of opioids in rats

Compound	Receptor affinity[#] IC₅₀ (nM)	Analgesic activity* ED₅₀ (mg/kg iv)	Analgesic potency relative to morphine	Acute toxicity* LD₅₀ (mg/kg iv)	Safety margin LD₅₀/ED₅₀
morphine	27	3.21	1	223	70
fentanyl	25	0.011	290	3.05	280
(+)- <i>cis</i> -3-methyl-fentanyl	1.3	0.00058	5530	0.98	1860
carfentanil	0.4	0.00032	10030	3.39	10590

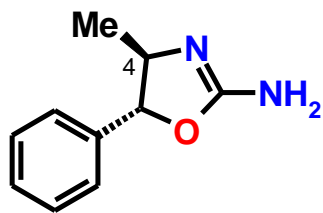
[#]against [³H]naltrexone, rat brain prep.; ^{*}tail withdrawal assay

Stahl *et al* (1977) *Eur J Pharmacol* **46**, 199; Van Bever *et al* (1976) *Arzneim-Forsch* **26**, 1548

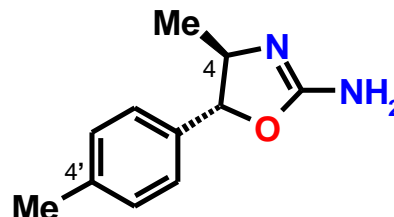
Amino rex analogs have not become extinct



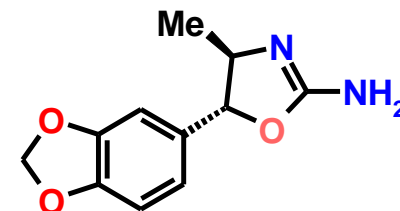
aminorex



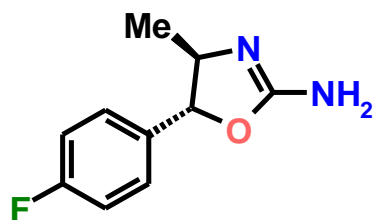
4-MAR, *U4Euh*



4,4'-DMAR

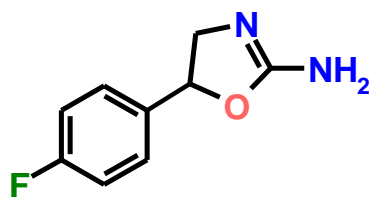


3',4'-MDMAR



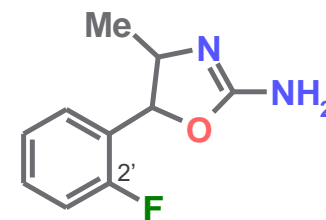
4'-F-4-MAR

Reported to EMCDDA
August 2018



4'-F-aminorex

Known* but has not
been detected

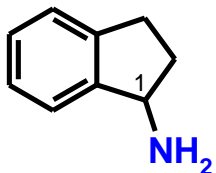


2'-F-4-MAR

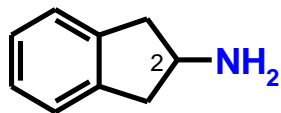
*Described on an
internet forum*

Maier *et al* (2018) *ACS Chem Neurosci* (in print); *Poos *et al* (1963) *J Med Chem* **6**, 266

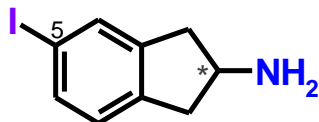
Aminoindan 'stimulants' – never really made it (?)



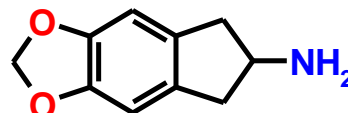
1-AI



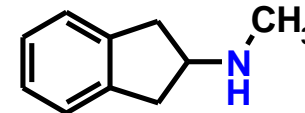
2-AI (Su-8629)



5-IAI

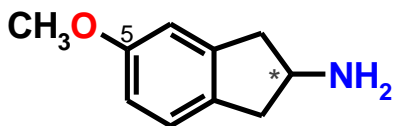


MDAI



N-Me-2-AI

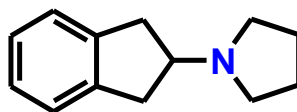
All 5 reported to EMCDDA (since 2006)



(±)-5-MeO-2-AI (MEAI)

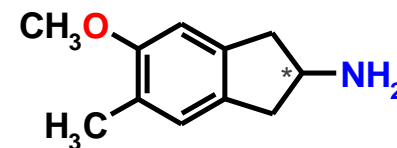
Non-opioid analgetic[#]

LD₅₀ = 86 mg/kg (rat, iv)



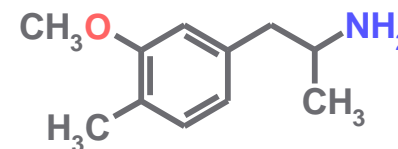
1-(indan-2-yl)pyrrolidine

Amphetamine-like stimulant^{*}



MMAi

Serotonin releaser

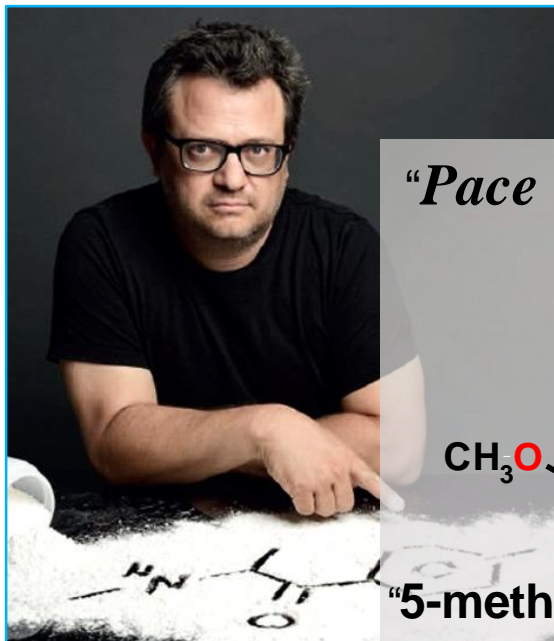


3,4-MMA

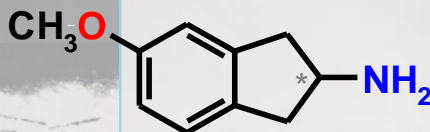
[#]Richter & Schenck (1956) DE 952 441 (Schering); ^{*}Solomons & Sam (1973) *J Med Chem* **16**, 1330

AlcoSynth, Chaperone, Alcohol Alternative, *Pace*

The odd couple...



"Pace is healthier than alcohol"



"5-methoxy-2-aminoindan"

MEAI

2-amino-5-methoxyindan

5-methoxy-2,3-dihydro-1*H*-inden-2-amine

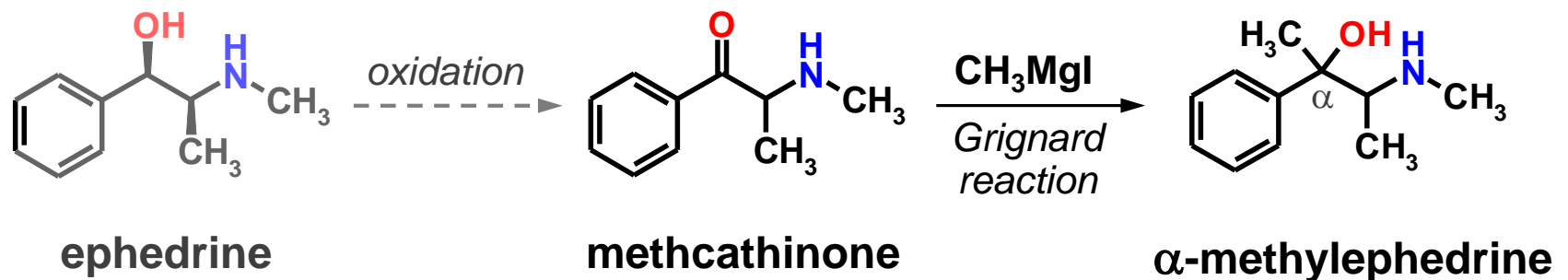


"This product is neither regulated nor scheduled in the USA or Canada."

"This product has not been evaluated by the FDA."

Golan E (2016) Alcoholic beverage substitutes. WO 2016/092547
Shimshoni et al (2018) *Toxicol Appl Pharmacol* **29**, 343

Move over cathinones, here I come !? – V. Grignard



**Reported to EMCDDA
October 2018**

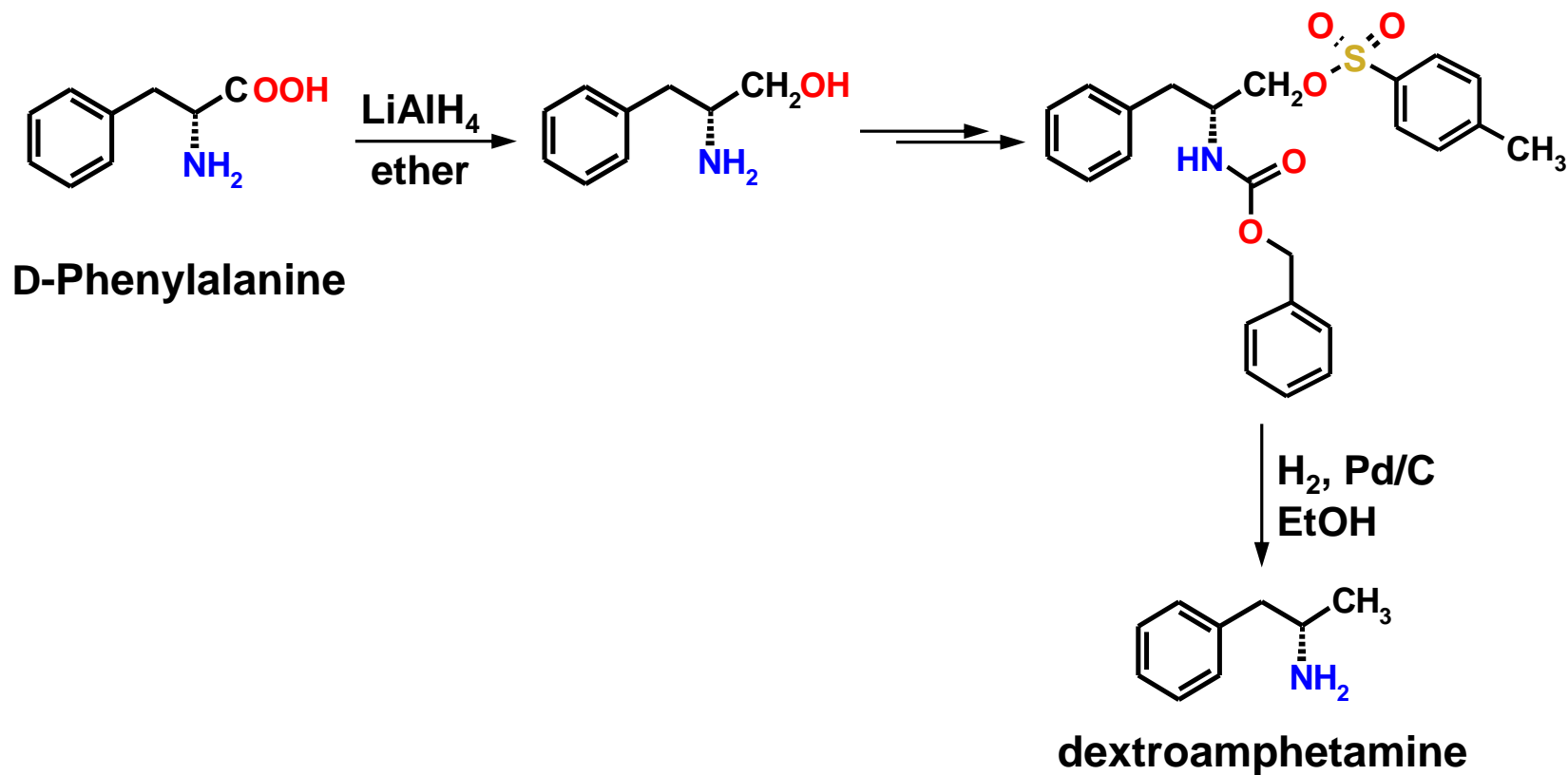
$\text{LD}_{50} = 390 \text{ mg/kg}$
mouse, oral

$\text{LD}_{50} = 342 \text{ mg/kg}$
mouse, oral

***ephedrine-like
action***
 $\text{LD}_{50} = 1100 \text{ mg/kg}$
mouse, oral

Lévy & Sergent-Montsarrat (1931) *Paris Medical* **21**, 148; Suter & Weston (1942) *J Am Chem Soc* **64**, 2451

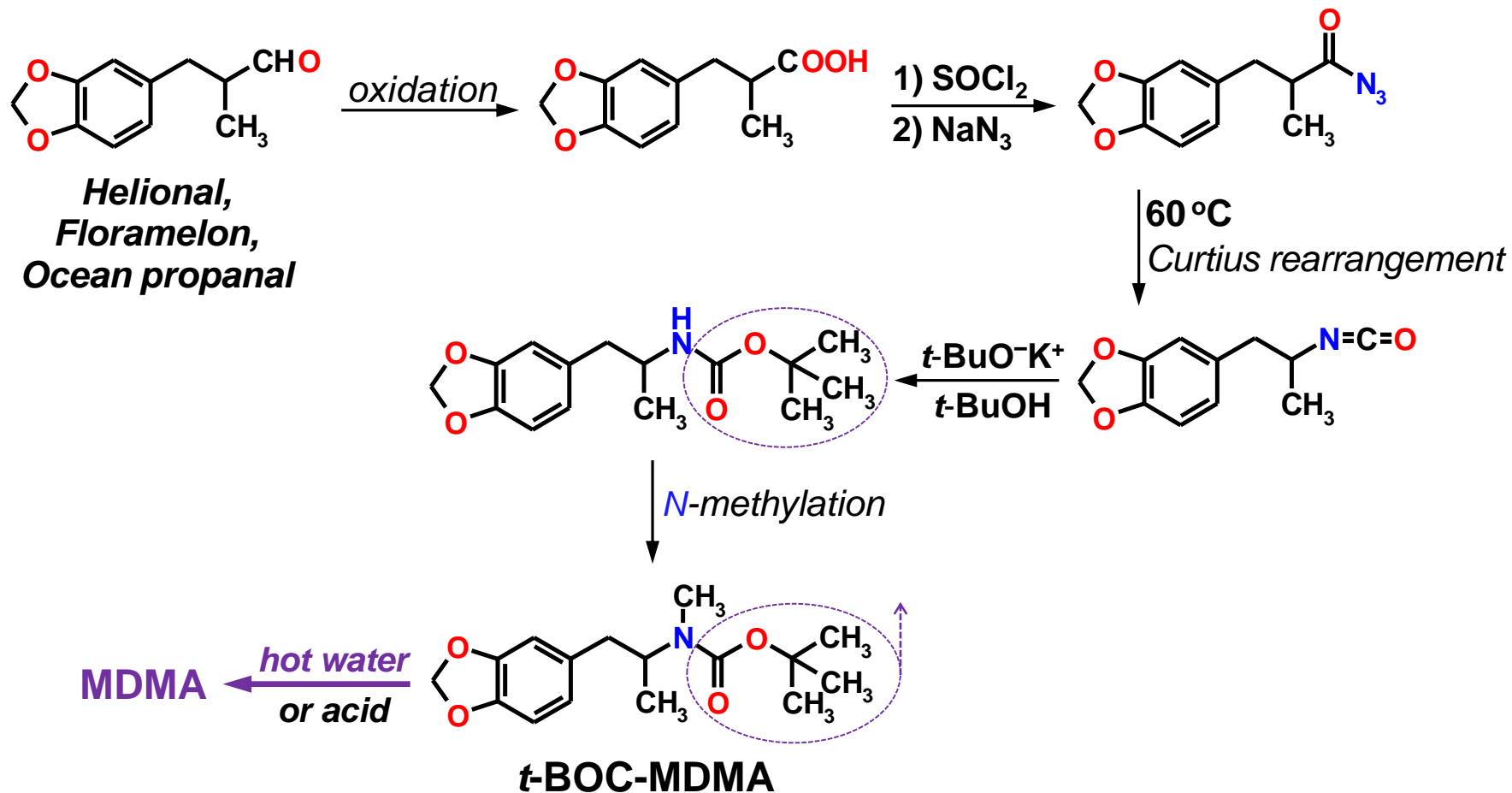
New synthetic route leads to a masked drug



Repke *et al* (1978) *J Pharm Sci* **67**, 1167; Sugie *et al* (2018) *Forensic Toxicol* **36**, 261; Salouros (2018) *Aust J Forensic Sci* **5**, 689

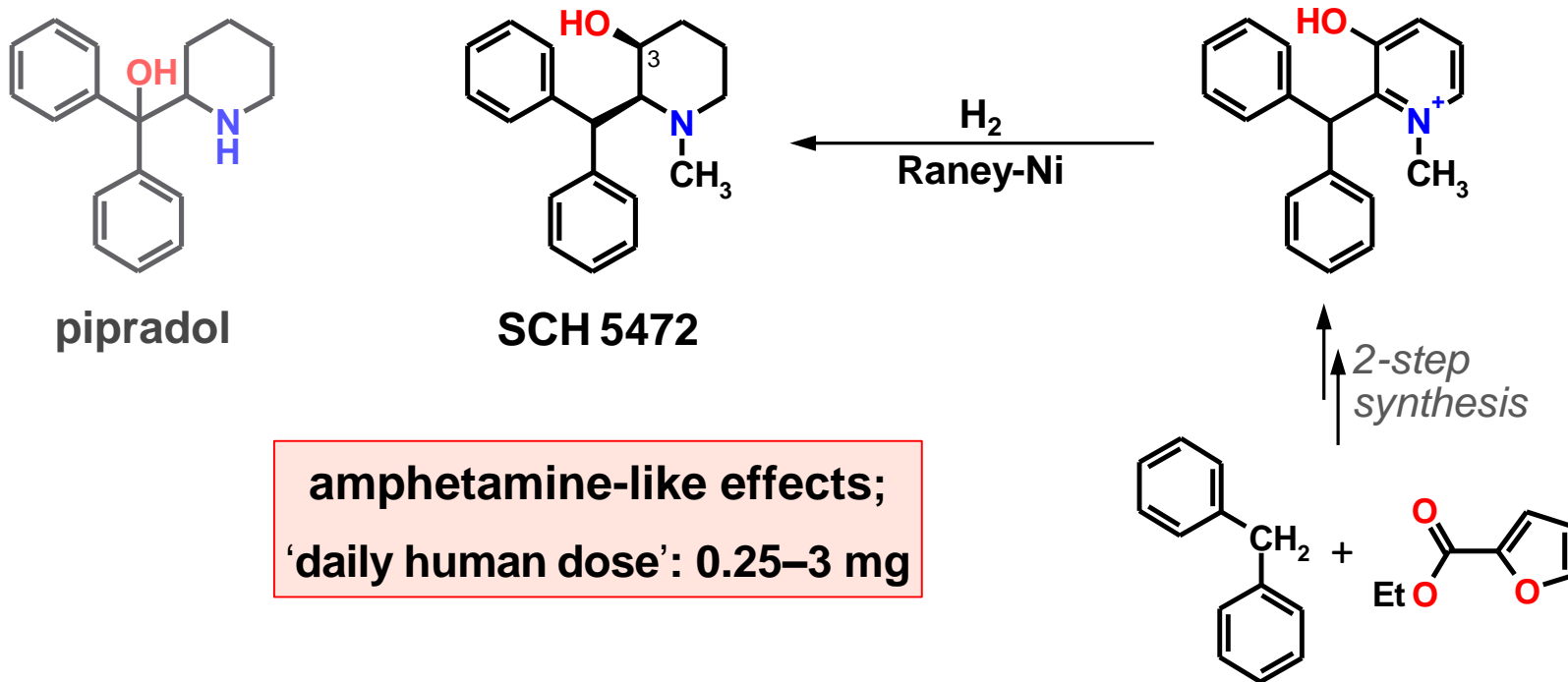
From a fragrance to *Instant Ecstasy*

New synthetic route leads to masked drugs



Schulze (2010) *Synth Commun* **40**, 1461; Westphal *et al* (2016) *Toxichem Krimtech* **83**, 92;
Collins *et al* (2017) *Drug Test Anal* **9**, 399

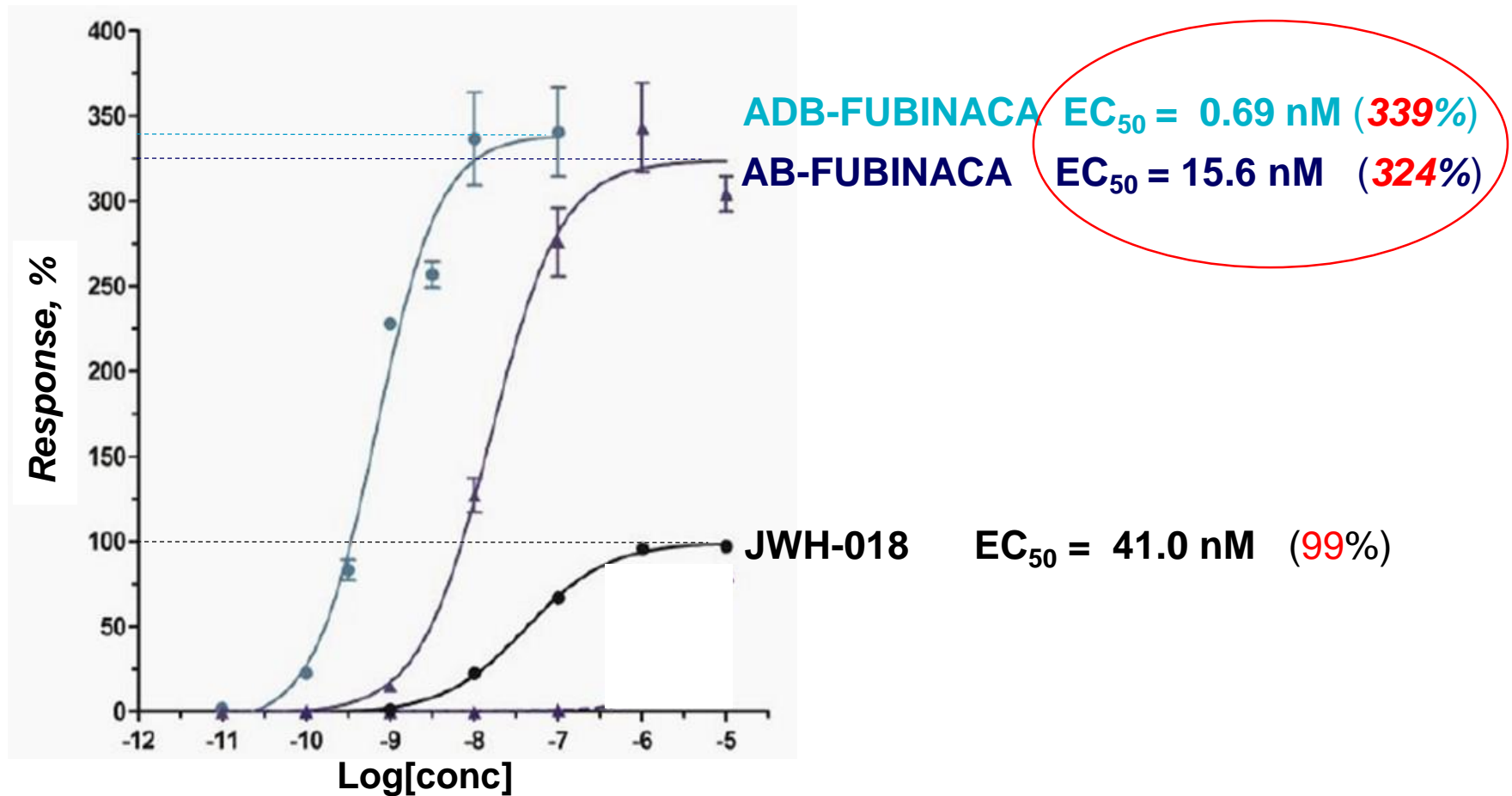
SCH 5472 – a pipradol-related piperidinol clinically tested antidepressant stimulant (1960)



Walter *et al* (1968) *J Med Chem* **11**, 792; White & Archer (2013) in *Novel Psychoactive Substances* (Dargan & Wood, eds) pp 233-259

Do EC₅₀ values predict pharmacological responses?

Half-max. effective concentration (EC₅₀, nM), max. response (*E*_{max}, %) cell-based β-arrestin NanoLuc reporter assay

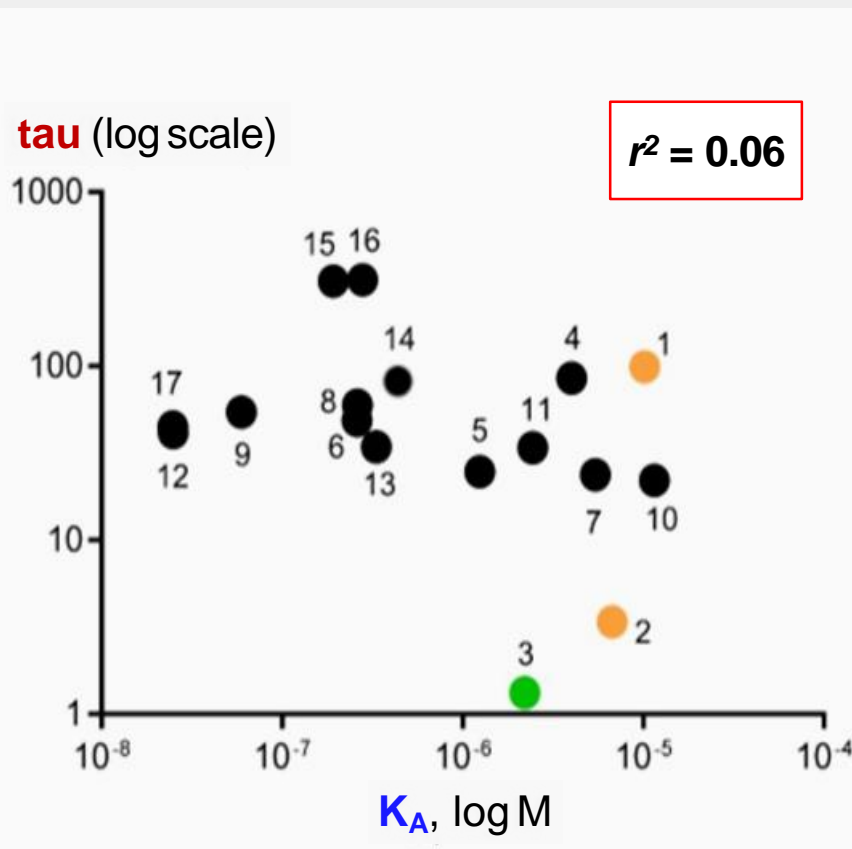


Noble *et al* (2018) *Drug Test Anal* doi: 10.1002/dta.2517

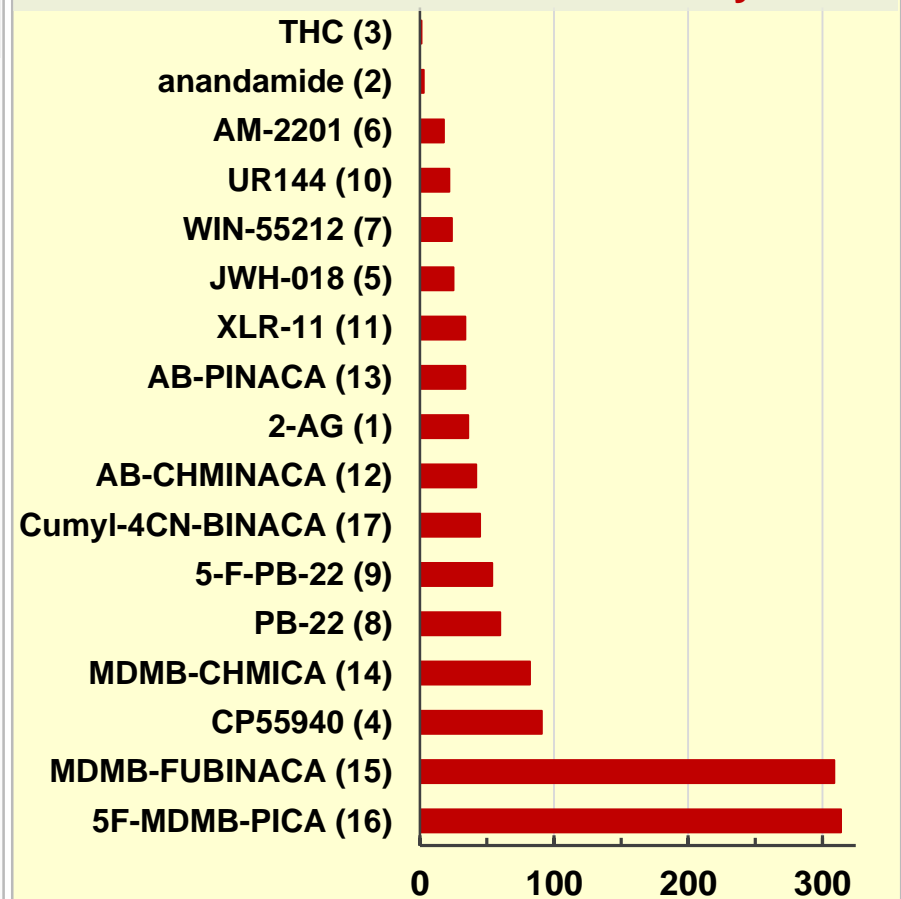
CB1 receptor affinity and efficacy do not correlate

use of *in vitro* data for “toxicity” prediction is problematic

Correlation of operational **efficacy** (τ) and functional **affinity** (K_A)



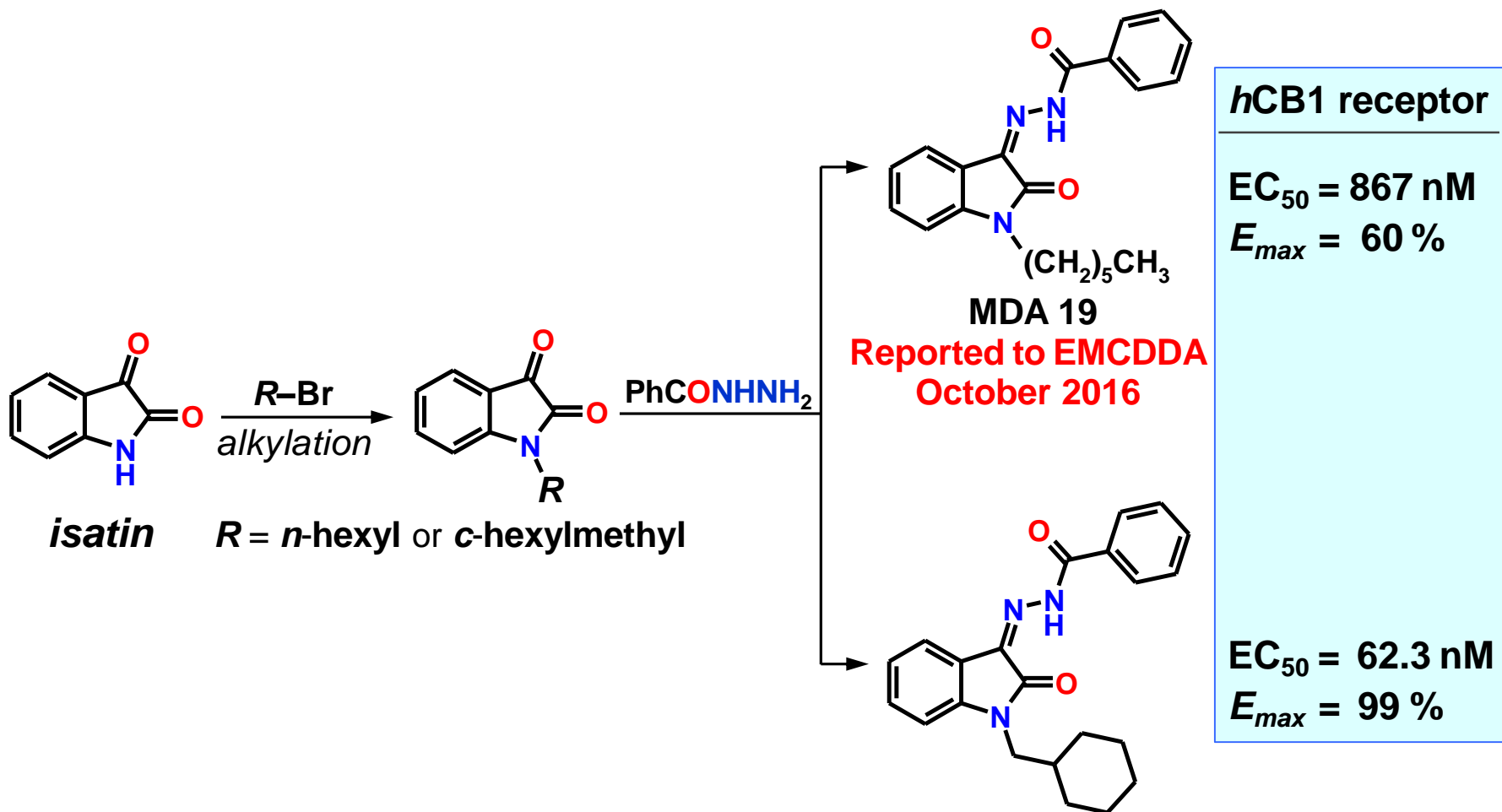
Rank order of relative **efficacy**



Sachdev *et al* (2018) *bioRxiv* 385583. doi: 10.1101/385583

Facile synthesis of *isatin*-based cannabinoids

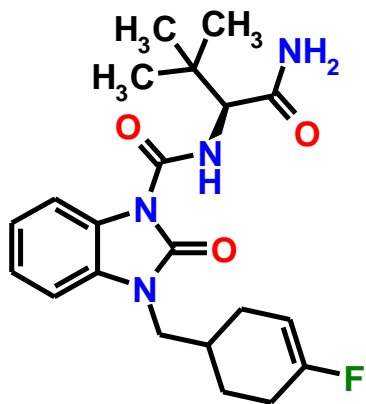
Yet only **one** has been detected



Diaz *et al* (2008) *J Med Chem* **51**, 4932; Xu *et al* (2010) *Anesth Analg* **111**, 99

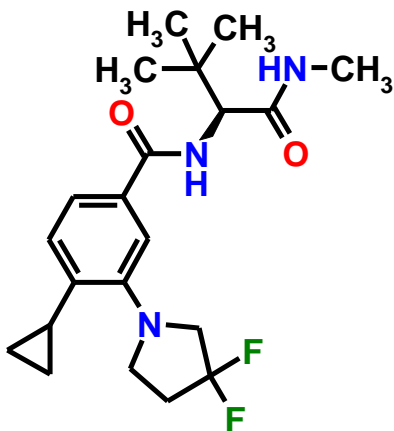
Structurally diverse(?) cannabinoids from literature

data for *hCB1* receptor



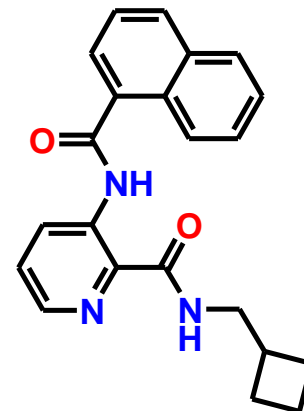
$K_i = 0.15 \text{ nM}$
 $EC_{50} = 0.87 \text{ nM}$

Pfizer
Ando *et al*, 2008



$EC_{50} = 42 \text{ nM}$

Hoffmann-La Roche
Gavelle *et al*, 2017

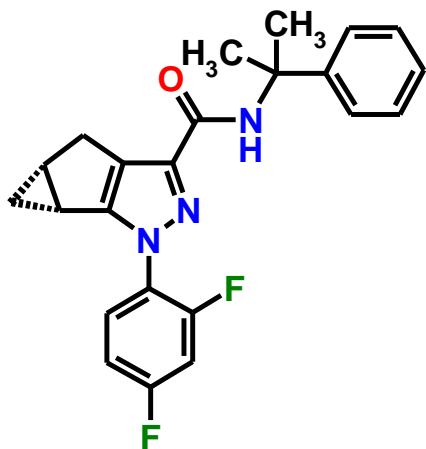


$K_i = 6.1 \text{ nM}$
 $EC_{50} = 23 \text{ nM}$ ($E_{max} = 110\%$)

AstraZeneca
Plowright *et al*, 2013

Weird tricyclic pyrazole in Phase 2 clinical trial

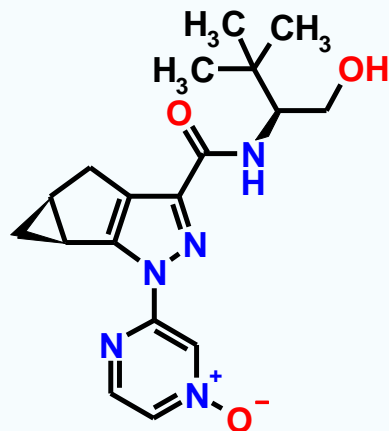
data for *hCB1* and *hCB2* receptors (E_{max} , %)



hCB1: $EC_{50} = 15.6$ nM (65)

hCB2: $EC_{50} = 0.9$ nM (87)

Arena Pharma
Han *et al*, 2015

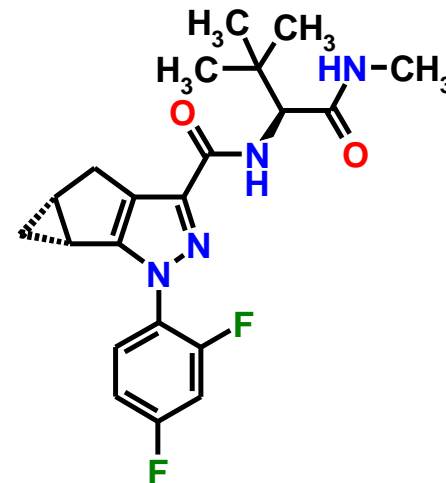


olorinab, APD371

hCB1: $EC_{50} = >10,000$ nM

hCB2: $EC_{50} = 6.2$ nM (106)

Arena Pharma
Han *et al*, 2017



hCB1: $EC_{50} = 1.1$ nM

hCB2: $EC_{50} = 0.17$ nM

Arena Pharma
Jones *et al*, 2011

Mieux vaut prévoir sans certitude que de ne pas prévoir du tout.

***It is far better to foresee even without certainty than
not to foresee at all.***

Henri Poincaré (1854–1912)

mathematician, theoretical physicist, engineer, philosopher of science

In: *La Science et l'Hypothèse* (1902); *The Foundations of Science* (1913)