Pharmacology of New Synthetic Stimulants and Opioids Appearing in Recreational Drug Markets

Michael H. Baumann, Ph.D.
Designer Drug Research Unit
IRP, NIDA, NIH
Baltimore, MD

Presented at ASAM State of the Art Course 2022

Disclosure Information

Michael H. Baumann, Ph.D.

- My research program is funded by the IRP, NIDA, NIH, US government
- I have no conflicts to disclose

Session Learning Objectives

At the end of the session, you will be able to:

- Understand the phenomenon of new psychoactive substances (NPS).
- Understand the biological effects of currently emerging stimulant-like NPS, especially synthetic cathinones.
- Understand the biological effects of currently emerging opioid-like NPS, known as novel synthetic opioids (NSOs).

New Psychoactive Substances (NPS) are Engineered to Evade Drug Control Laws

- Created by clandestine chemists who use biomedical & patent literature for malicious purposes
- Cheap and easy to obtain from internet, drug dealers, etc.
- Used without detection, as toxicology tests may not identify the substances
- Constantly evolving to stay ahead of drug control legislation

Madras, *Curr Top Behav Neurosci* . 2017;32:1-18

NPS are Best Classified Based on Their Pharmacological Targets in the CNS

- Stimulant NPS induce amphetamine-like effects by impairing the normal function of DA transporters (DAT)
- Cannabinoid NPS induce cannabis-like effects by acting as agonists at CB1 receptors (CB1R)
- Opioid NPS induce morphine-like effects by acting as agonists at mu-opioid receptors (MOR)

Madras, *Curr Top Behav Neurosci* . 2017;32:1-18

The Increasing Number & Diversity of NPS Requires Rapid Risk Assessment

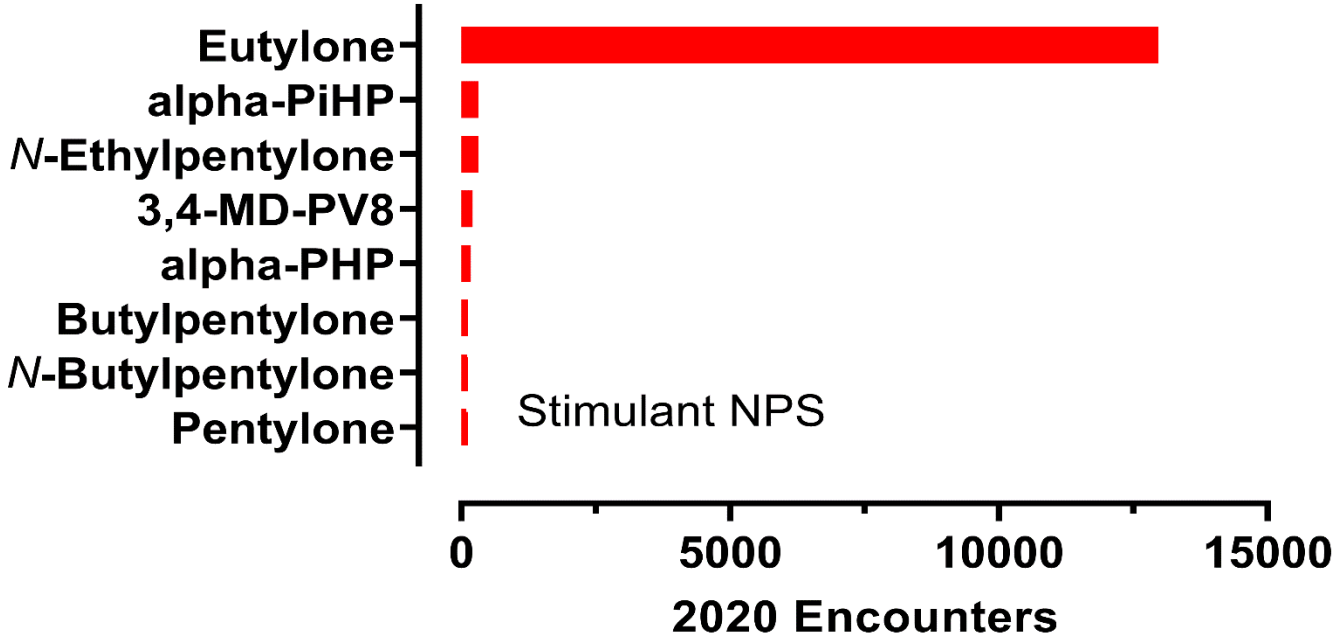
- Clinical casework and forensic analysis are key first steps in assessing the risks posed by emerging drugs
- *In vitro* assays in tissues and cells provide information about sites of drug action – e.g., receptors, transporters, enzymes
- *In vivo* studies in laboratory animals are used to validate *in vitro* findings, with respect to bioavailability, potency, and efficacy

Baumann et al., Trends Pharmacol Sci. 2018 Dec;39(12):995-998.

The Designer Drug Research Unit (DDRU) was Established to Address the NPS Problem

- Our **mission** is to collect, analyze, and disseminate up-to-date information about the biological effects of NPS
-
- The **goals** of the DDRU include:
    1. Preclinical evaluation – to determine pharmacology
    2. Risk assessment – to evaluate potential toxicity
    3. Forensic investigation – to determine PD/PK
    4. Data dissemination – publications and presentations

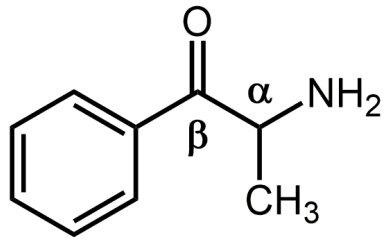
Eutylone was the Most Encountered Stimulant NPS in the US During 2020-2021



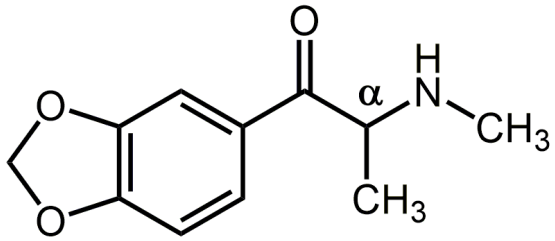
Natl Forensic Laboratory Information Syst (NFLIS), 2021

Eutylone is Found as Powders, Crystals, or Tablets, Often Sold as MDMA Or “Molly”

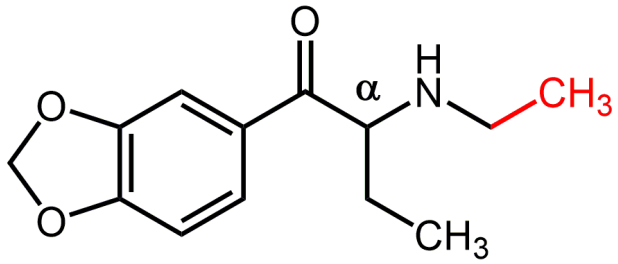
Eutylone and its Isomers are Analogs of the "Bath Salt" Cathinone, Methylone



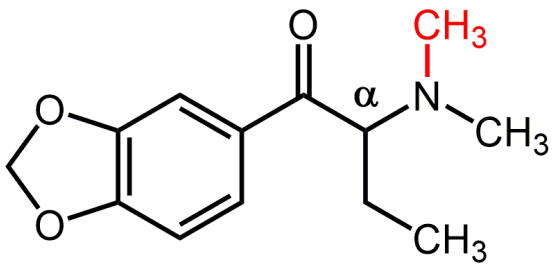
Cathinone



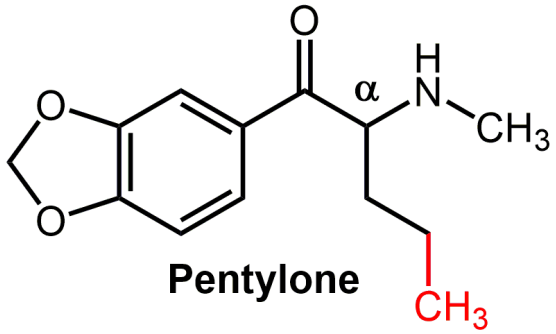
Methylone



Eutylone



Dibutylone



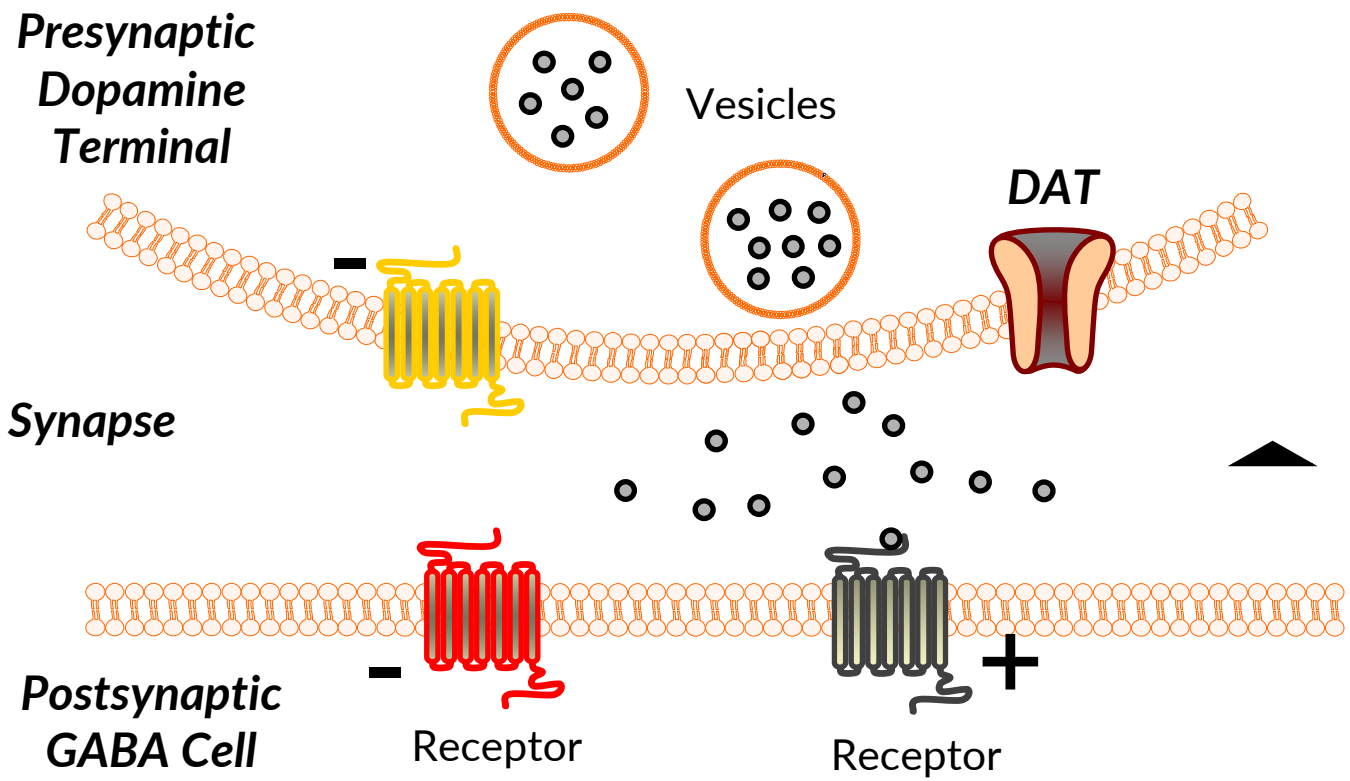
Pentylone

Eutylone Use is Associated With Serious Intoxications and Overdose

- Eutylone was first synthesized as an appetite suppressant in the late 1950s, but was never approved for clinical use
- Adverse symptoms include agitation, hallucinations, delirium, violent behaviors, palpitations, hypertension
- Fatalities usually involve cardiac arrest, or excited delirium, with accompanying hyperthermia and multisystem organ failure

Krotulski et al., *J Anal Toxicol.* 2021 Feb 6;45(1):8-20.

Stimulant NPS Target Dopamine Transporters (DAT) as Inhibitors or Substrates (Releasers)

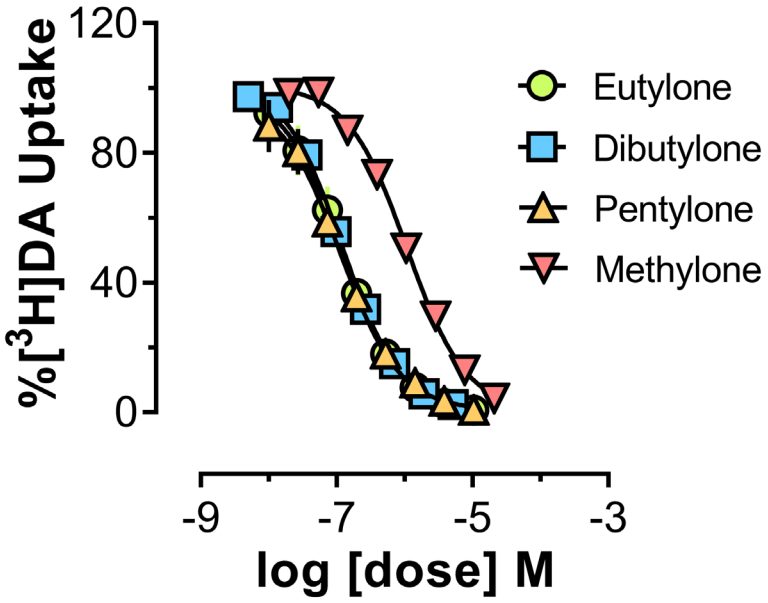


We Examined the Effects of Eutylone and its Isomers Using *In Vitro* and *In Vivo* Methods

- *In vitro* functional assays in rat brain synaptosomes
  - Inhibition of [^{3}H]dopamine uptake at DAT & [^{3}H]5-HT uptake at SERT
- *In vivo* methods in laboratory rodents
  - Locomotor activity in male C57Bl/6J mice

Glatfelter et al., ACS Chem Neurosci. 2021 Apr 7;12(7):1170-1177

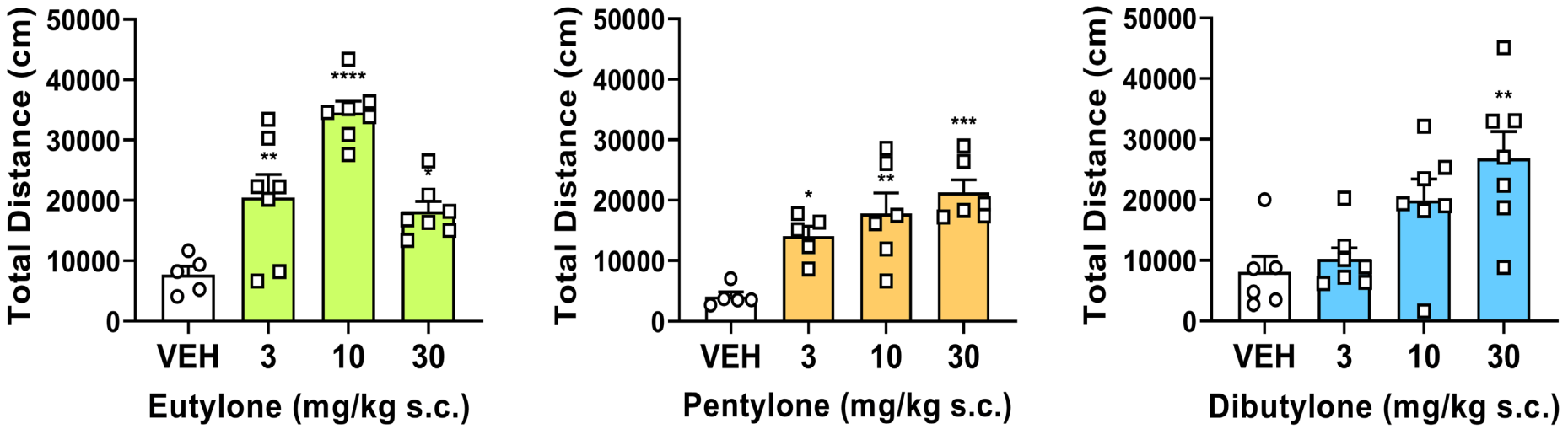
Eutylone and its Isomers are Potent Uptake Inhibitors, with Preference for DAT



Drug	*DAT Uptake IC_{50} (nM)*	*SERT Uptake IC_{50} (nM)*	*DAT/ SERT ratio*
Eutylone	117	686	5.9
Dibutylone	119	>10,000	>84
Pentylone	115	1243	10.8
Methylone	1081	1580	1.5
MDMA	1572	238	0.2

Glatfelter et al., ACS Chem Neurosci. 2021 Apr 7;12(7):1170-1177

Eutylone and its Isomers Induce Locomotor Stimulation, but Eutylone is More Efficacious



Glatfelter et al., ACS Chem Neurosci. 2021 Apr 7;12(7):1170-1177

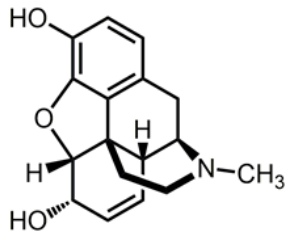
The United States is Experiencing an Unprecedented Opioid Overdose Epidemic

- The US recorded more than 100,000 drug overdose deaths during 2021, a situation exacerbated by COVID-19
- Most overdose deaths involve “synthetic opioids other than methadone” (ICD-10 codes T40.4 or T40.6), mainly fentanyl and its analogs
- Layered upon this grim situation is the emergence of novel synthetic opioids (NSOs) that act as potent mu-opioid agonists

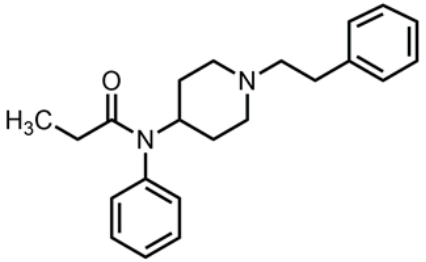
https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

NSOs are Found as Powders, Counterfeit Pills, and Adulterants in Heroin and Cocaine

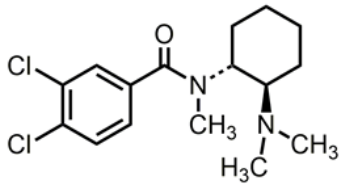
Non-fentanyl NSOs are Appearing in Recreational Drug Markets Worldwide



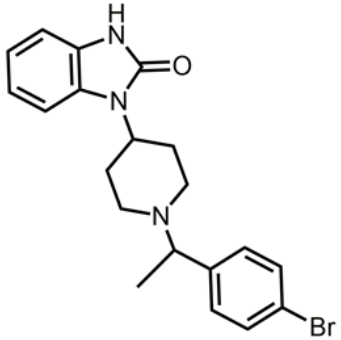
Morphine



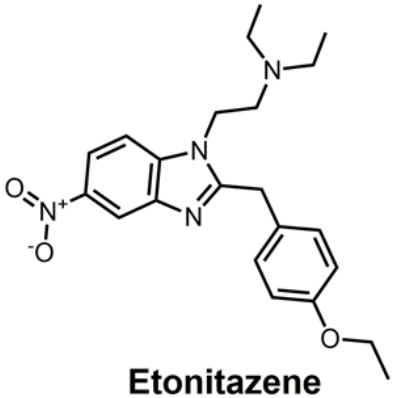
Fentanyl



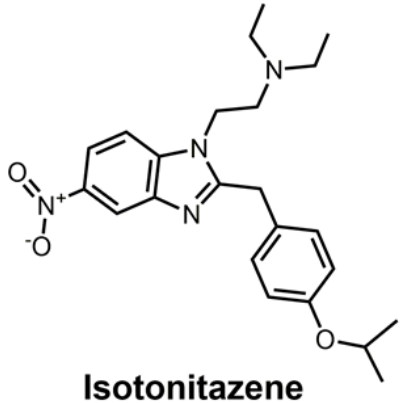
U-47700



Brorphine



Etonitazene



Isotonitazene

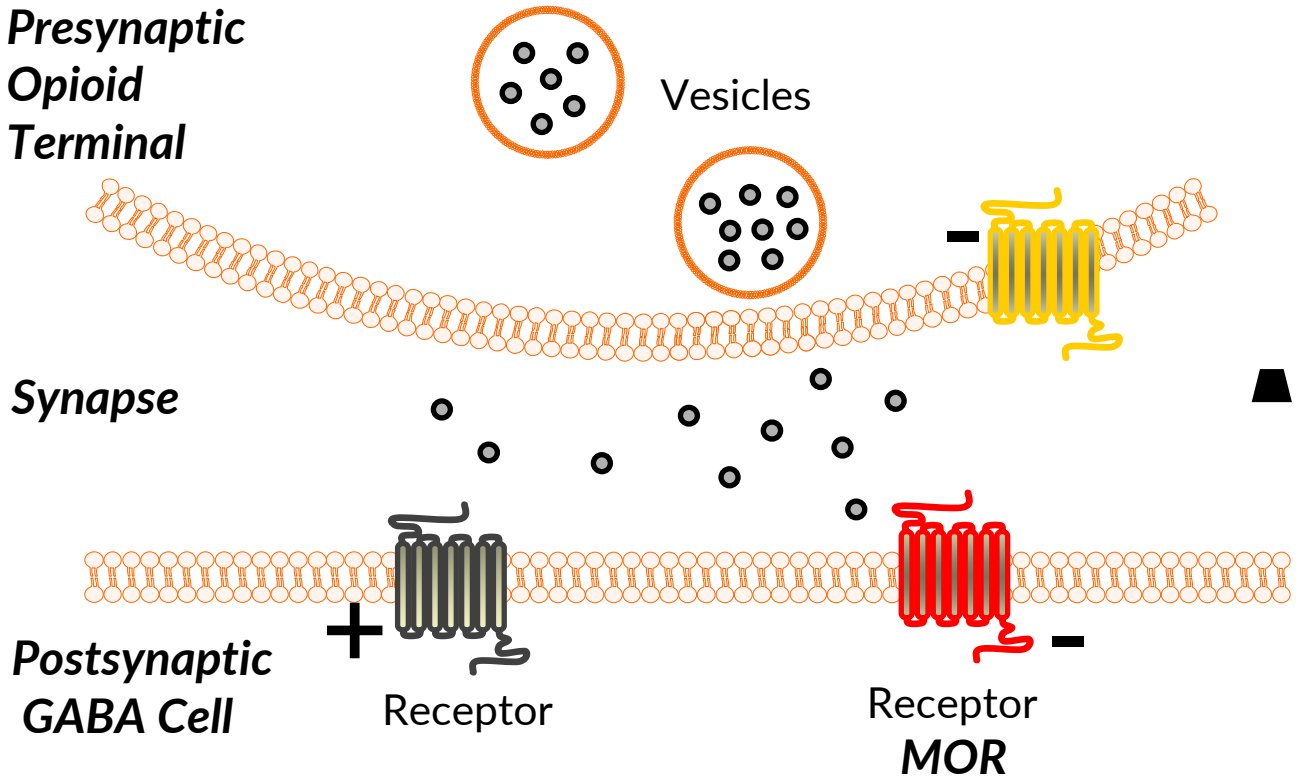
- Legislation banning fentanyl analogs has fostered the appearance of non-fentanyl NSOs
- Analogs of etonitazene have emerged in street drug markets during 2021

Isotonitazene Misuse is Associated with Serious Intoxications and Overdose

- Etonitazene, and related “nitazenes”, were developed as analgesics in the 1960s, but were not approved for clinical use
- Isotonitazene first emerged in US recreational drug markets in late 2019 and early 2020
- Adverse symptoms include stupor, coma, bradycardia, and respiratory depression, which can be fatal

Krotulski et al., J Anal Toxicol. 2020 Jul 31;44(6):521-530.

NSOs Target Mu-opioid Receptors (MOR) as Fully Efficacious Agonists



We Examined the Effects of Non-fentanyl NSOs Using *In Vitro* And *In Vivo* Methods

- *In vitro* receptor assays in brain tissue and cells
  - Binding at MOR, delta- (DOR), and kappa-opioid receptors (KOR)
  - Inhibition of cAMP formation in cells transfected with MOR and Gi
- *In vivo* pharmacodynamic effects in rats
  - Male rats fitted with telemetric temperature transponders
  - Analgesia (hot plate), catalepsy (scores), body temperature

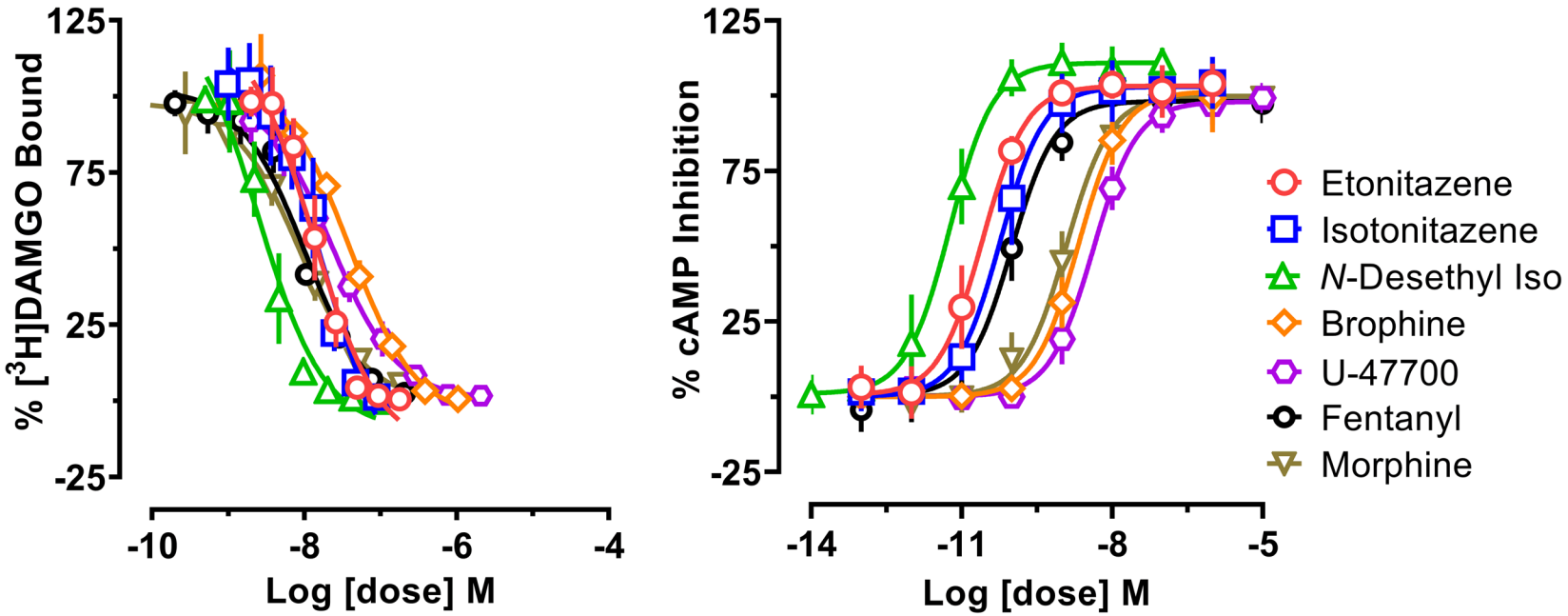
Baumann et al., unpublished

Nitazenes, and Other NSOs, Display Selective Affinity at MOR Over DOR & KOR

	MOR binding Ki (nM)	DOR binding Ki (nM)	KOR binding Ki (nM)	MOR/DOR Ratio	MOR/KOR Ratio
Etonitazene	13.1	592	762	45	58
Isotonitazene	14.9	1068	179	72	12
N-Desethyl Iso	2.4	262	1095	109	456
Brorphine	32.8	848	579	26	18
U-47700	15.4	1112	181	72	12
Fentanyl	6.5	479	204	74	31
Morphine	5.4	228	74	42	14

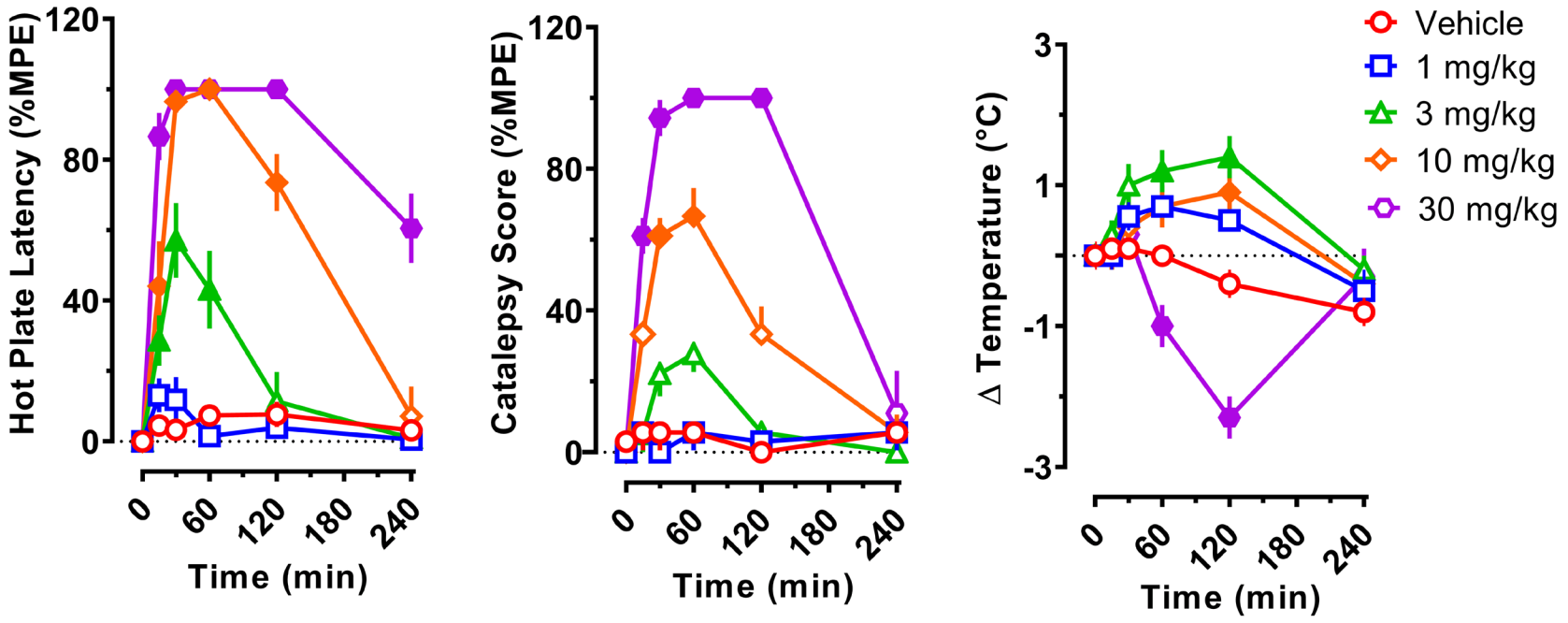
Baumann et al., unpublished

All NSOs are MOR Agonists *In Vitro*, but Affinity Does Not Predict Functional Potency



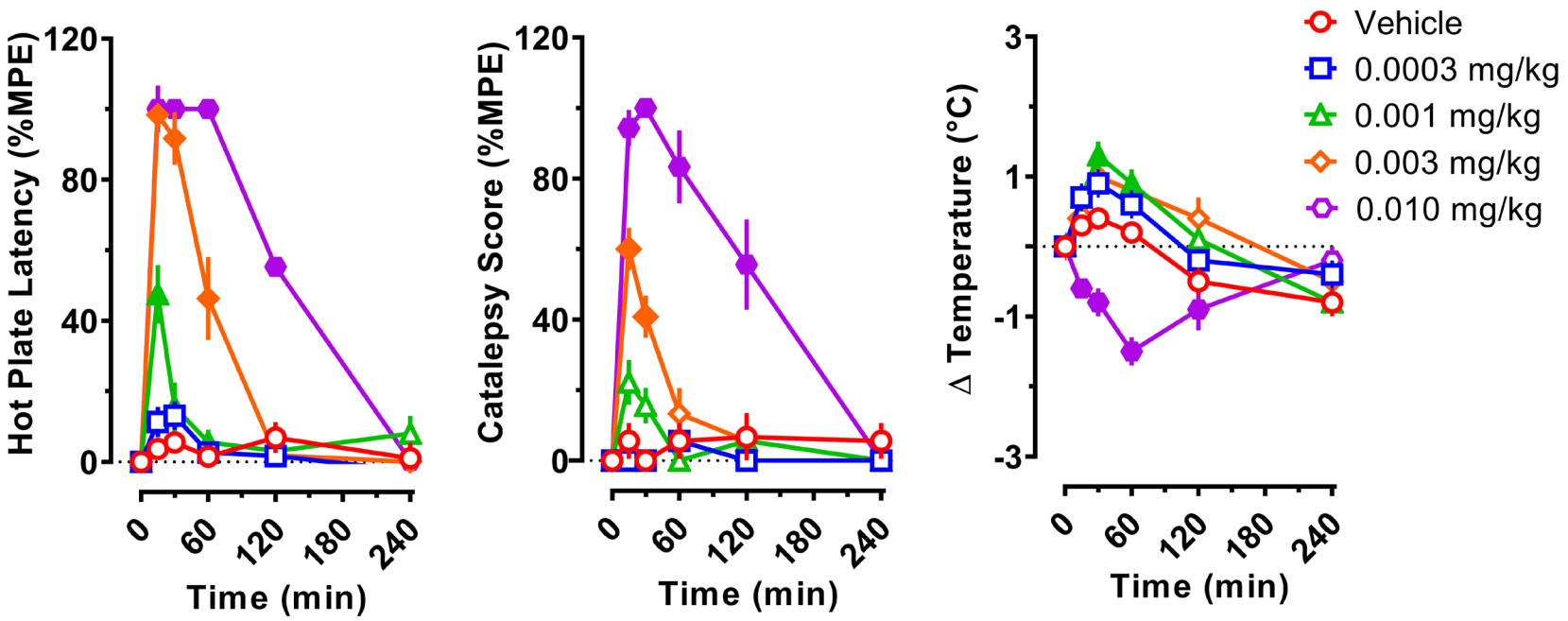
Baumann et al., unpublished

The Opioid Agonist Morphine Produces Analgesia, Catalepsy, and Hypothermia in Rats



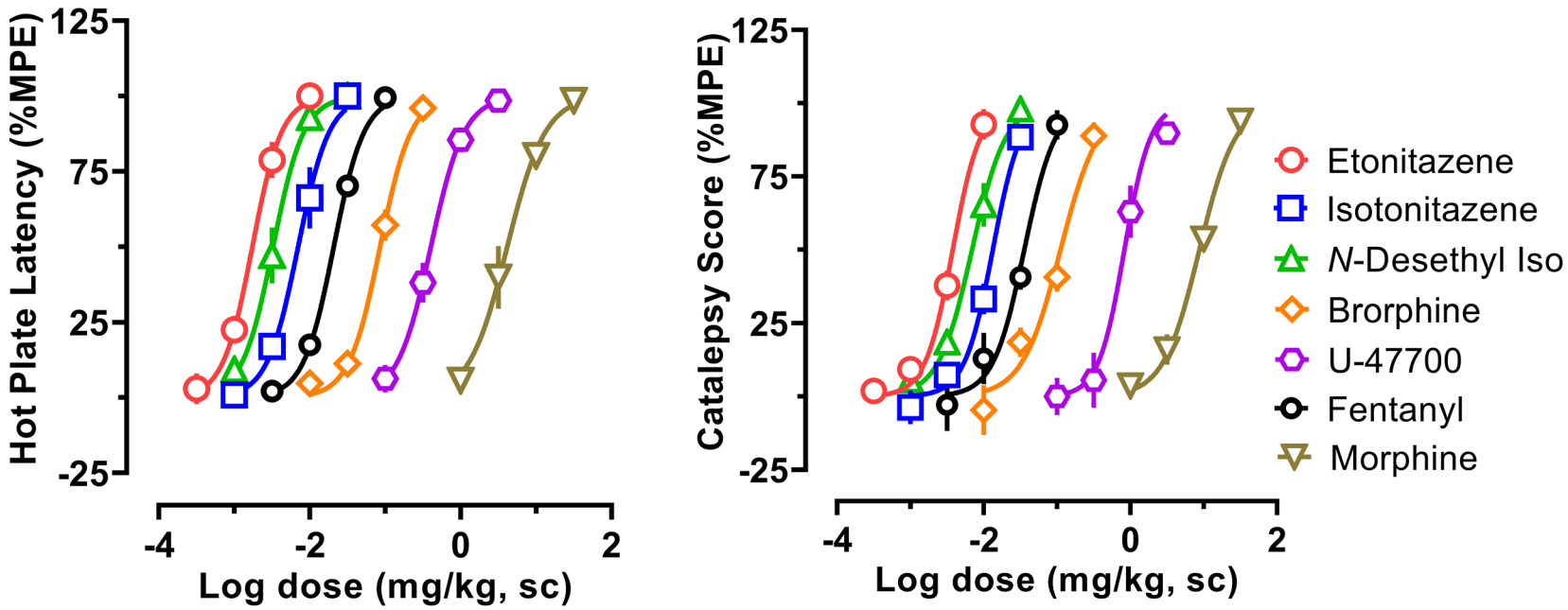
Baumann et al., unpublished

Etonitazene is ~1000-fold More Potent Than Morphine in Producing Opioid Effects *In Vivo*



Baumann et al., unpublished

All NSOs are More Potent Than Morphine, and Nitazenes are More Potent Than Fentanyl



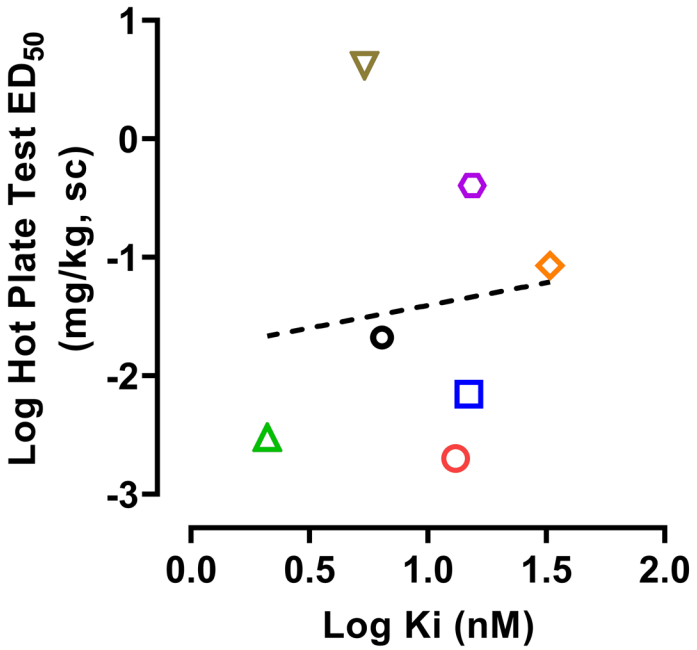
Baumann et al., unpublished

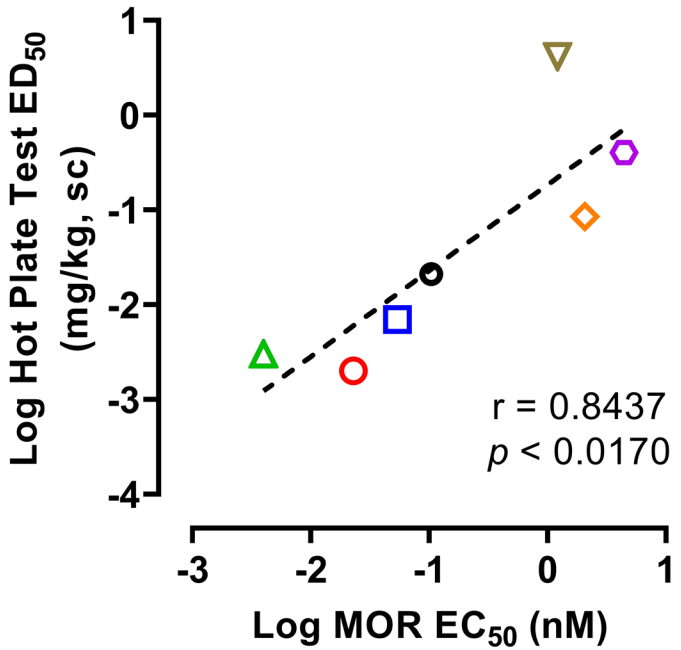
In Vivo Drug Potency is Related to *In Vitro* MOR Functional Potency But Not Affinity

	Antinociception ED_{50} (mg/kg)	Catalepsy ED_{50} (mg/kg)	MOR binding Ki (nM)	MOR function EC_{50} (nM)
Etonitazene	**0.002**	**0.004**	**13.1**	**0.023**
Isotonitazene	0.007	0.014	14.9	0.054
N-Desethyl Isoto	0.003	0.007	0.8	0.004
Brorphine	0.085	0.141	32.8	2.062
U-47700	0.404	0.832	15.4	4.468
Fentanyl	0.021	0.039	6.5	0.104
Morphine	**4.197**	**8.749**	**5.4**	**1.213**

Baumann et al., unpublished

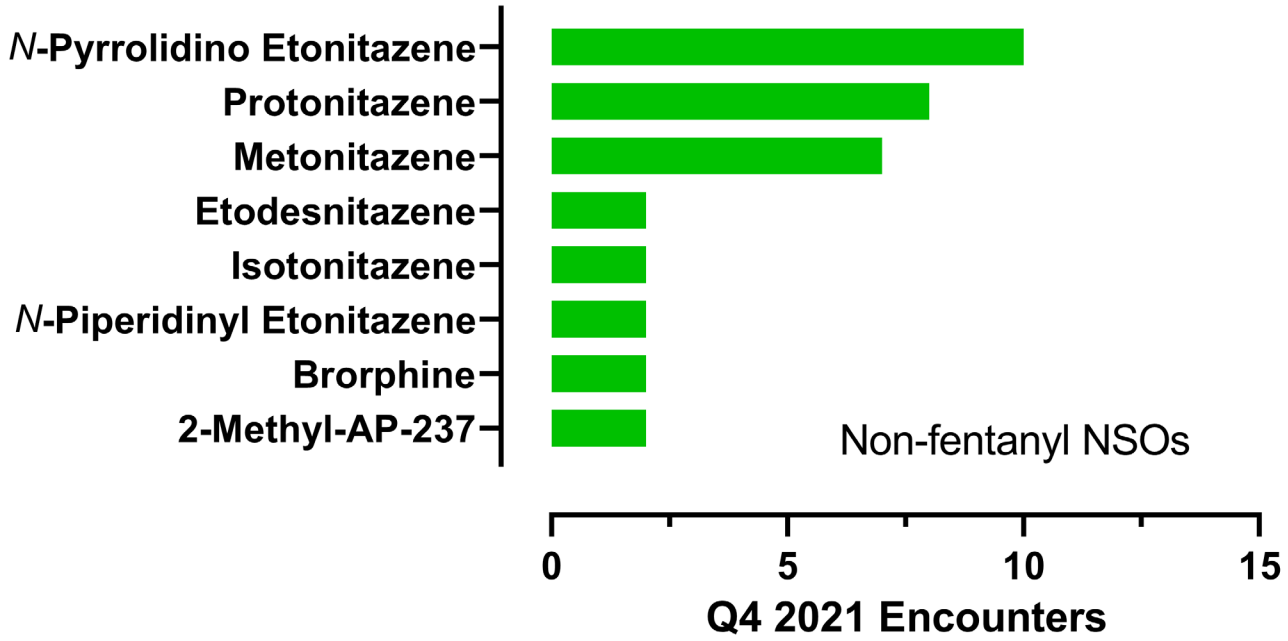
In Vivo Drug Potency is Correlated With *In Vitro* MOR Function But Not Affinity





Baumann et al., unpublished

Additional Nitazene Analogs Were Identified in Human Casework During 2021



Center for Forensic Science Research & Education (CFSRE), 2021

Key Takeaways

- Stimulant NPS, like eutylone, are potent DAT inhibitors
  - Stimulant properties of eutylone are distinct from those of MDMA
  - Eutylone in counterfeit Ecstasy pills could present risks to users

- NSOs, like isotonitazene, are potent MOR agonists
  - Nitazenes are more potent that fentanyl *in vivo*
  - *In vivo* potency is predicted by *in vitro* MOR function but not affinity
  - NSOs present grave risk to users who are unknowingly exposed