

*Designer Drugs: The Dark Side of Organic Synthesis*



**Jennifer Nguyen**  
MacMillan Group  
Literature Talk  
November 15, 2024

*Organic synthesis advances pharmaceutical drug discovery*



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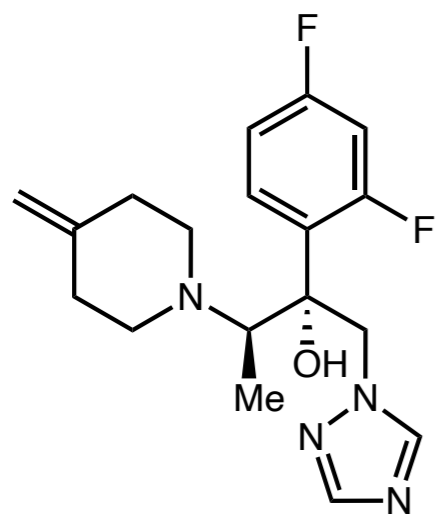
*Organic synthesis advances pharmaceutical drug discovery*



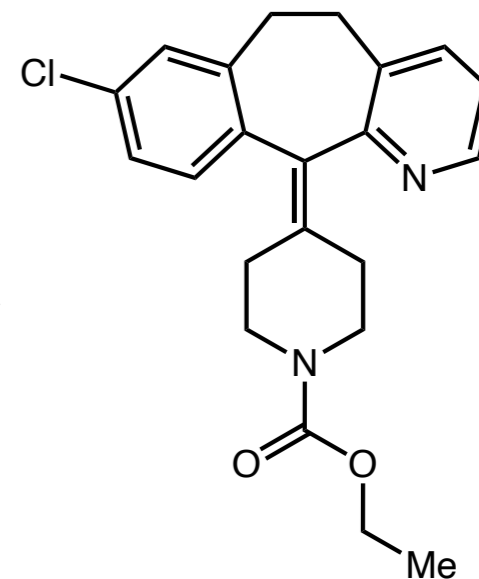
**Drugs can be made anywhere, anytime**



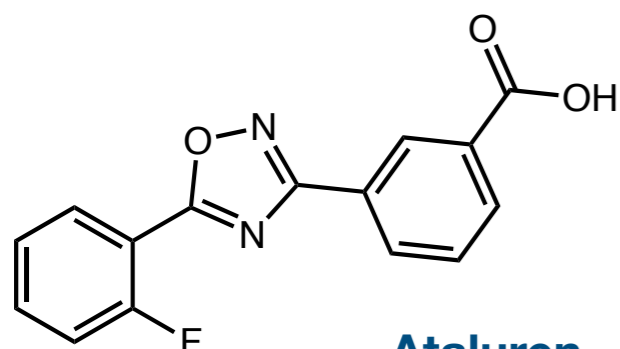
# Organic synthesis advances pharmaceutical drug discovery



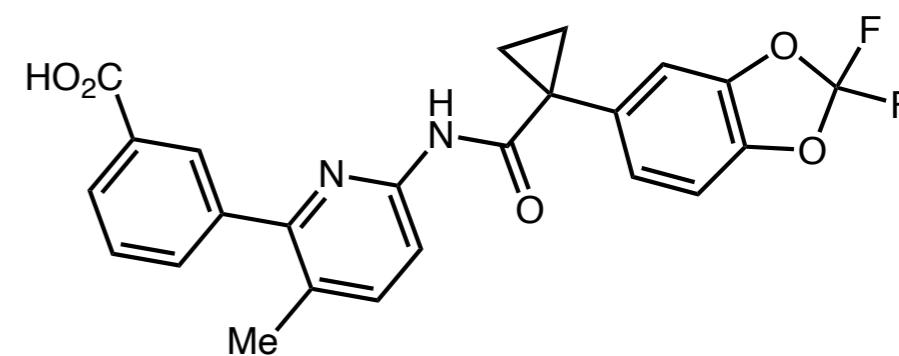
**Efinconazole**  
antifungal



**Loratadine**  
antihistamine

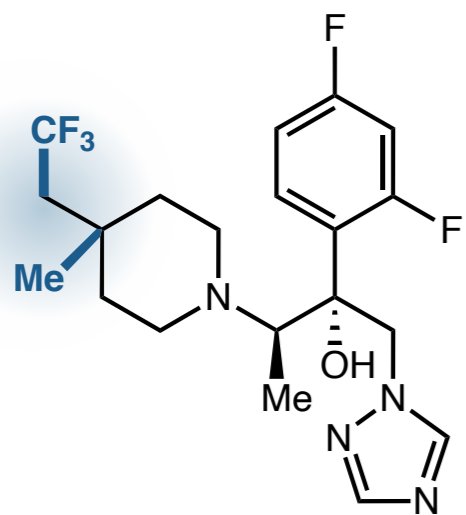


**Ataluren**  
muscular dystrophy

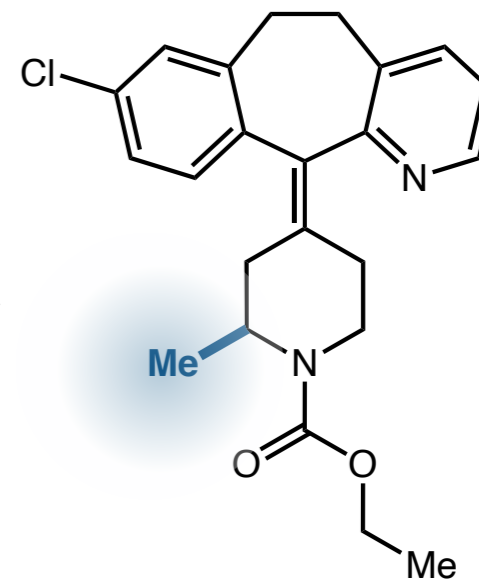


**Lumacaftor**  
cystic fibrosis treatment

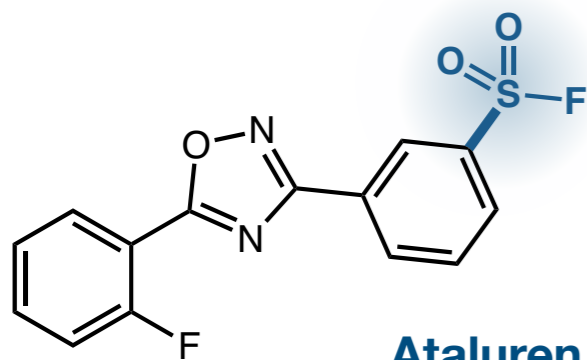
# Organic synthesis advances pharmaceutical drug discovery



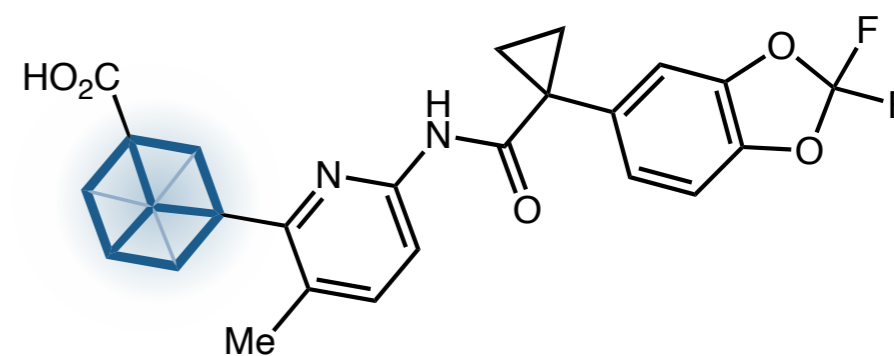
**Efinconazole**  
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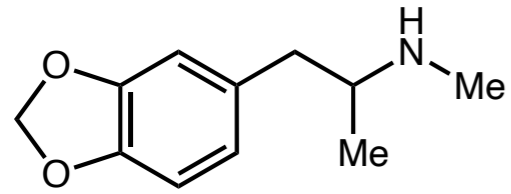


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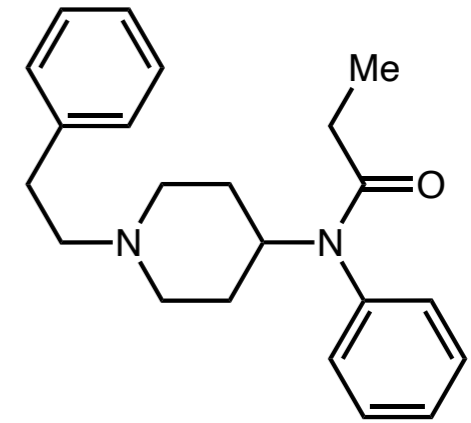


**Lumacaftor**  
cystic fibrosis treatment

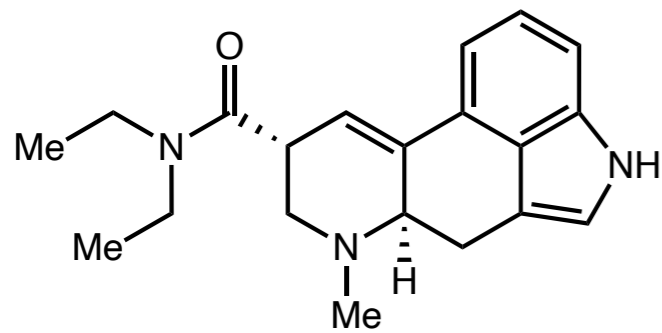
*...but it also advances illicit drug discovery*



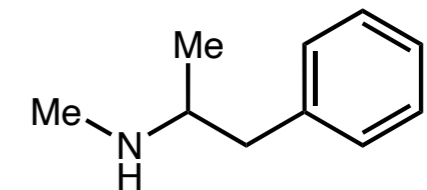
**Ecstasy**



**Fentanyl**



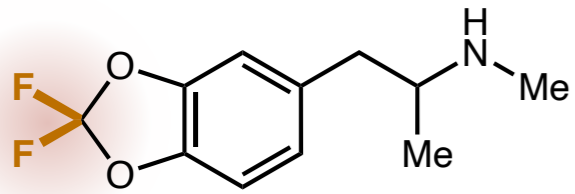
**LSD**



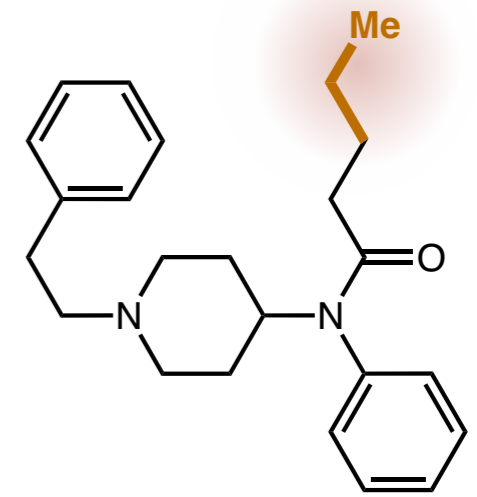
**Methamphetamine**



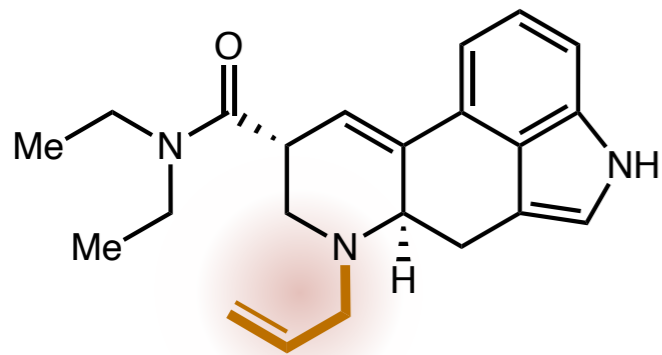
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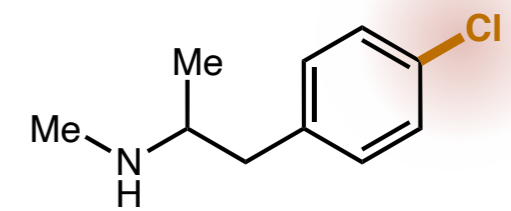
**Ecstasy**



**Fentanyl**



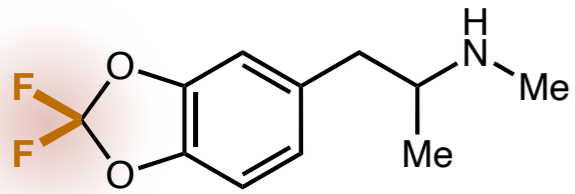
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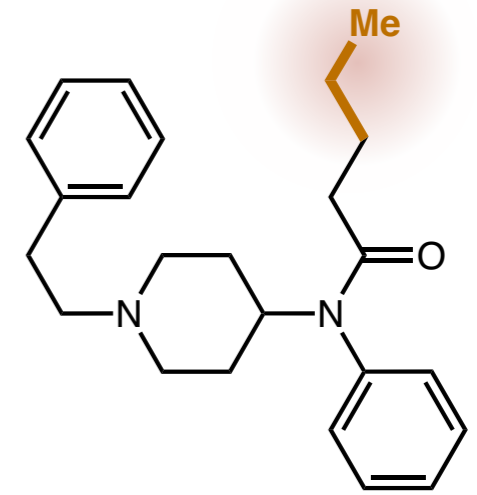
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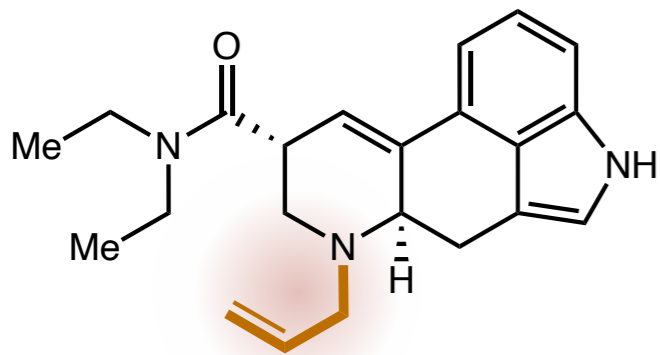
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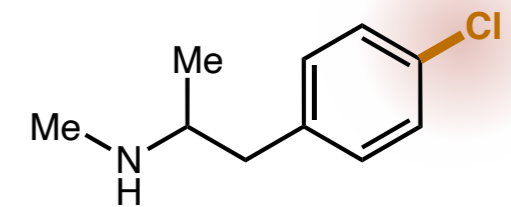
~~Ecstasy~~



~~Fentanyl~~

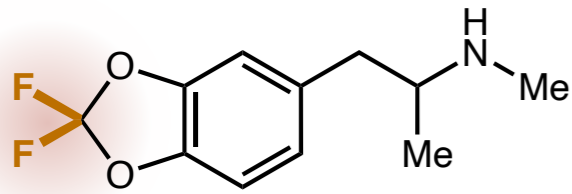


~~LSD~~

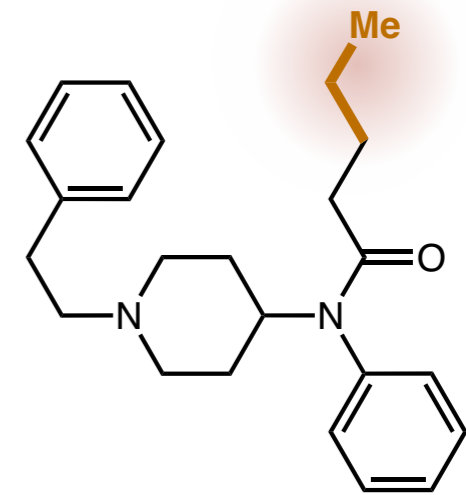


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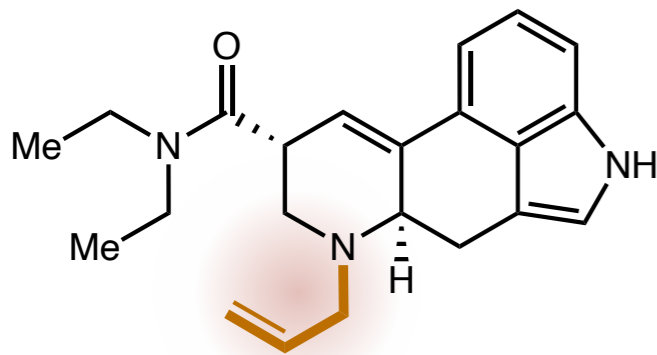
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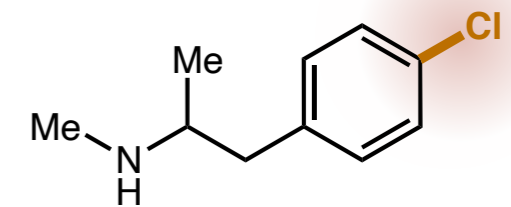
~~Fentanyl~~

### Designer drug

a synthetic analog of a legally restricted or prohibited drug, devised to circumvent drug laws



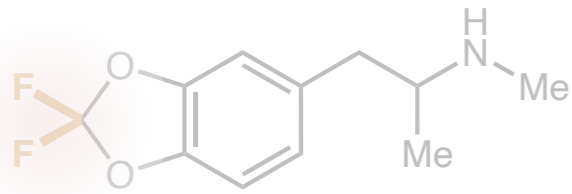
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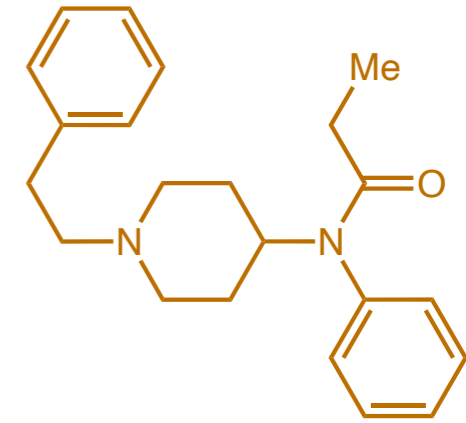
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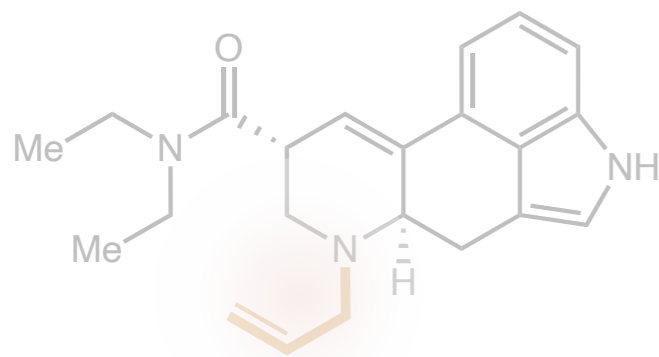
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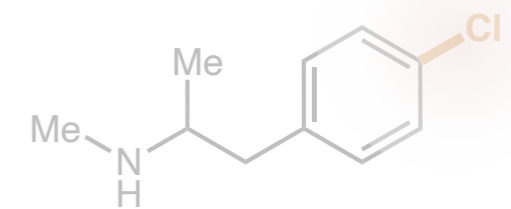
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**LSD**



**Methamphetamine**

## *Development of fentanyl (1960)*



**Paul Janssen**



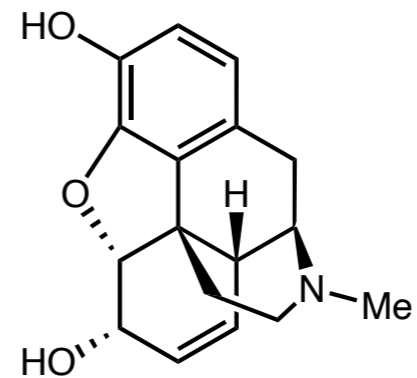
## Development of fentanyl (1960)



Paul Janssen



Developed as a more potent painkiller than morphine



Morphine

*from opium poppies*



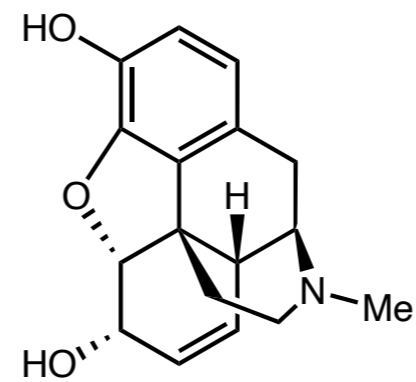
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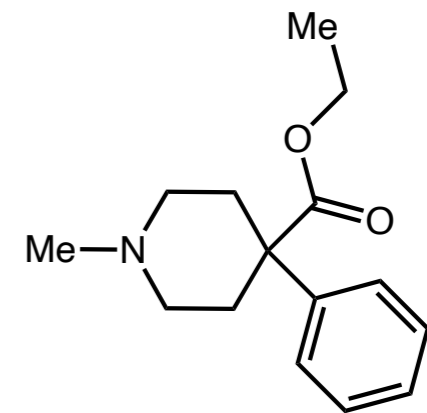


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Morphine

*from opium poppies*



Meperidine

*synthetic*

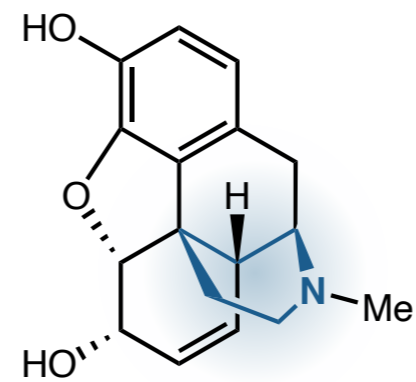
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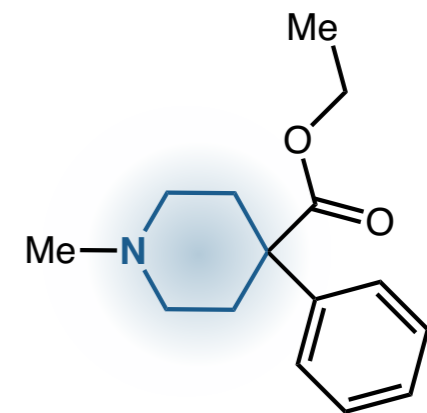


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*from opium poppies*



Meperidine

*synthetic*

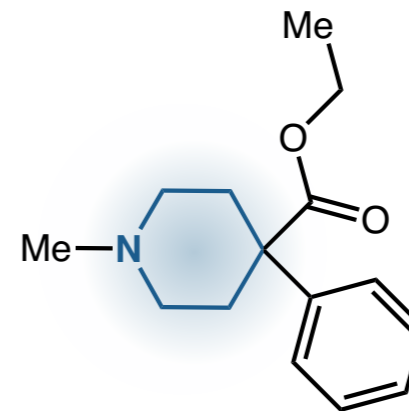
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Meperidine

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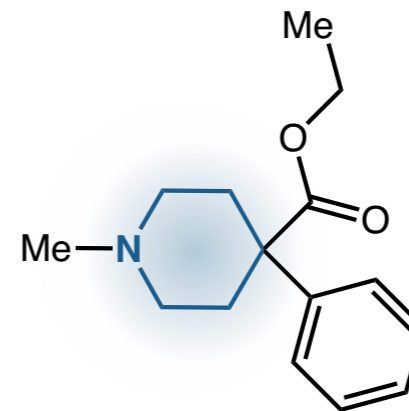
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Meperidine

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- About 10x less potent than morphine

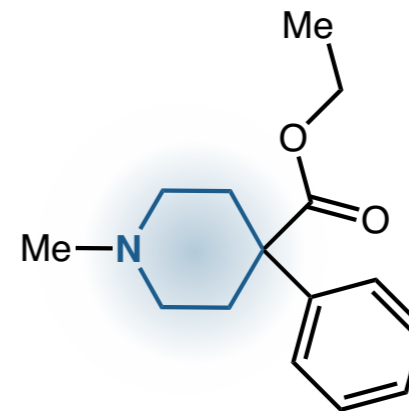
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Developed as a more potent painkiller than morphine



Meperidine

*synthetic*

- About 10x less potent than morphine
- Poorly lipid soluble

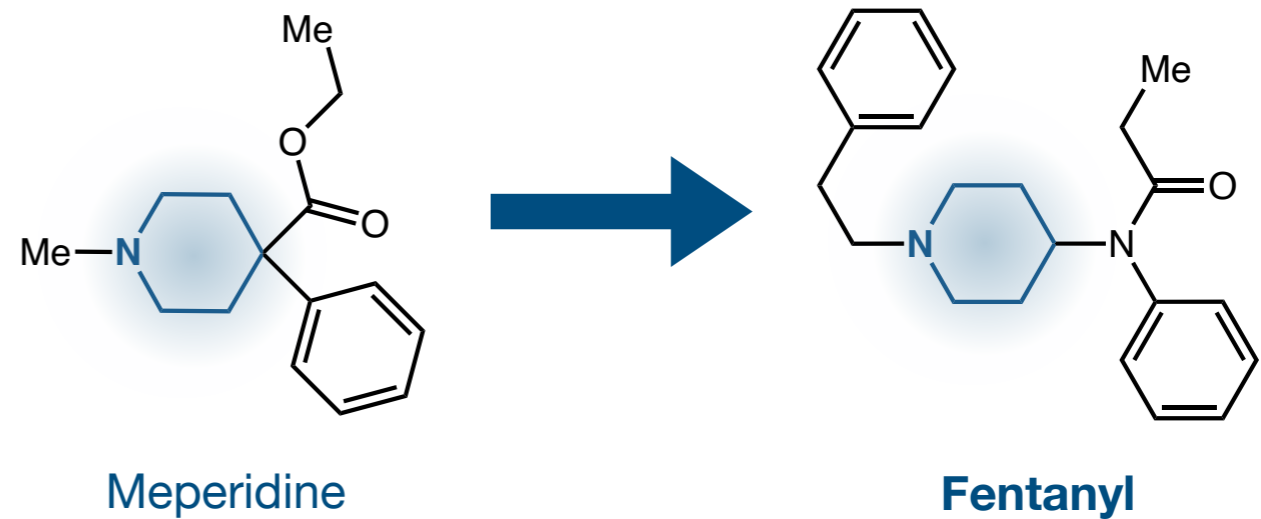
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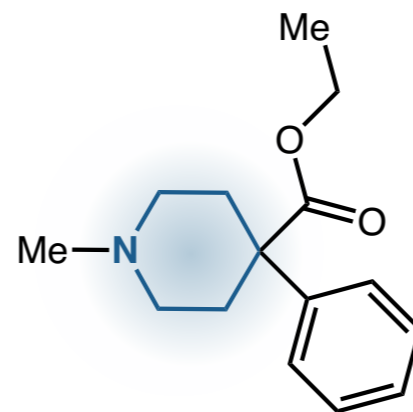
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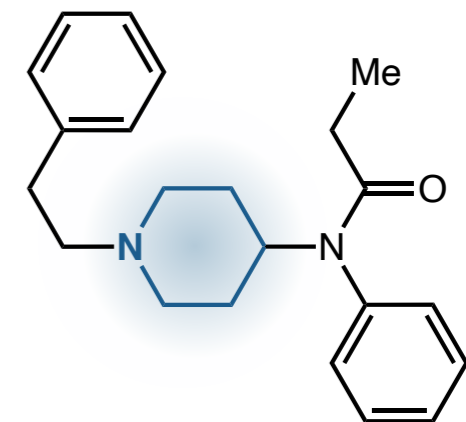
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Developed as a more potent painkiller than morphine



Meperidine



Fentanyl

- $\log P = 2.98$
- Crosses BBB in 1-2 min



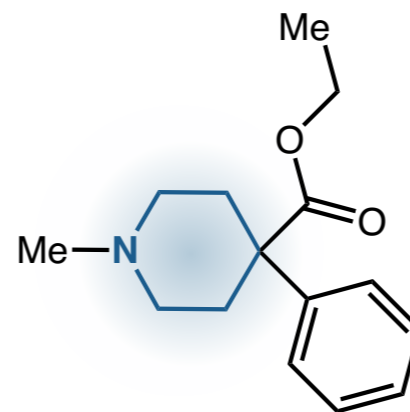
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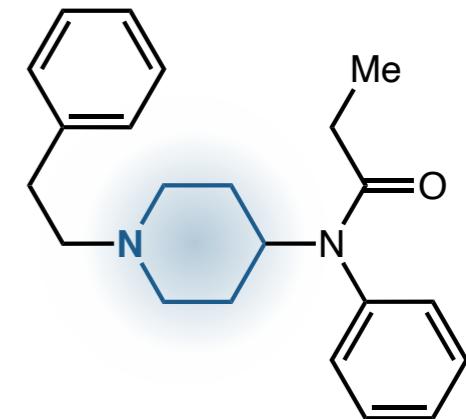
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Meperidine

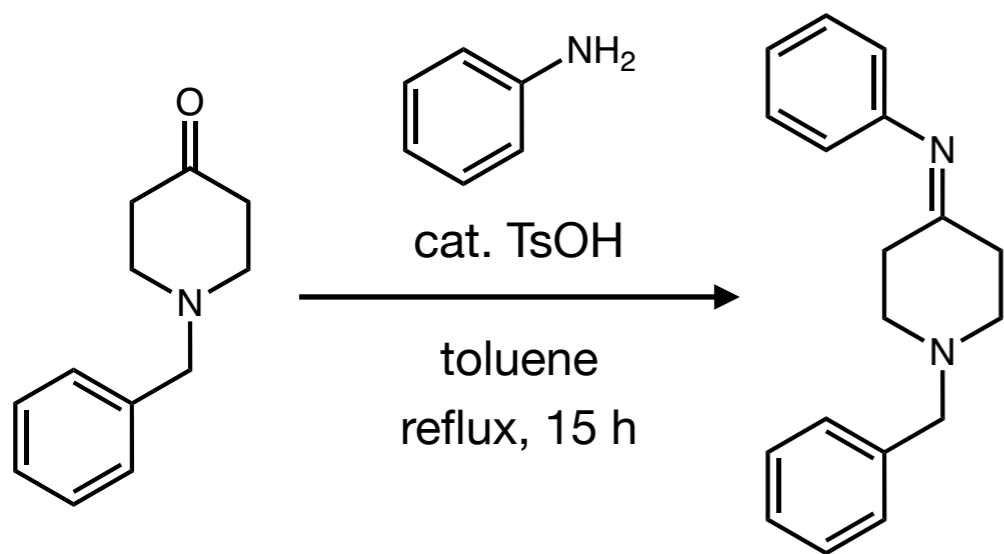


Fentanyl

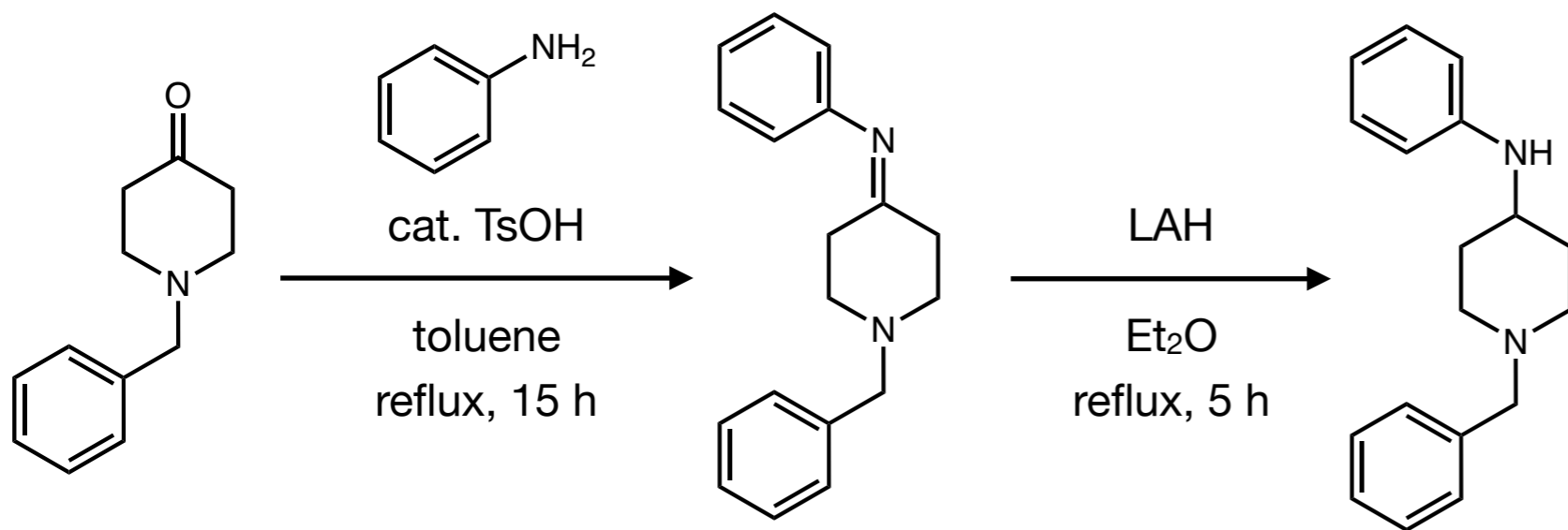
- $\log P = 2.98$
- Crosses BBB in 1-2 min
- **80-100x more potent than morphine**

*Janssen synthesis of fentanyl (1965)*

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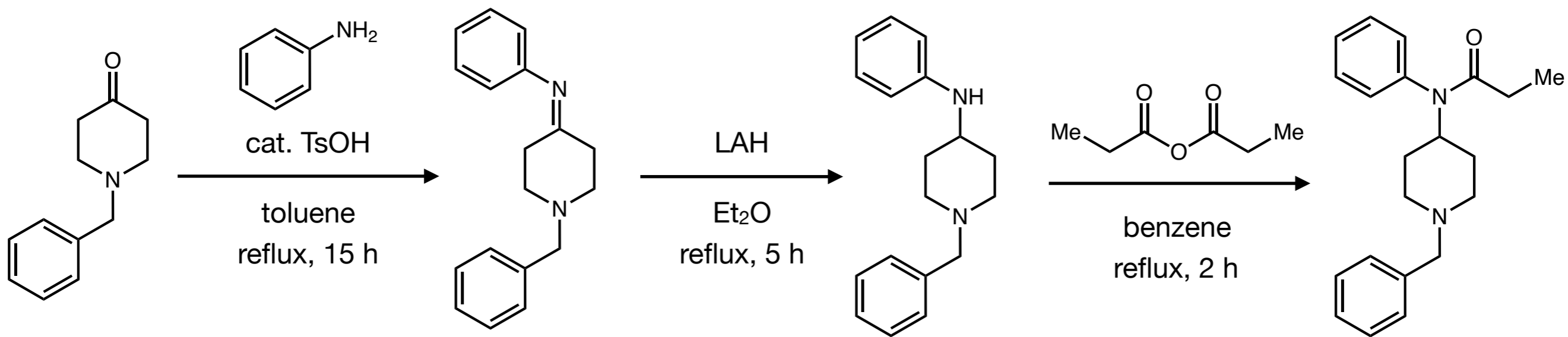


*Janssen synthesis of fentanyl (1965)*

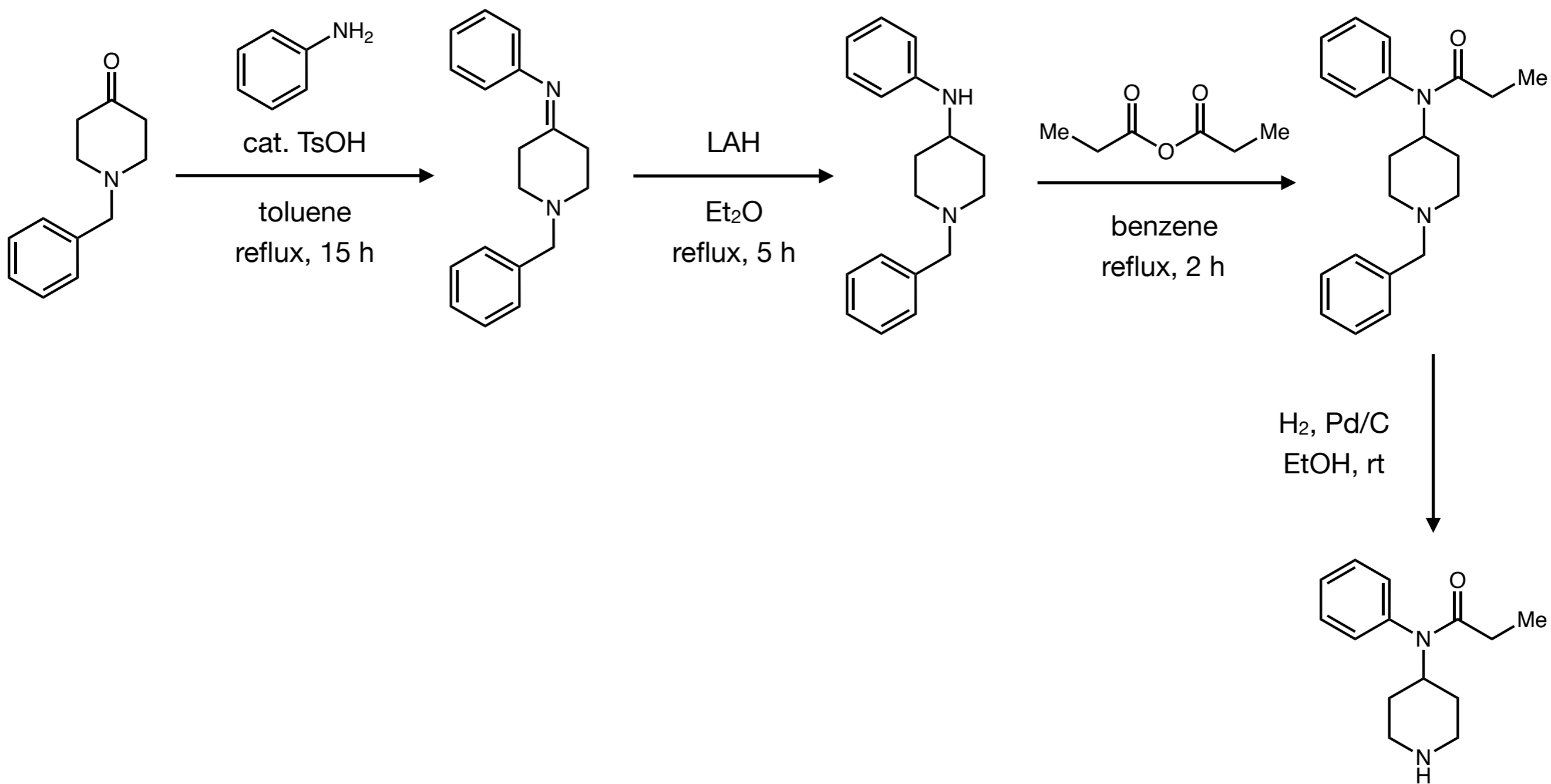




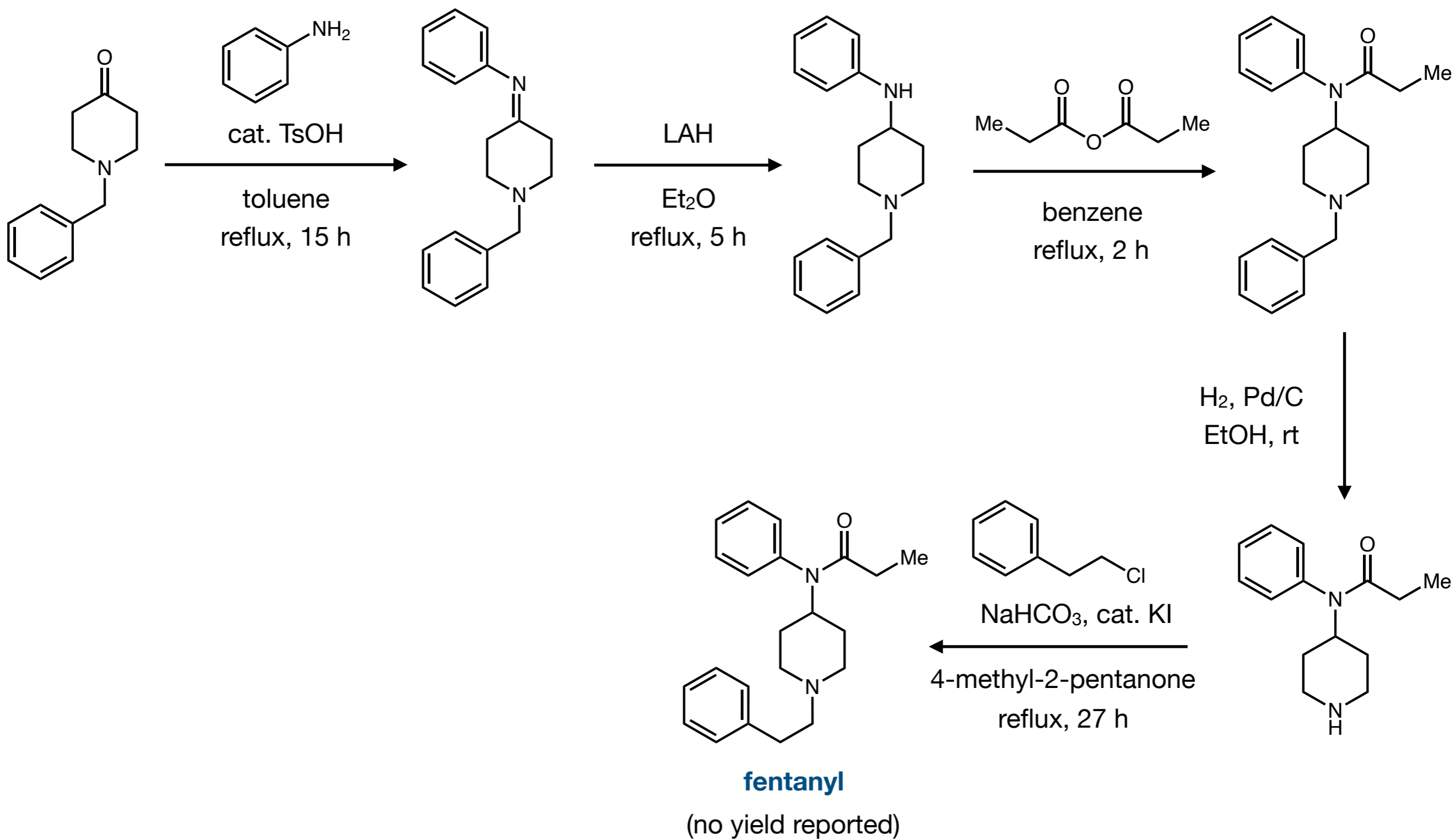
*Janssen synthesis of fentanyl (1965)*



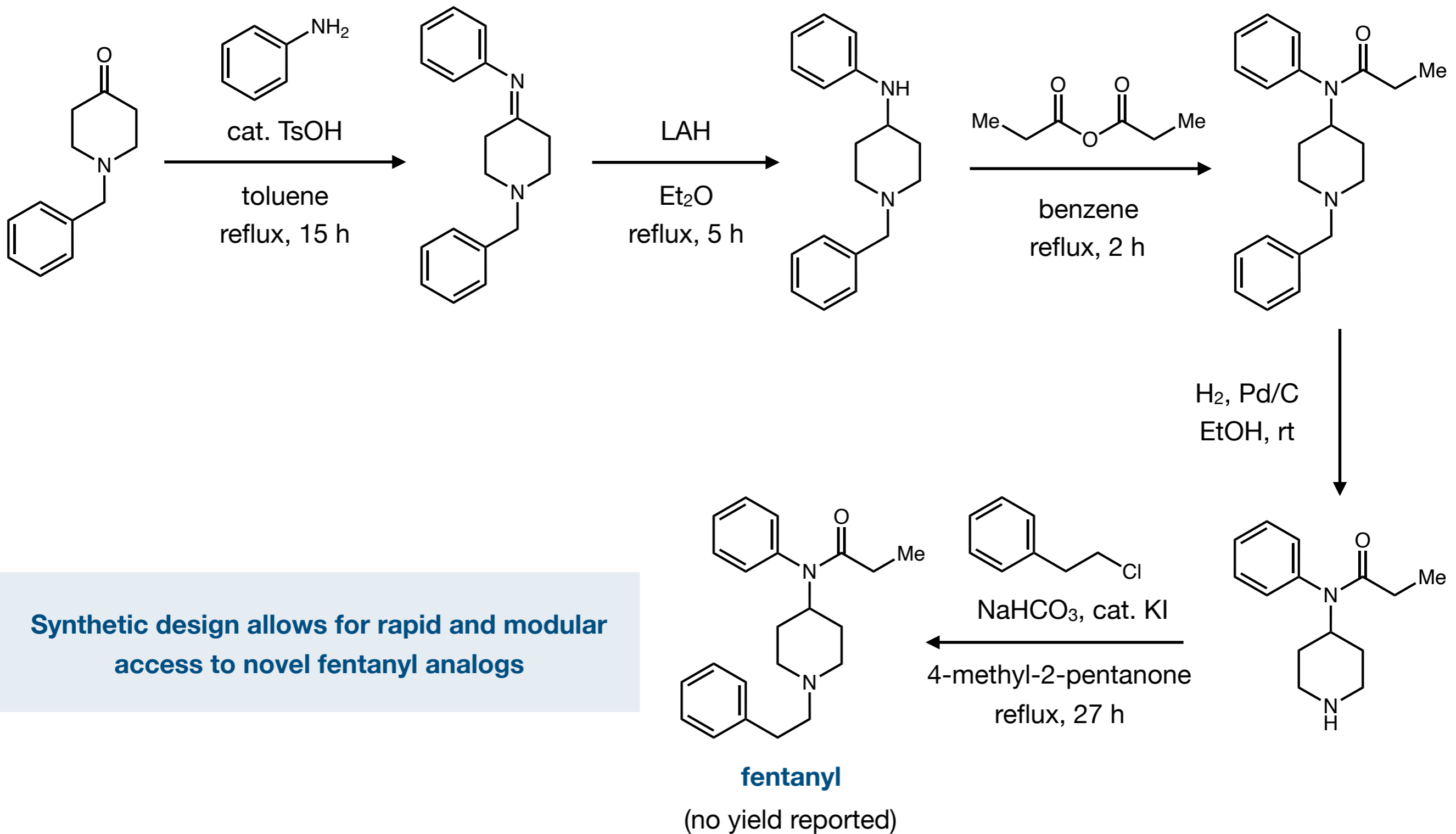
# Janssen synthesis of fentanyl (1965)



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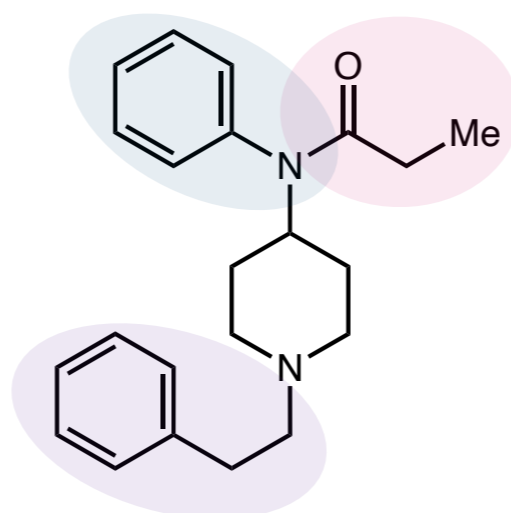
# Janssen synthesis of fentanyl (1965)



**Synthetic design allows for rapid and modular access to novel fentanyl analogs**

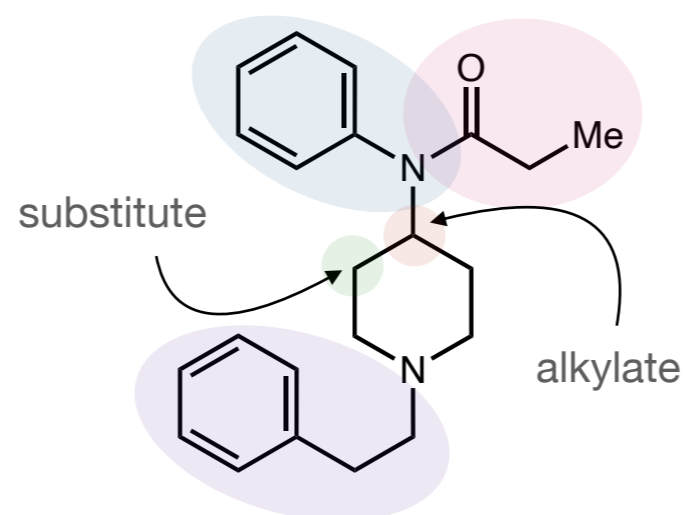


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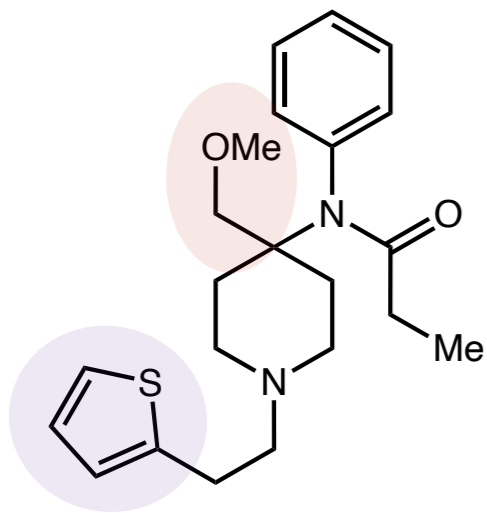
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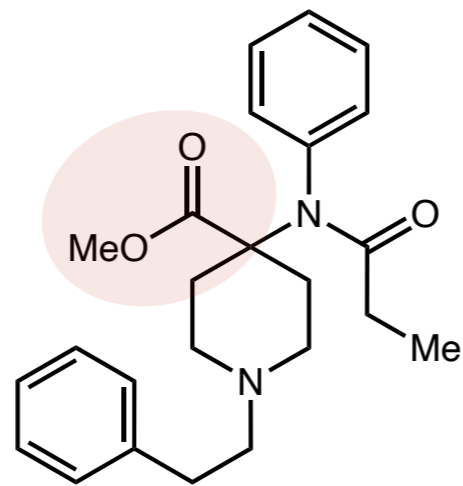


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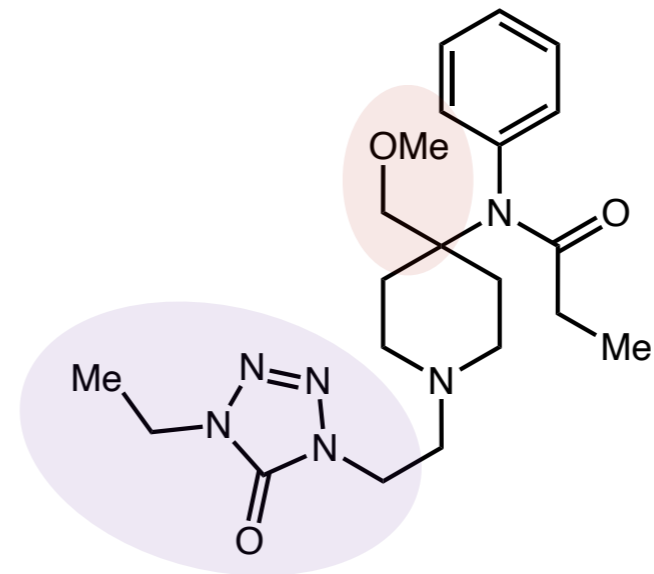
## Fentanyl analogs developed by Janssen (1970s)



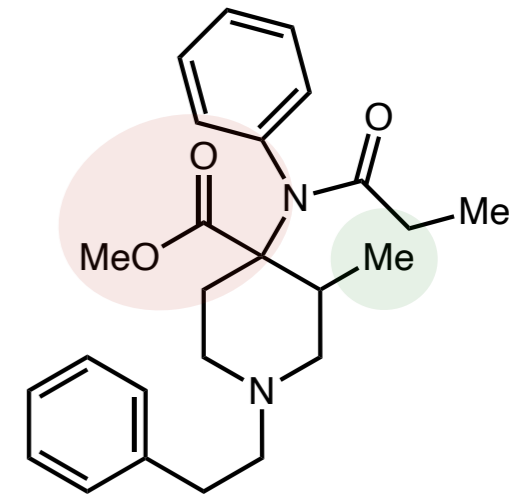
Sufentanil (1974)



Carfentanil (1974)



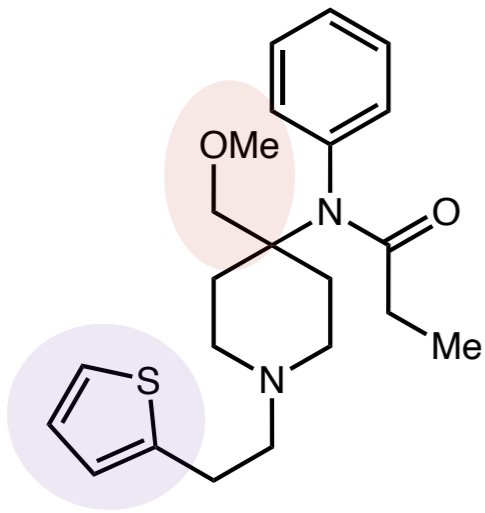
Alfentanil (1976)



Lofentanil (1976)

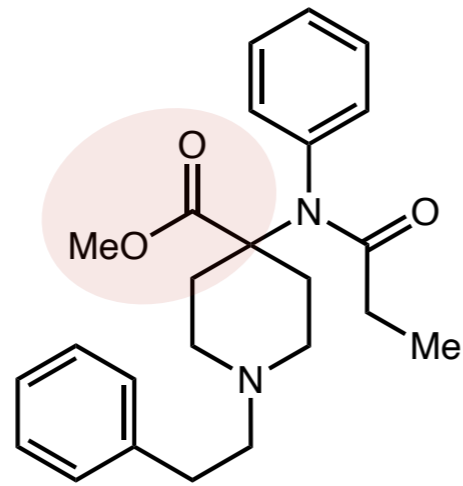
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## Fentanyl analogs developed by Janssen (1970s)



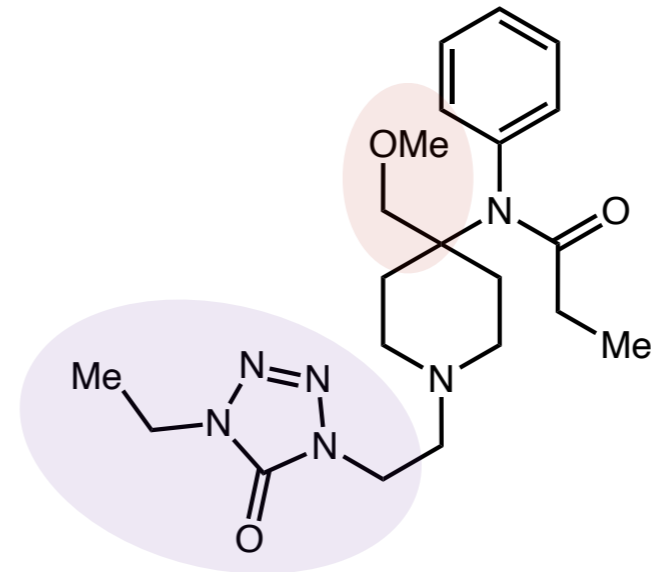
Sufentanil (1974)

**5-10x more potent**



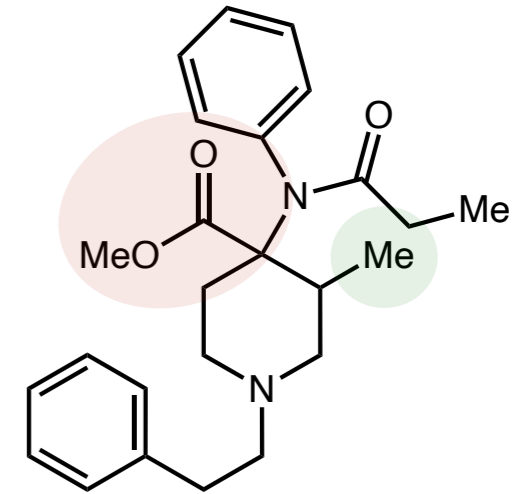
Carfentanil (1974)

**100x more potent**



Alfentanil (1976)

**5x less potent**



Lofentanil (1976)

**>100x more potent**

**Highly potent drugs**

*Fentanyl analogs developed by Janssen (1970s)*



A lethal dose of fentanyl (2 mg)

**Highly potent drugs**



*Fentanyl analogs developed by Janssen (1970s)*



A lethal dose of fentanyl (2 mg)

**Highly potent drugs**



**High potential for abuse**

*Incidents of fentanyl abuse emerge (1970s)*

## Potential lethal drug stolen from clinic

A drug stolen from a veterinary clinic in Carlisle is extremely dangerous and could cause death, an official said Tuesday. Police.

Troopers said the drug Somlethyl was stolen from the Carlisle Veterinarian Small Animal Clinic on Route 11 Monday night or early Tuesday.

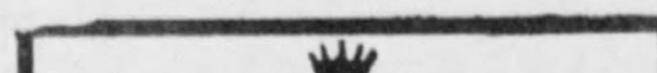
Dr. Robert L. Rill Jr., who reported the burglary, said that the use of the drug

could be fatal unless properly administered. In a local radio transmission the drug is used in the animals, and it can

**High potential for abuse**

including Demerol, morphine, and acetaminophen, also were taken.

Anyone with information regarding the burglary is asked to contact the State Police at the Carlisle substation.



# Ex-employee is arrested in hospital drug theft

*e emerge (1970s)*

Grand Prairie police Thursday arrested one person in Grand Prairie and recovered a large quantity of drugs taken during a Monday night burglary of the narcotics locker at the Grand Prairie Community Hospital.

The drugs recovered by police detectives Doug Crahtree and Phil

lice that the hospital drugs were on the market.

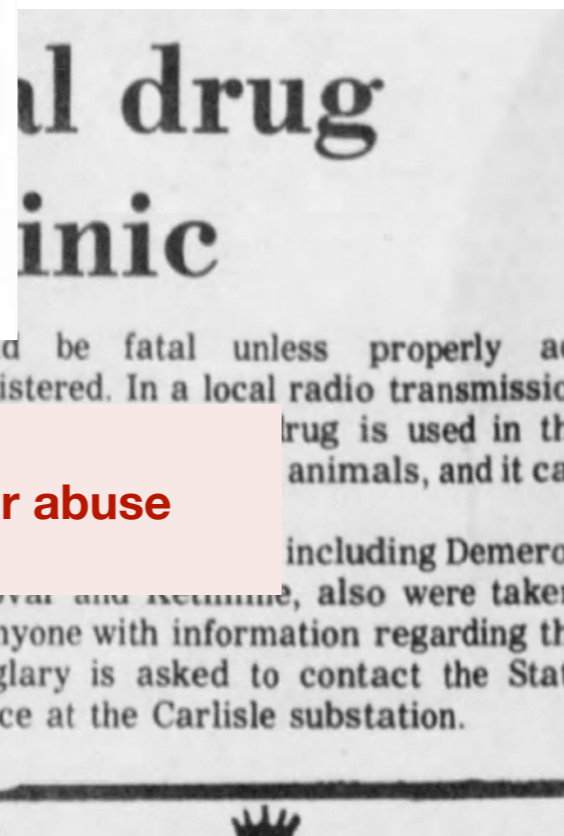
Those arrests led officers Thursday to the former hospital employee who led officers to the drugs which were locked in a locker at the Greyhound Bus Station in Dallas.

Drugs taken in the burglary included large quantities of

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# Thief Gets Poisonous Narcotic

MARTINEZ—Sheriff's deputies today are looking for a burglar who took narcotics from a West Pittsburg veterinarian's office and whose life may be in danger.

Among the drugs he stole was a small bottle of "innovar-vet,"

# Ex-employee is arrested in hospital drug theft

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# Doctor denies giving drugs to himself during surgery

By Mitchell Locin

AN ANESTHESIOLOGIST accused of administering narcotics to himself during surgery denied the charges Wednesday and suggested that a disagreement with another doctor prompted the complaint.

Dr. Mohammed Ali Navabi-Madar, an anesthesiologist at St. Elizabeth's Hospital, bared his forearms at the state Medical Disciplinary Board hearing to

his testimony as a hardworking, dedicated professional who worked long hours and who handled 300 or 400 more operations a year than did other anesthesiologists at the hospital.

HE SAID HE had a good working relationship with Dr. Philip G. Coleman, a surgeon who testified at an earlier hearing that Navabi-Madar's actions imperiled the success of an intricate lung operation last April. But Navabi-Madar said he had a disagreement with Cole



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# Doctor denies giving drugs to himself during surgery

# Death, severe brain damage blamed on pre-surgery drug

By RUTH ELLEN THOMPSON  
Newhouse News Service  
ST. LOUIS — A once-vivacious 26-year-old woman is kept alive by tubes in a Cleveland clinic.

against McNeil Laboratories, Inc., of Fort Washington, Pa., manufacturer of a common link between these persons — the drug Innovar.

Various physicians and hospitals are named as

agency. To date, the FDA has said only that it had "an overkill" of such reports and that it is conducting a thorough investigation.

DePaul Hospital here has discontinued use of the drug.

and brain damage.

Adriani said the AMA's board of directors tried to force the council on drugs to delete the words "not recommended" from its drug evaluation of Innovar in a volume

care for their disabled daughter. "To pay for her care will bankrupt me, but that's not the important thing," Foster said. "We will put whatever we have to into it."

The Fosters' suit says they

after Innovar was first marketed.

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A suit seeking \$1 million on his behalf says he was given Innovar during an emergency operation at a hospital near his home in Rochester, N.Y., and suffered permanent brain damage and partial paralysis.

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anesthesiologist at St. Elizabeth's Hospital, bared his forearms at the state Medical Disciplinary Board hearing to

iled the success of an intricate lung operation last April. But Navabi-Madar said he had a disagreement with Colo



# Ex-employee is arrested in hospital drug theft

Grand Prairie police Thursday arrested one person in Grand Prairie and recovered a large quantity of drugs taken during a Monday night burglary of the narcotics locker at the Grand Prairie Community Hospi-

lice that the hospital drugs were on the market.

Those arrests led officers Thursday to the former hospital employe who led officers to the drugs which were locked in a locker at the Grey-tation in Dallas.

## Medic charged

A suburban doctor has been charged with injecting himself with narcotics while overseeing an operation, state officials announced.

The Illinois Department of Registration and Education made the charges and said it was seeking to revoke the license of Dr. Mohammed Ali Navabi-Madar, 41, Park Ridge.

The complaint lodged against Navabi-Madar on Nov. 12 accused him of injecting himself with a depressant drug (sublimazen) while he served as an anesthesiologist during a lung operation at St. Elizabeth Hospital on Chicago's northwest side.

High potential for abuse

# Doctor denies giving drugs to himself during surgery

## Death, severe brain damage blamed on pre-surgery drug

By RUTH ELLEN THOMPSON  
Newhouse News Service  
ST. LOUIS — A once-vivacious 26-year-old woman is kept alive by tubes in a Cleveland clinic.

against McNeil Laboratories, Inc., of Fort Washington, Pa., manufacturer of a common link between these persons — the drug Innovar.

Various physicians and hospitals are named as

agency. To date, the FDA has said only that it had "an overkill" of such reports and that it is conducting a thorough investigation.

DePaul Hospital here has discontinued use of the drug.

and brain damage.

Adriani said the AMA's board of directors tried to force the council on drugs to delete the words "not recommended" from its drug evaluation of Innovar in a volume

care for their disabled daughter. "To pay for her care will bankrupt me, but that's not the important thing," Foster said. "We will put whatever we have to into it."

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# Thief Gets Poisonous Narcotic

MARTINEZ — Sheriff's deputies today are looking for a burglar who took narcotics from a West Pittsburg veterinarian's office and whose life may be in danger.

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## *Two unusual drug overdose deaths (1979)*



- China White (“Real Powerful Heroin”)



## *Two unusual drug overdose deaths (1979)*



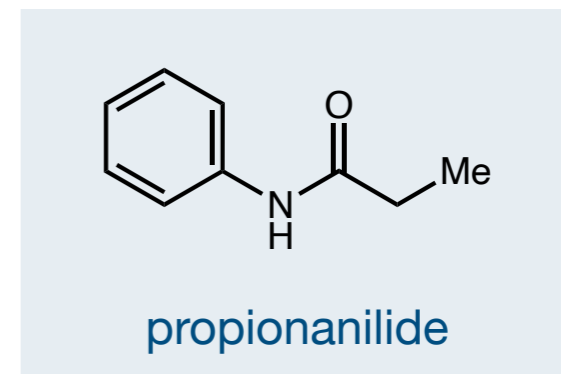
- China White (“Real Powerful Heroin”)
- No heroin or other narcotics detected by toxicological analysis



## Two unusual drug overdose deaths (1979)



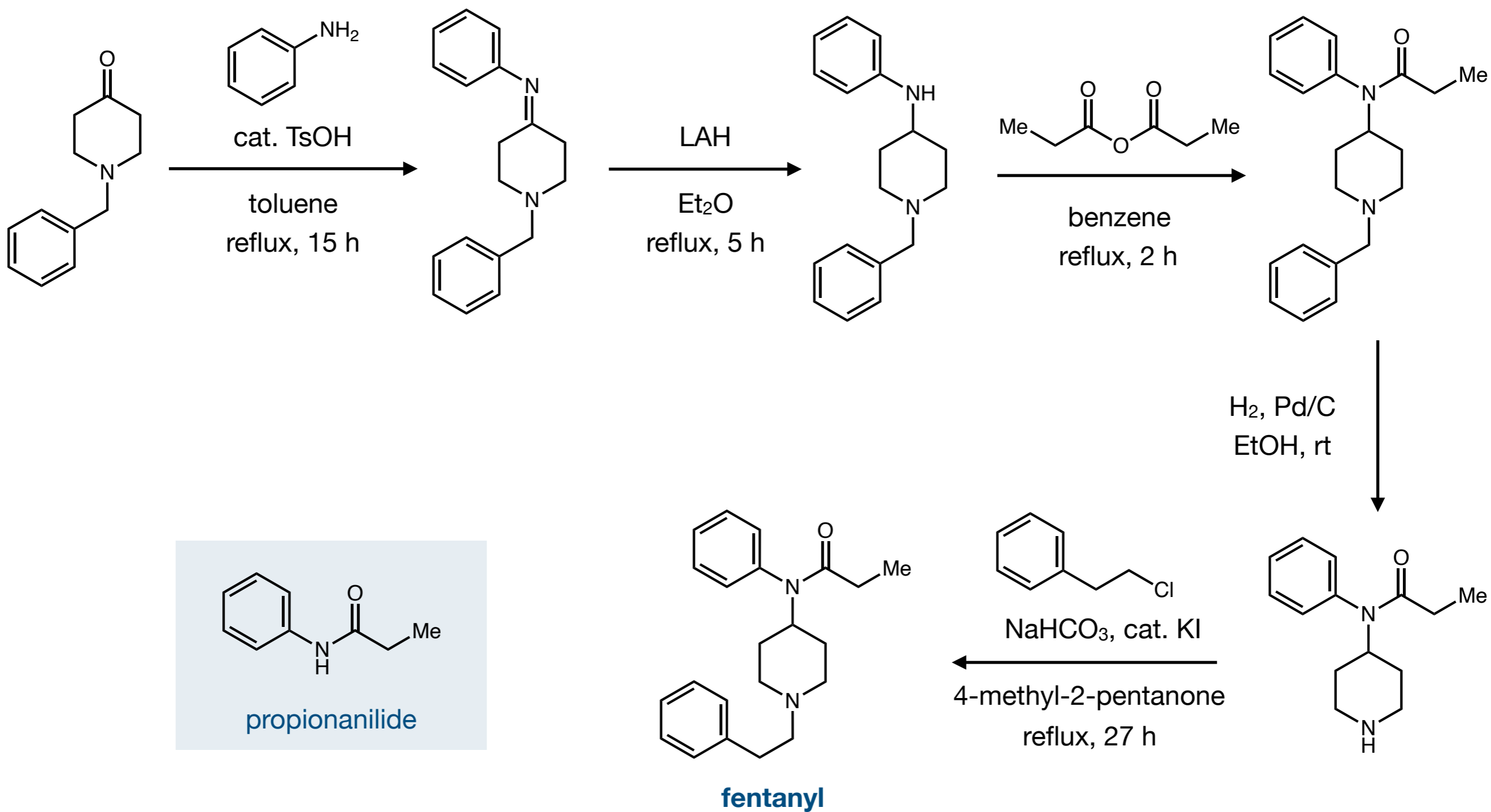
- China White (“Real Powerful Heroin”)
- No heroin or other narcotics detected by toxicological analysis
- Two major compounds detected:



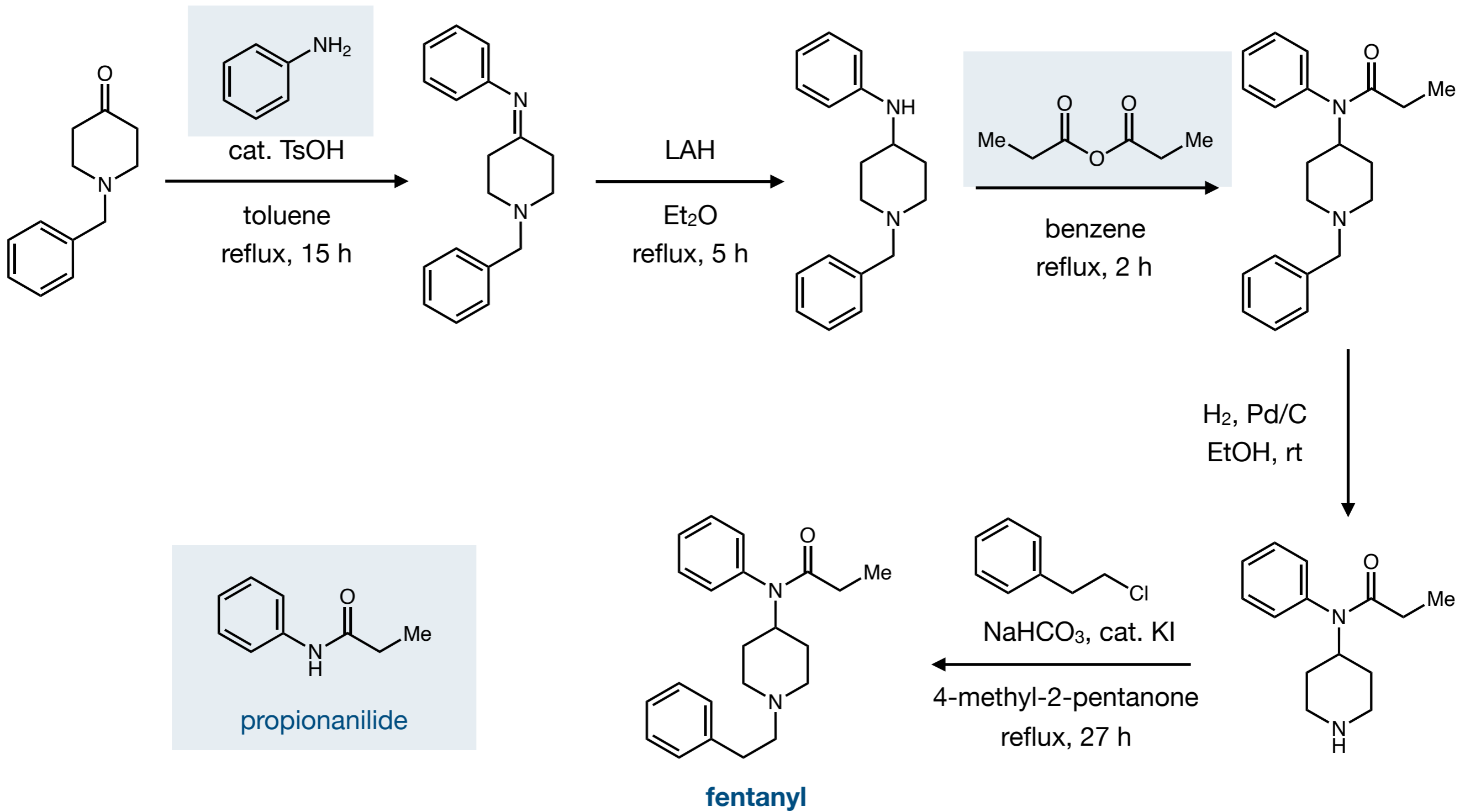
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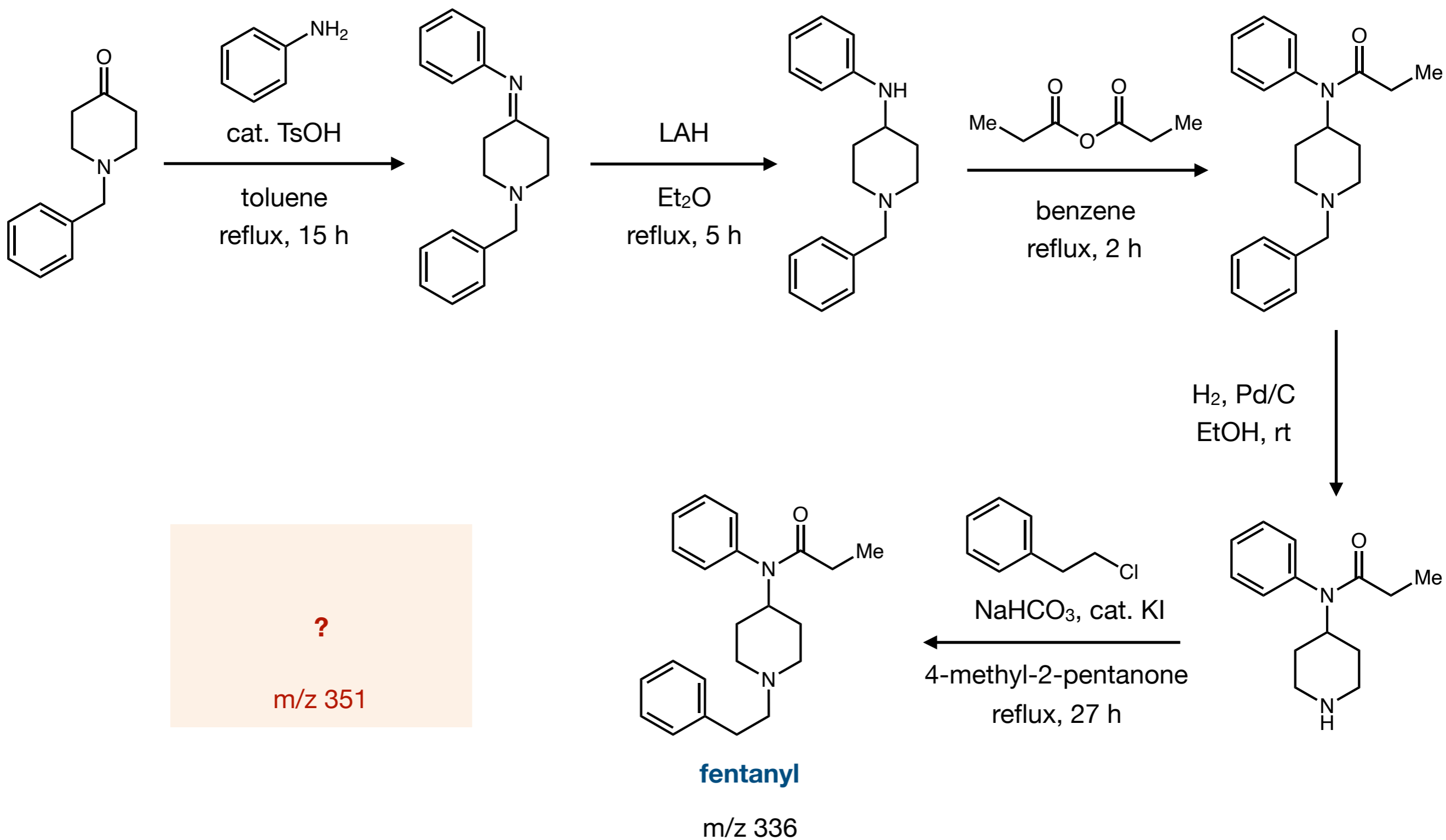


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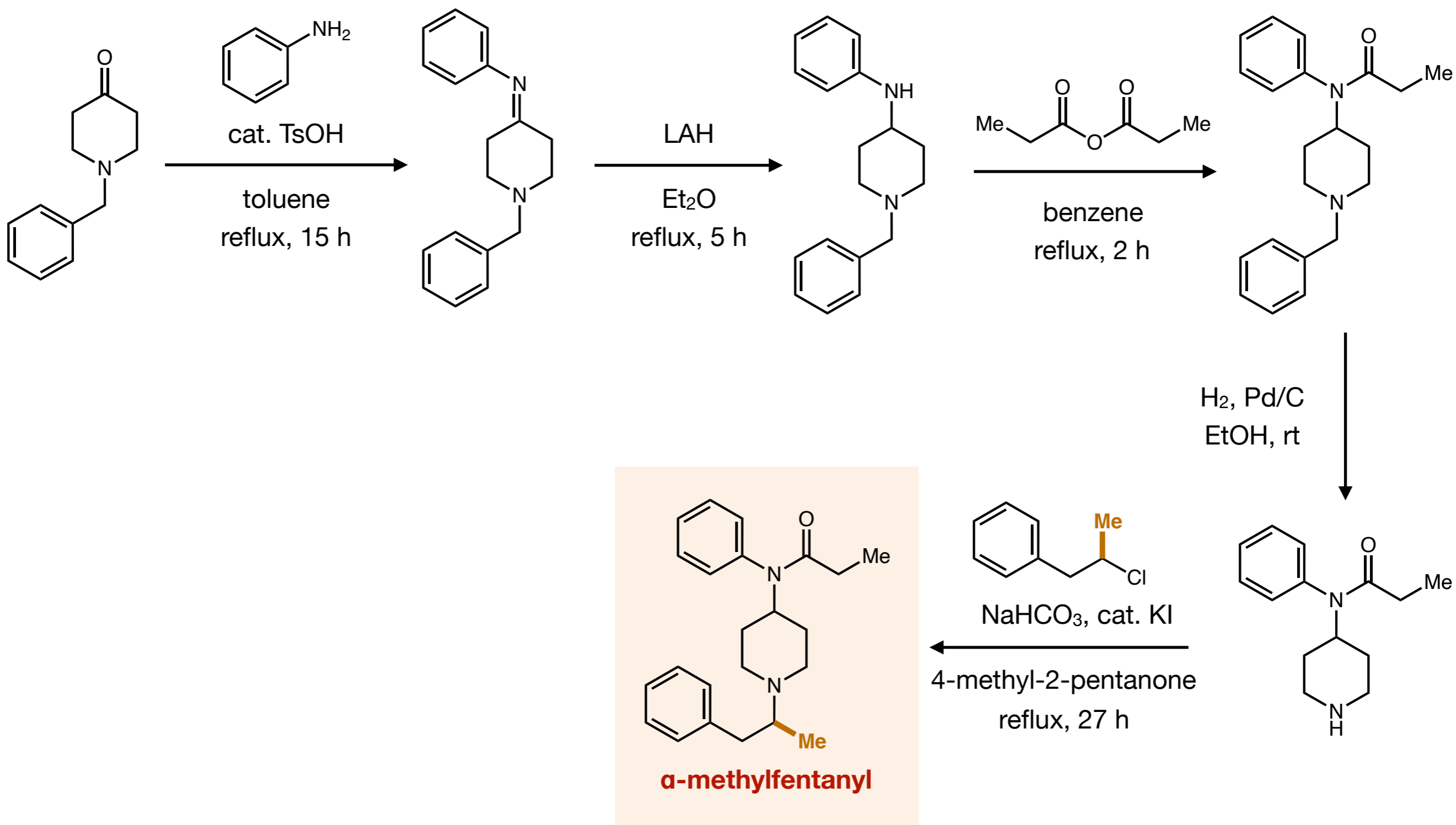




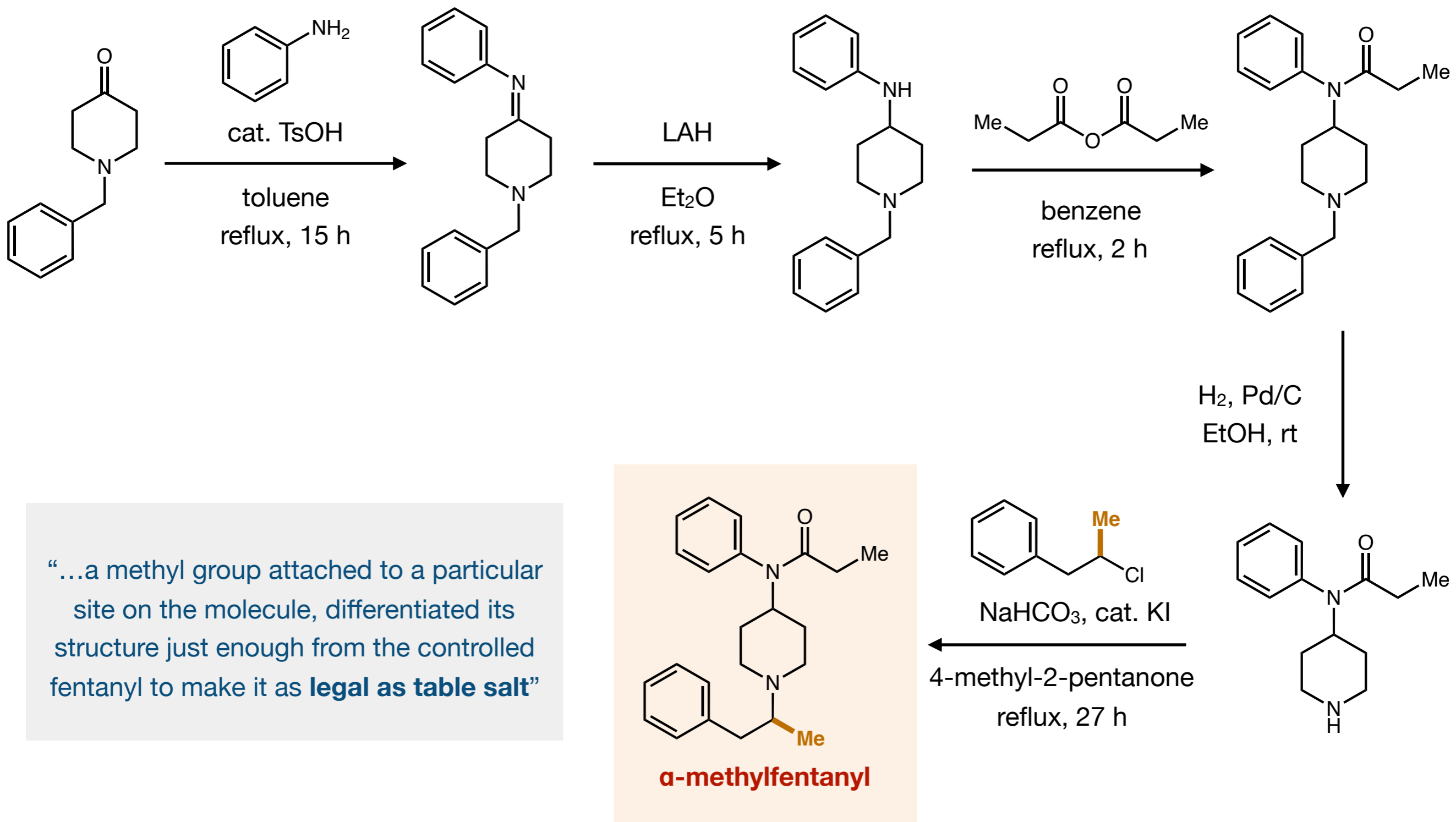
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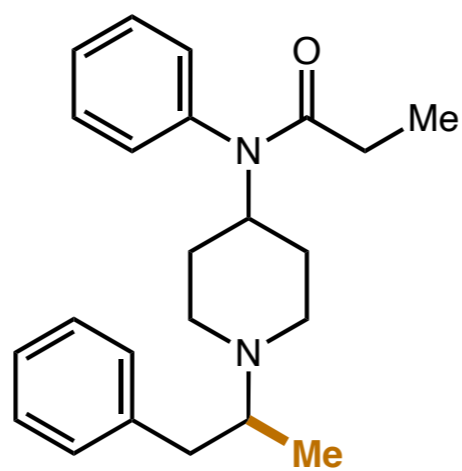


## Two unusual drug overdose deaths (1979)



“...a methyl group attached to a particular site on the molecule, differentiated its structure just enough from the controlled fentanyl to make it as **legal as table salt**”

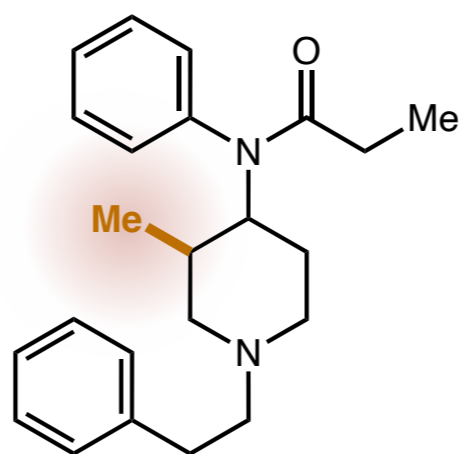
1981



**α-methylfentanyl**

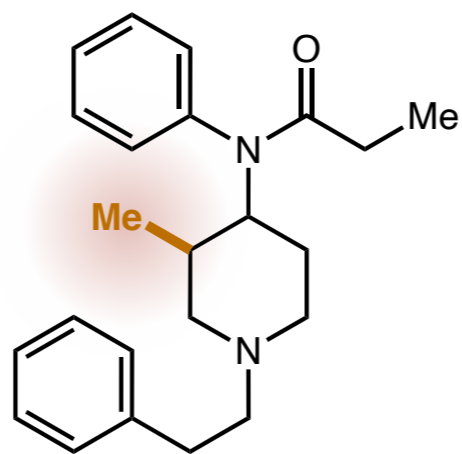
Classified as a Schedule I narcotic

1984



**3-methylfentanyl**

1984

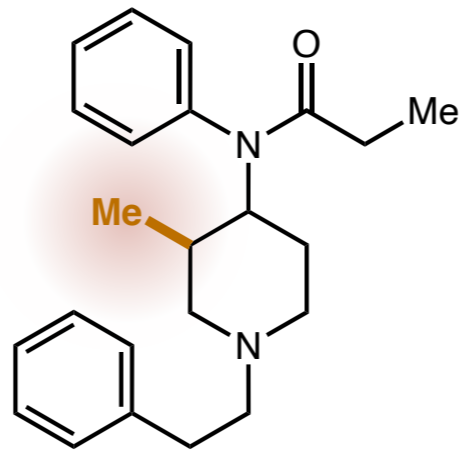


**3-methylfentanyl**

Responsible for 16 overdose cases in PA



1984



**3-methylfentanyl**

Responsible for 16 overdose cases in PA

**50x more potent** than fentanyl

## The rise of underground chemists (1980s)

# Street chemists deal in death — but it's legal

**DESIGNER DRUGS**, from Page 1C

genuine heroin may believe it is synthetic, Gilliam said. "If someone says, 'I have some China White (a synthetic heroin) . . . you have no way of knowing if it's China White or this guy's just saying it is. So you get some one time and use it and it's no problem. Then you get some that happens to be the (synthetic stuff) and you treat it as you did the last, which was actually heroin, and you're in trouble," he said.

The term designer drugs, now out of



needed for each dose.

The amount of heroin in the body fluids of someone who overdosed on heroin is about 1,000 times greater than the amount of fentanyl derivatives found in a fentanyl derivatives overdose victim, said Henderson.

listed, or scheduled, on the Controlled Substances Act are covered by that law. Drugs can be added to the list, but only after authorities have reviewed the history and current pattern of abuse of the drug, the significance of its abuse, and the risk to the public, according to the DEA's DeFauw.

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### Chemist's \$780m drug charges

Washington: A chemist of Du Pont Co has been arrested on charges of making a powerful heroin-like "designer drug" with a street value of more than US\$100 million (about HK\$780 million), the Justice Department said.

Michael Hovey, 32, who worked for Du Pont's experimental laboratory in Wilmington, Delaware, was charged with manufacturing and distributing an ounce of three-methyl-fentanyl, a drug up to 1,000 times more potent than pure heroin.

American drug agents said the seizure was the largest ever of a drug that has become increasingly popular in the past five years.

The Justice Department said Hovey initially received

a down payment US\$40,000 (about HK\$312,000) for the drug from an undercover agent.

He was arrested on Sunday in a wooded area near Wilmington while attempting to pick up an additional US\$260,000 (about HK\$2 million).

The department said Hovey was to have supplied three more ounces of the drug and six ounces of methamphetamine after a third payment of US\$700,000 (about HK\$5.46 million).

The investigation was initially launched by Du Pont's security department. Hovey was ordered to be held in custody.

—Reuters

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# Raiders Arrest 2 Chemists Seize Makings of Narcotic

Federal drug agents arrested two chemists, including a North Hollywood man, on suspicion of manufacturing an illegal drug that is 1,000 times more powerful than morphine, authorities said Friday.

Kenneth Marvin Baker of West Hollywood was arrested Thursday night and Luther Dixon of North

duce more than 100 million doses of the drug, Granados said.

"This particular substance is 1,000 times stronger than morphine," Granados said. "It is the same substance that 97 overdoses have been attributed to in the San Jose-Fresno area during the past year."



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# Chemist Sentenced In D.C. Drug Case

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By Nancy Lewis  
Washington Post Staff Writer

A 38-year-old research chemist who was arrested in September at the Naval Research Laboratory after he was videotaped in his lab there attempting to make an extremely potent form of a heroin

But the heroin substitute was being manufactured for "professional narcotics distributors" with possibilities to organized crime, sources said. If Hodes had completed manufacturing the 3-methyl fentanyl, they said, it could have markedly changed the heroin distribution network on the East Coast.

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### Chemist's \$780m drug charges

# Juggling molecules of death

THE drug — 1,000 times more powerful than heroin — is designed in a clandestine laboratory by a renegade chemist, a brilliant phantom who has earned the grudging respect of pharmacologists.

It is cut innumerable times and passed off as Persian White, the caviar of heroin.

It is sold in the redwood suburbs north of San Francisco to chic young professionals, junkies in hot tubs.

It killed 49 people last year. It is cheap, addictive and perfectly legal.

By tinkering with the molecular structure of fentanyl, a synthetic painkiller routinely used in surgery, the unknown chemist has created the latest fad to come out of California — "designer" heroin.

"We're talking about a world-class medicinal chemist," said Dr Gary Henderson, a pharmacologist at the

could endlessly frustrate the law:

New variations can be turned out faster than they can be identified and outlawed. And when they are finally made illegal, a sophisticated "designer" can create a new, legal drug merely by altering the molecule. The users are the guinea pigs.

"This is very, very frightening," said Chauncey Veatch, director of the California Department of Alcohol and Drug Programmes, which expects 78 people to die this year from designer drug overdoses.

To date, 90 people have died from such overdoses, 13 this year. The fear is that the

## Phantom chemist one step ahead of the law

investment in chemicals can produce a US\$2 million (about HK\$15.6 million) batch of synthetic heroin. There's just too much money there, it's just got to spread."

Dr Henderson has already heard rumours that underground chemists are heading to California to learn how to make fentanyl.

Right now, law enforcement can do little. If DEA

Thirty days is still plenty of time for a smart designer to change the formula.

So far, DEA chemists have uncovered 10 varieties of fentanyl. Only two are illegal, and two more are scheduled to be outlawed soon. The newest and deadliest, 3-methyl-fentanyl, became illegal on April 28.

"We believe it is the one connected with the deaths in

find out what the Government is up against.

From LSD in the 1960s to PCP in the 1970s, chemists have long tinkered with illicit substances to thwart the law and produce tailor-made effects.

The most famous designer was Augustus Owsley Stanley III, who manufactured high-grade LSD in the Haight-Ashbury district of San Francisco

was in December 1979. Soon, the deaths were happening at the rate of eight to 10 a year.

Then in 1983, 3-methyl-fentanyl appeared on the street sold as Persian White, the world's finest heroin. It was 1,000 times more powerful than heroin.

Forty-nine people overdosed in California, more than had died from synthetic heroin in all the previous years combined.

"This is your basic street research for profit with indifference about what happens to people," the DEA's Mr Haislip said.

Many of the dead were from California's new class of upscale junkies, who use her-

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"The concentrations we're seeing in the blood are parts per billion and parts per trillion," he said.

Drug agents estimate that a single chemist in eight hours could supply the nation's heroin demand for a day. A closetful of the drug could feed the nation's addicts for six months.

Dr Henderson speculates that the supply is now coming from "one, maybe two, very sophisticated labs."

Working for two weeks at a time, the labs can produce about 200 grams, enough for four million doses. The four or five raw materials, all available on the market, cost perhaps US\$200 (about HK\$1,560).

DEA chemist Cooper believes the drugs are the work of one man, perhaps a brilliant graduate student. Dr Henderson agrees: "He's the Owsley of the 1980s."

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## *Federal Analogue Act (1986)*

### 21 U.S. Code § 802

The term “controlled substance analogue” means a substance—

- (i) the chemical structure of which is **substantially similar** to the chemical structure of a controlled substance in schedule I or II;
- (ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule I or II; or
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**What constitutes substantial similarity?**

## *Criteria for establishing similarity*

- 1 the drug analogue acts on the brain in the same way as the parent drug



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**Radioligand binding assay**



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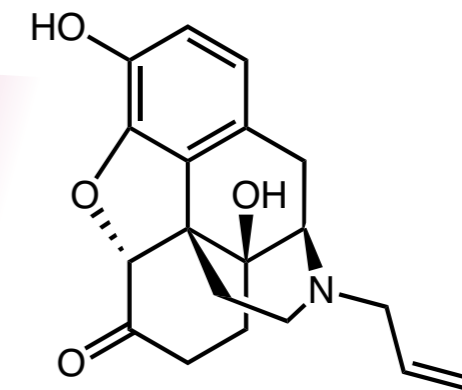


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- Measures competitive binding between [<sup>3</sup>H]naloxone and drug analog to opioid receptors in rat brain membranes

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naloxone

nonspecific opioid antagonist

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- 1 the drug analogue acts on the brain in the same way as the parent drug
- 2 the drug analogue must be structurally similar to the parent drug

## *Criteria for establishing similarity*

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**Mass spectrometry (MS)**

## *Criteria for establishing similarity*

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### **Mass spectrometry (MS)**

- Confirm mass and elucidate structure of the analog



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# Criteria for establishing similarity

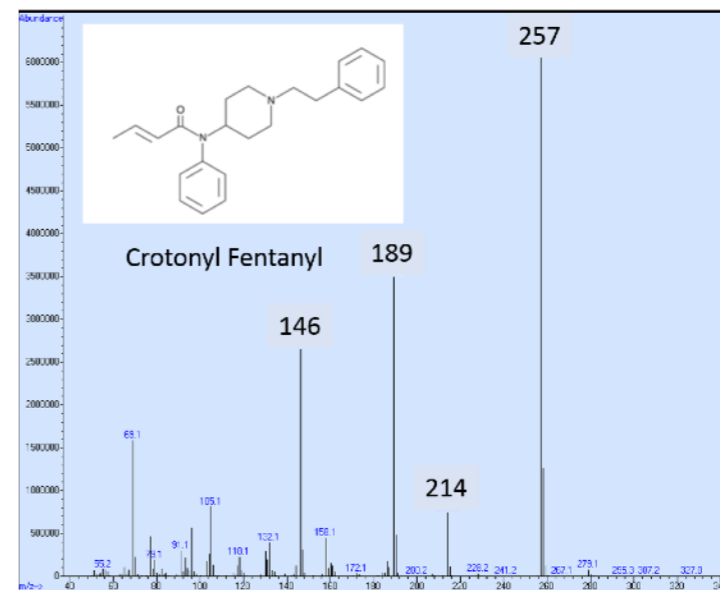
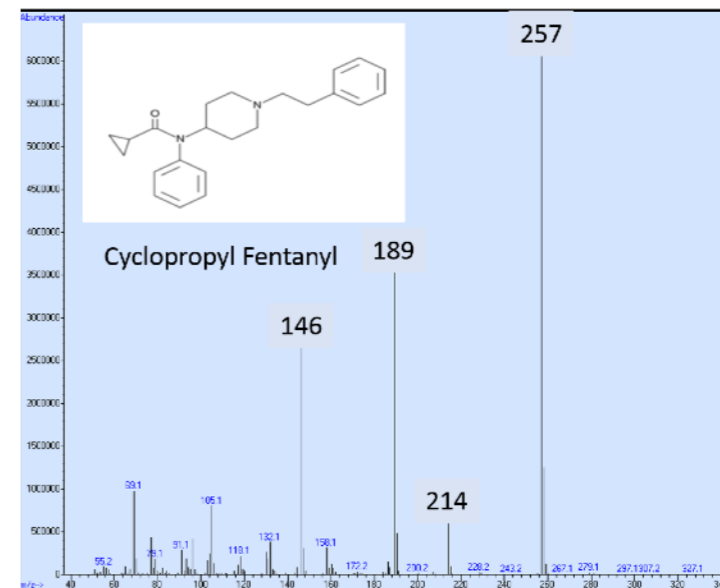
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- Isomers can be challenging to distinguish



## Criteria for establishing similarity

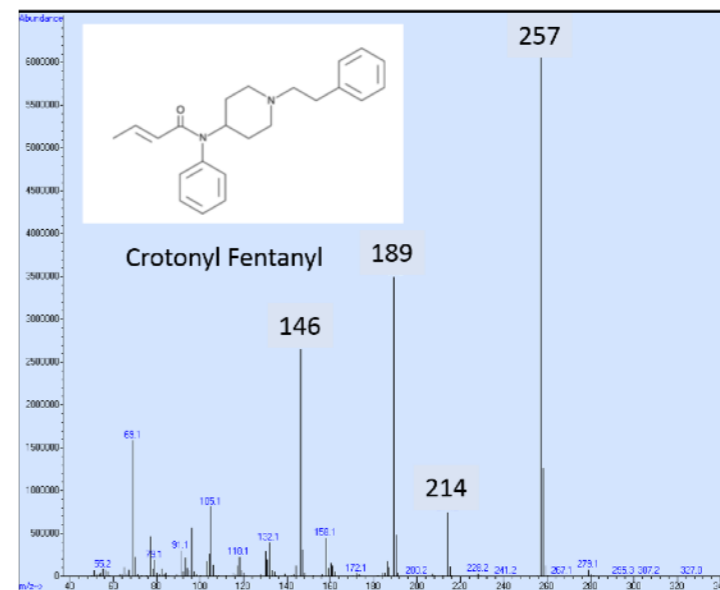
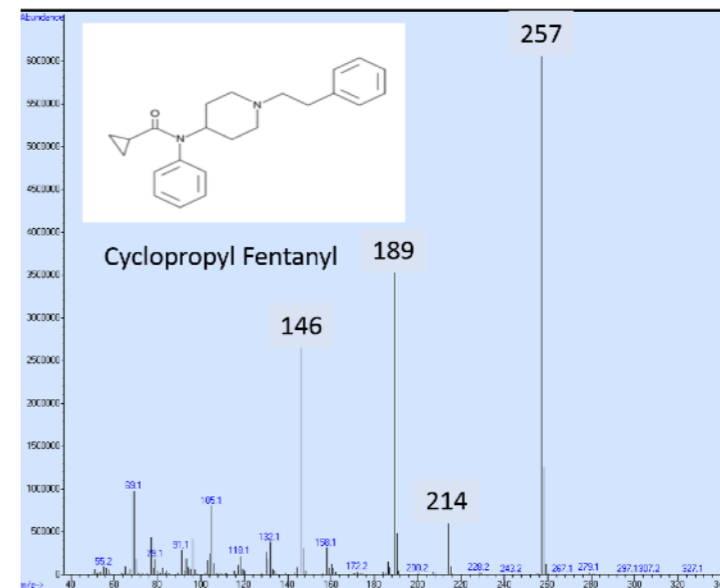
2

the drug analogue must be structurally similar to the parent drug



### Mass spectrometry (MS)

- Confirm mass and elucidate structure of the analog
  - Isomers can be challenging to distinguish
- Impurities and metabolites can provide clues to the analog's structure



## Criteria for establishing similarity

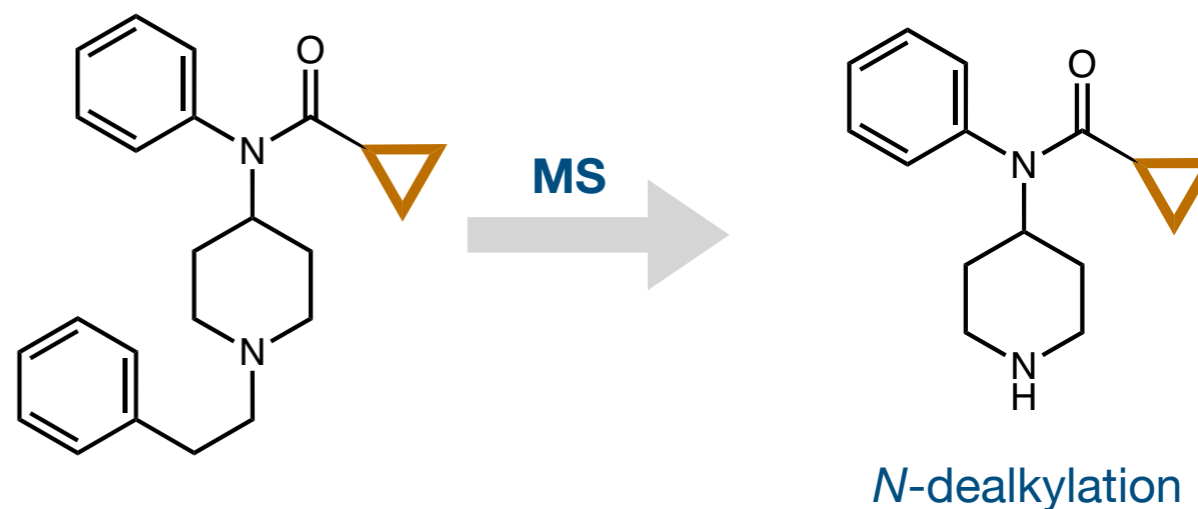
2

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**Mass spectrometry (MS)**

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## Criteria for establishing similarity

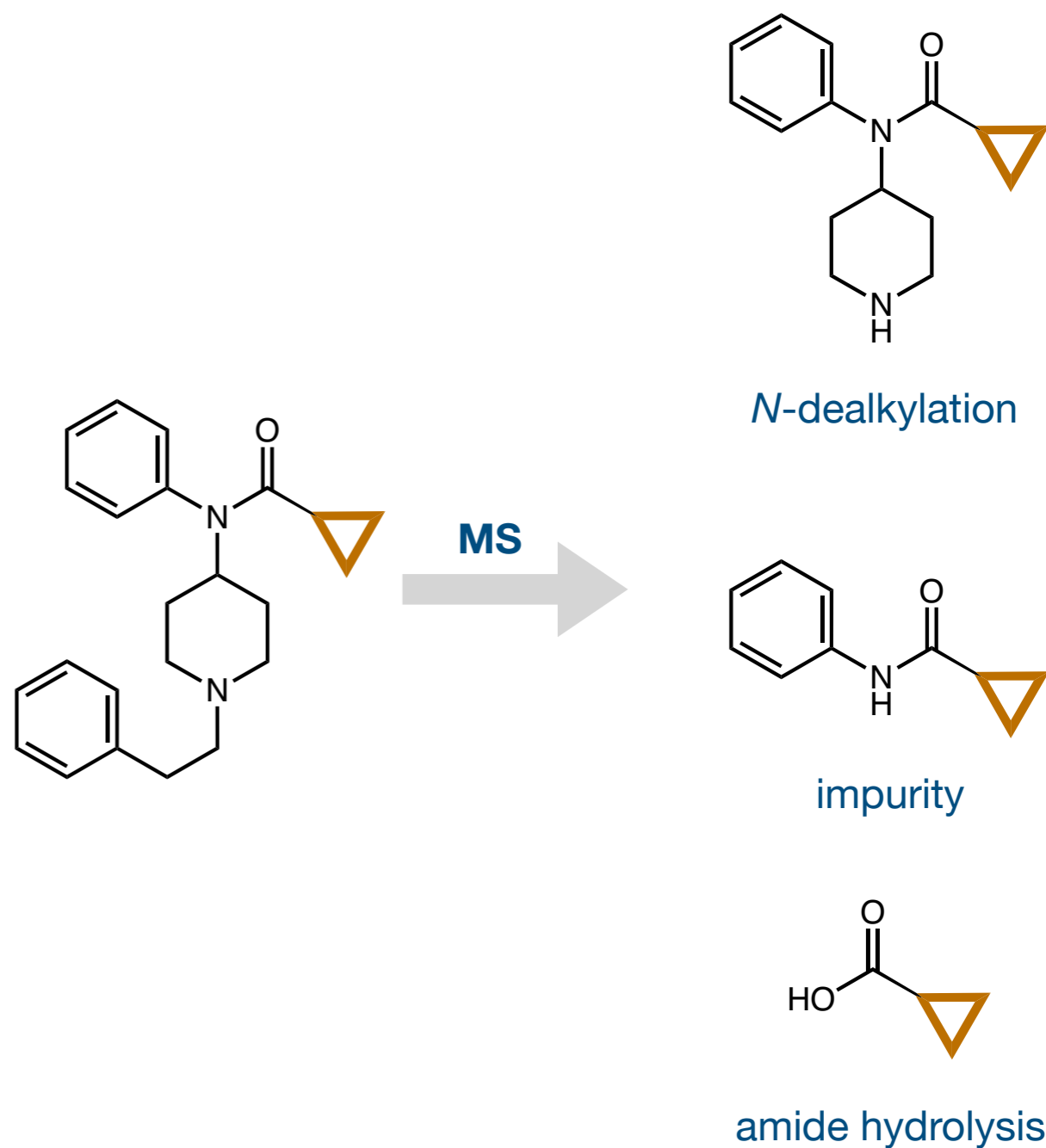
2

the drug analogue must be structurally similar to the parent drug



**Mass spectrometry (MS)**

- Confirm mass and elucidate structure of the analog
  - Isomers can be challenging to distinguish
- Impurities and metabolites can provide clues to the analog's structure





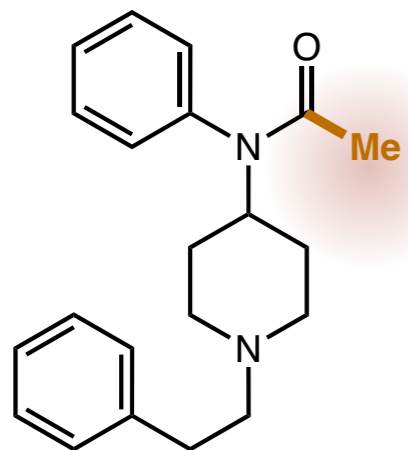
## *Criteria for establishing similarity*

- 1 the drug analogue acts on the brain in the same way as the parent drug
- 2 the drug analogue must be structurally similar to the parent drug

**The scheduling process for a new analog can take 2-3 years**

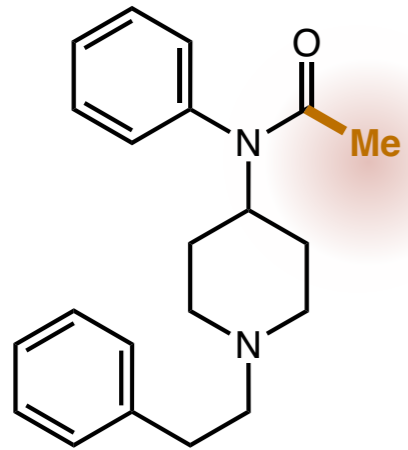
1988

8 additional novel fentanyl analogs identified

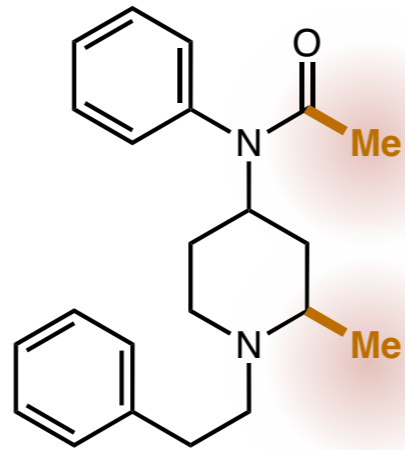


acetylfentanyl

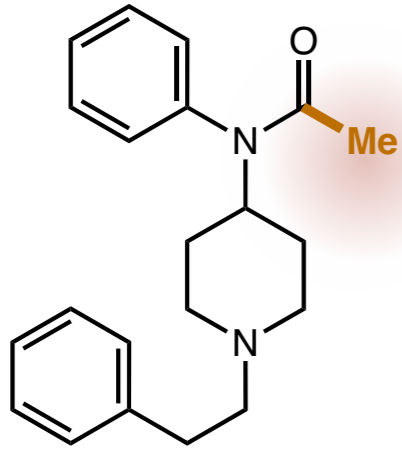
8 additional novel fentanyl analogs identified



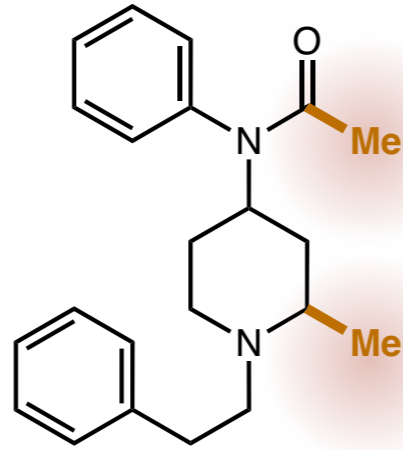
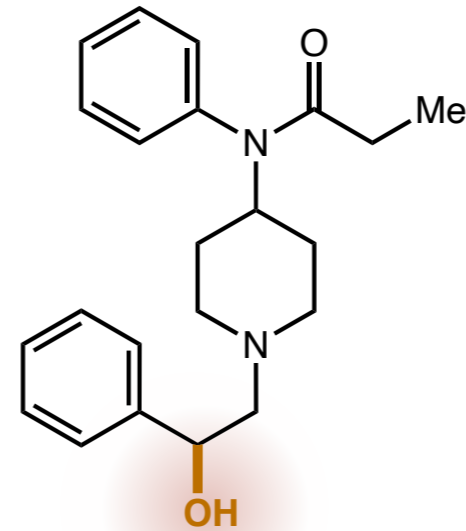
acetylfentanyl



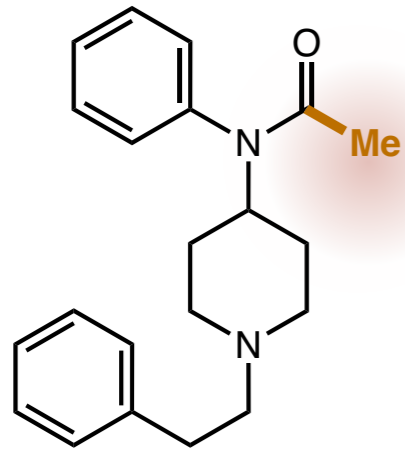
acetyl- $\alpha$ -methylfentanyl

**8 additional novel fentanyl analogs identified**

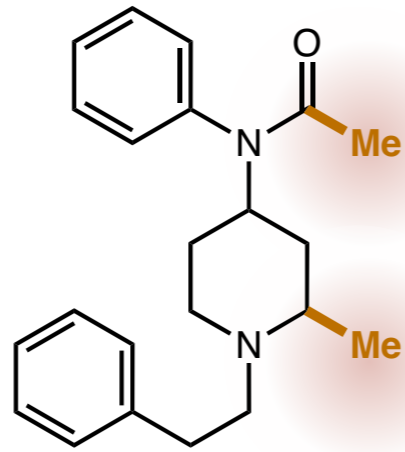
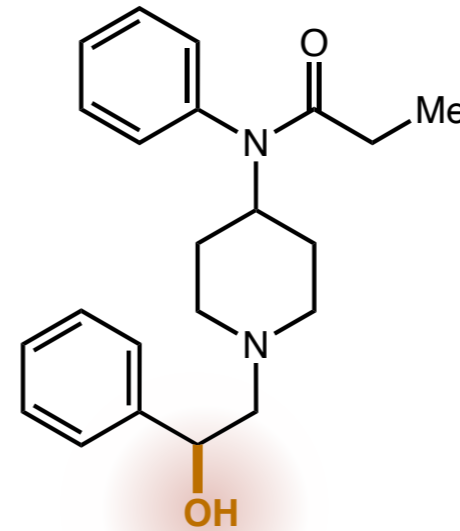
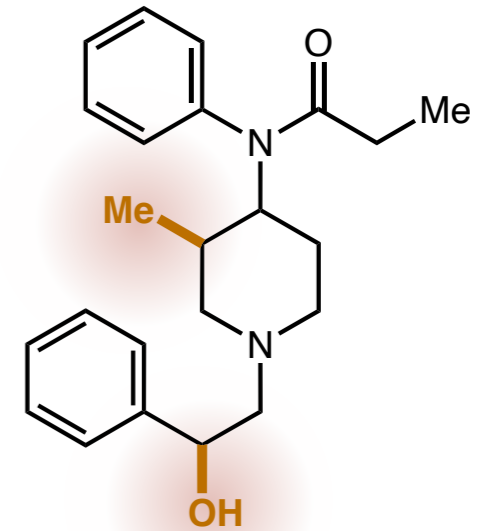
acetylfentanyl

acetyl- $\alpha$ -methylfentanyl $\beta$ -hydroxyfentanyl

## 8 additional novel fentanyl analogs identified

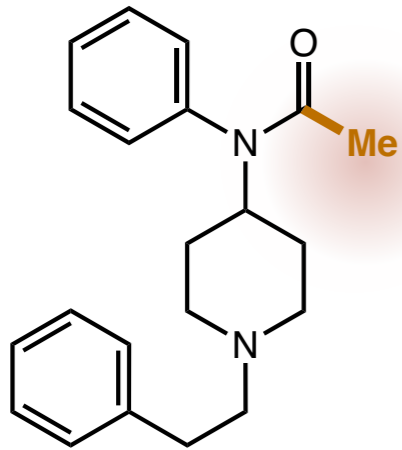


acetylfentanyl

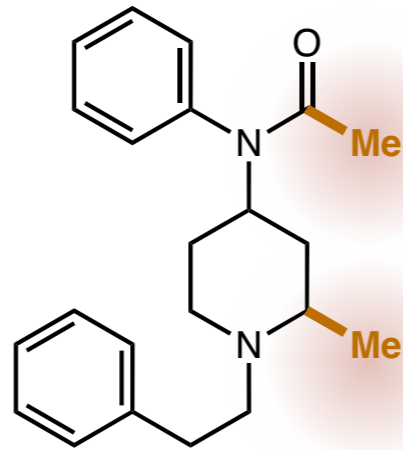
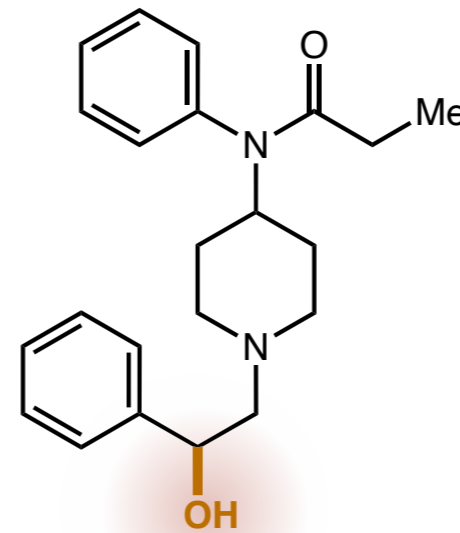
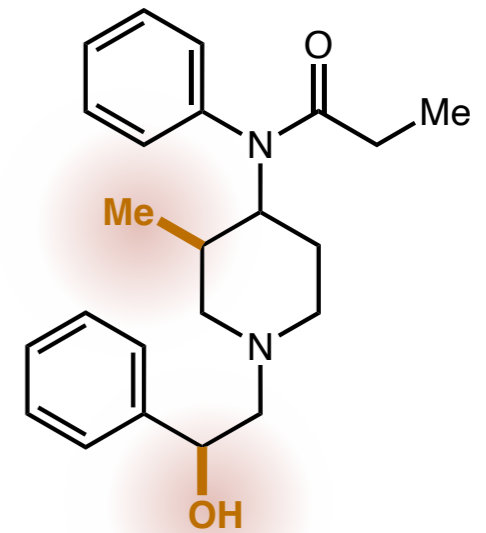
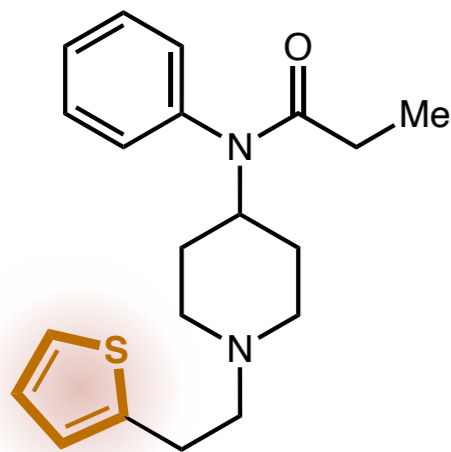
acetyl- $\alpha$ -methylfentanyl $\beta$ -hydroxyfentanyl $\beta$ -hydroxy-3-methylfentanyl



## 8 additional novel fentanyl analogs identified

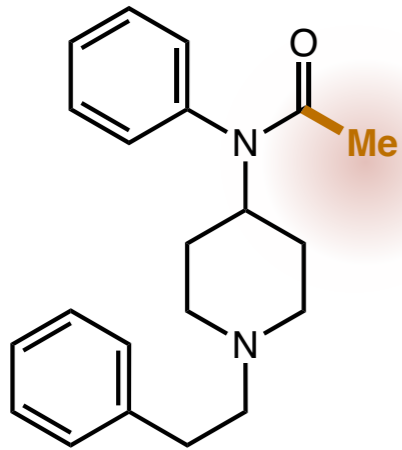


acetylfentanyl

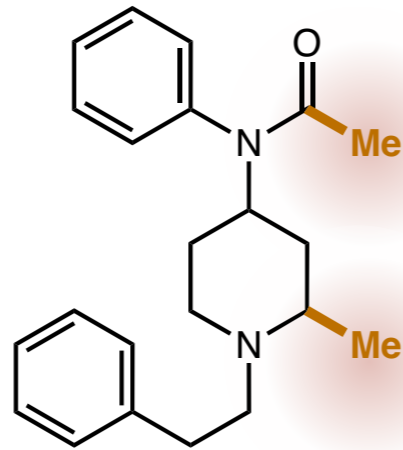
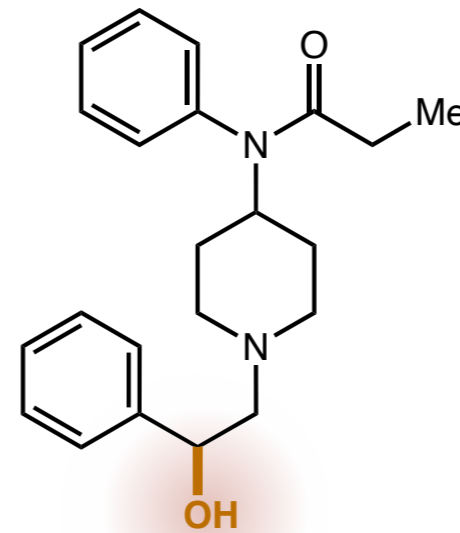
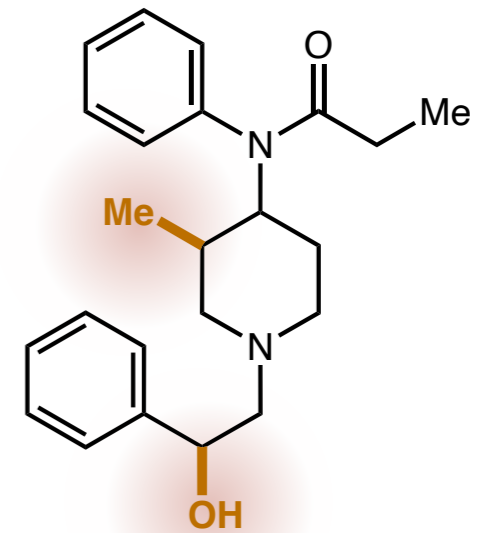
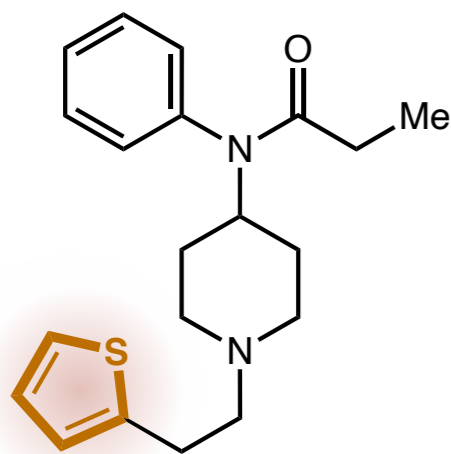
acetyl- $\alpha$ -methylfentanyl $\beta$ -hydroxyfentanyl $\beta$ -hydroxy-3-methylfentanyl

thiofentanyl

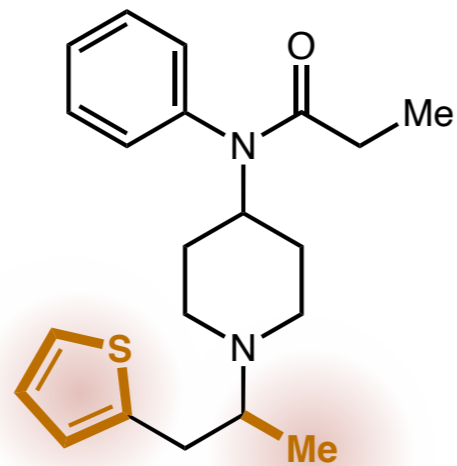
## 8 additional novel fentanyl analogs identified



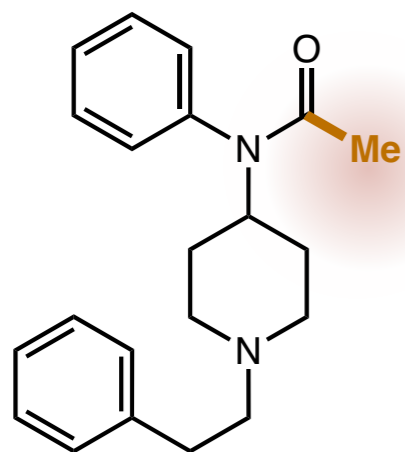
acetylfentanyl

acetyl- $\alpha$ -methylfentanyl $\beta$ -hydroxyfentanyl $\beta$ -hydroxy-3-methylfentanyl

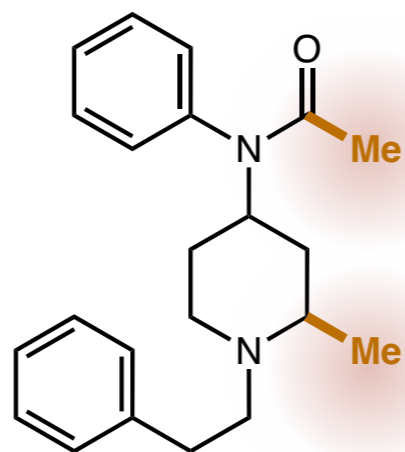
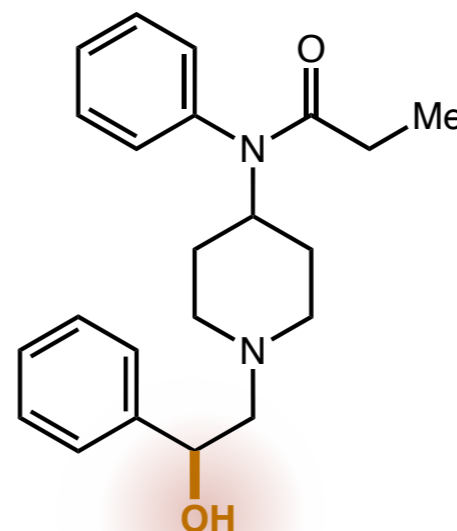
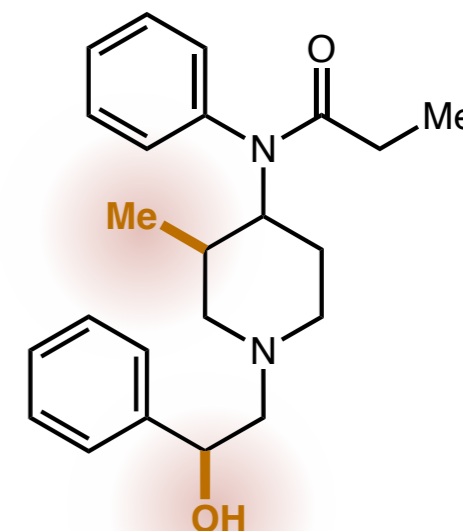
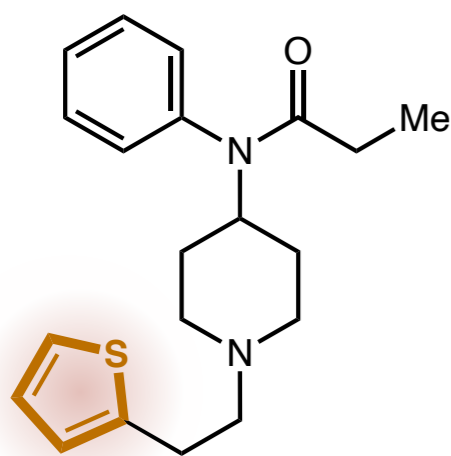
thiofentanyl

 $\alpha$ -methylthiofentanyl

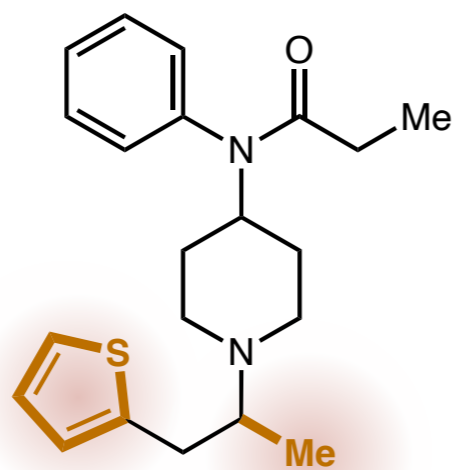
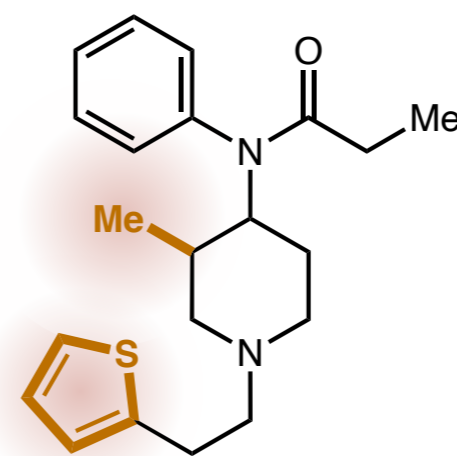
## 8 additional novel fentanyl analogs identified



acetylfentanyl

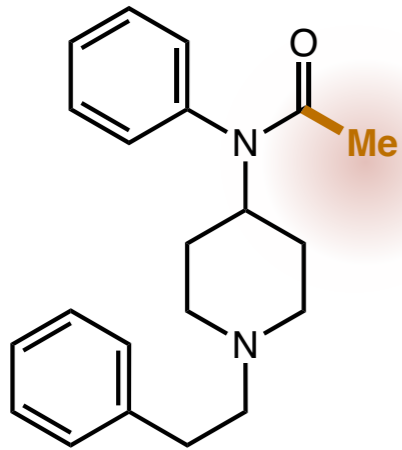
acetyl- $\alpha$ -methylfentanyl $\beta$ -hydroxyfentanyl $\beta$ -hydroxy-3-methylfentanyl

thiofentanyl

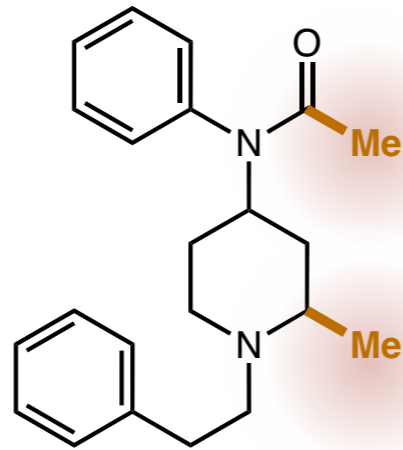
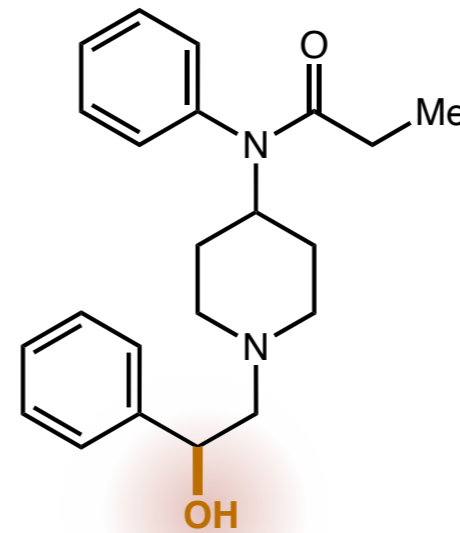
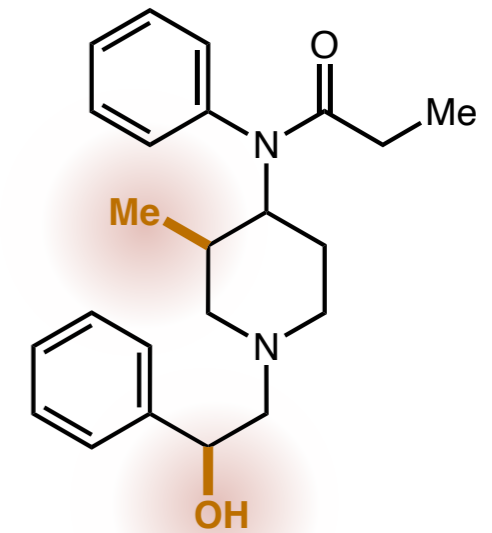
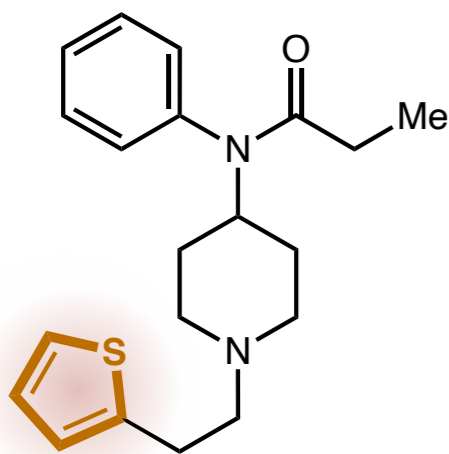
 $\alpha$ -methylthiofentanyl

3-methylthiofentanyl

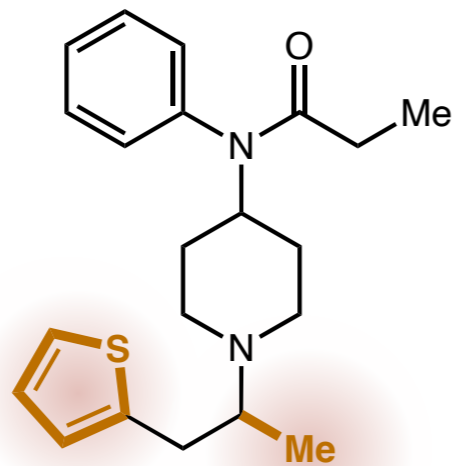
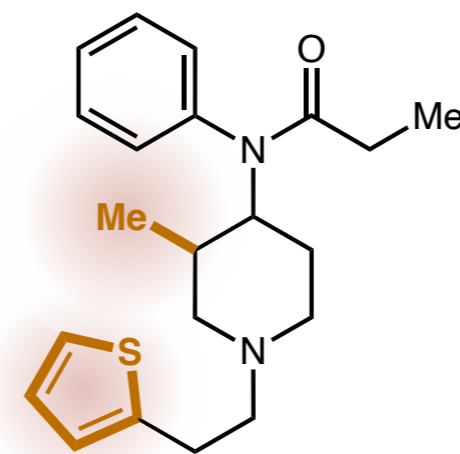
## 8 additional novel fentanyl analogs identified



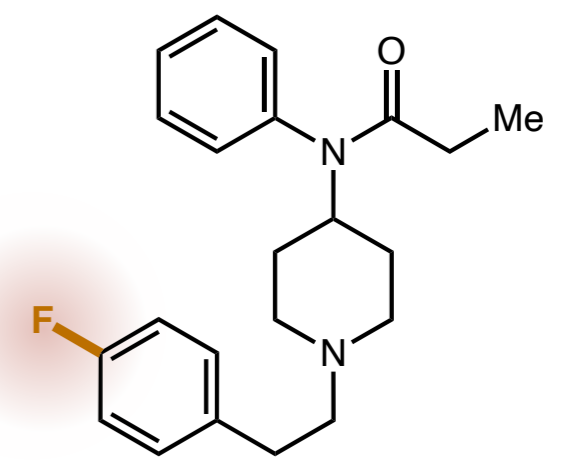
acetylfentanyl

acetyl- $\alpha$ -methylfentanyl $\beta$ -hydroxyfentanyl $\beta$ -hydroxy-3-methylfentanyl

thiofentanyl

 $\alpha$ -methylthiofentanyl

3-methylthiofentanyl

*p*-fluorofentanyl



## *Growth of the Internet (1990s)*





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Greater access to information



## *Growth of the Internet (1990s)*



Greater access to information



**Greater access to illicit drugs**



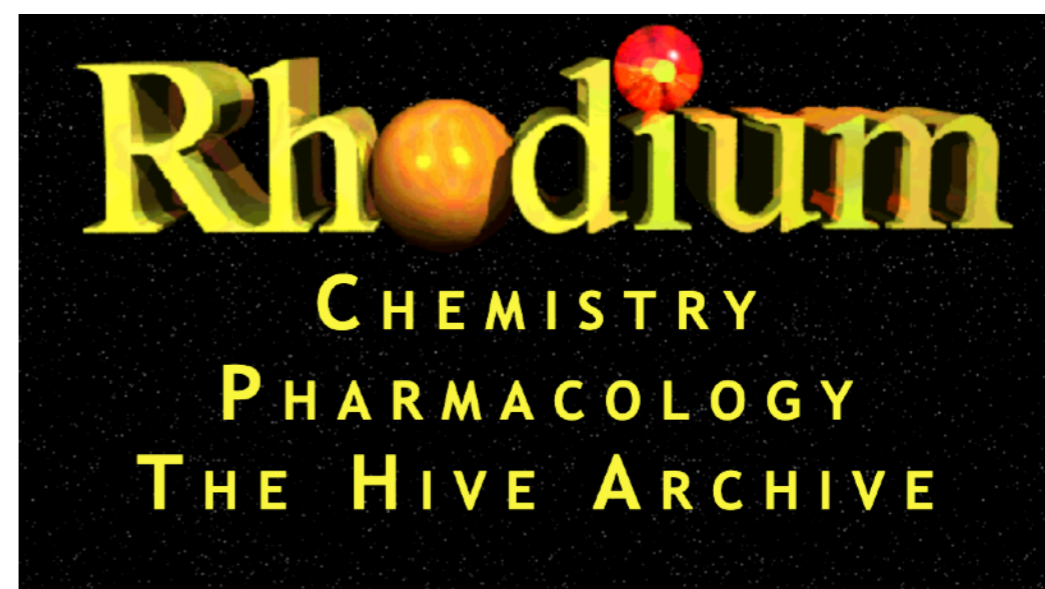
## *Growth of the Internet (1990s)*



Greater access to information



**Greater access to illicit drugs**



1997

# Siegfried synthesis of fentanyl (1998)

[WWW.RHODIUM.WS] [] [CHEMISTRY ARCHIVE]

Search

## SYNTHESIS OF FENTANYL

BY SIEGFRIED

HTML/Gfx by Rhodium

### INTRODUCTION

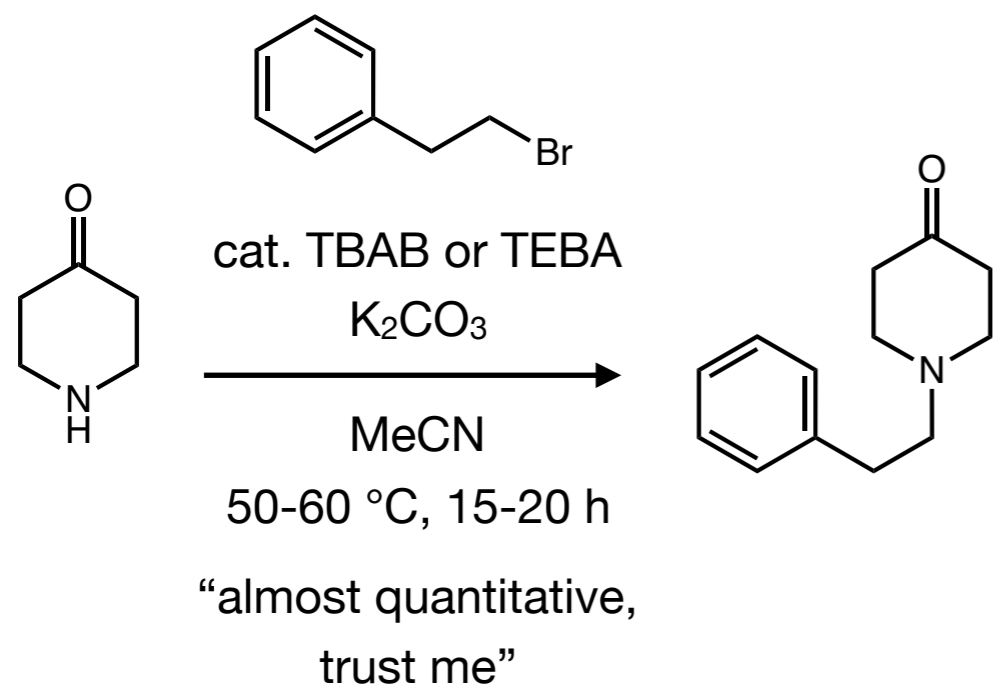
I'm french speaking organic chemist so excuse my rusty english [*most things corrected by me - **Rhodium***].

Fentanyl and its analogs are among of the most powerful opiate agonists, but their synthesis are often hard. Here is a synthesis of Fentanyl which can be easily adapted for the other analogs (*para*-Fluoro-Fentanyl, *alpha*-Methyl-Fentanyl).

This procedure is not theoretical and have been tested and improved many times over. This synthesis is conducted at room temperature so you don't need any special apparatus.

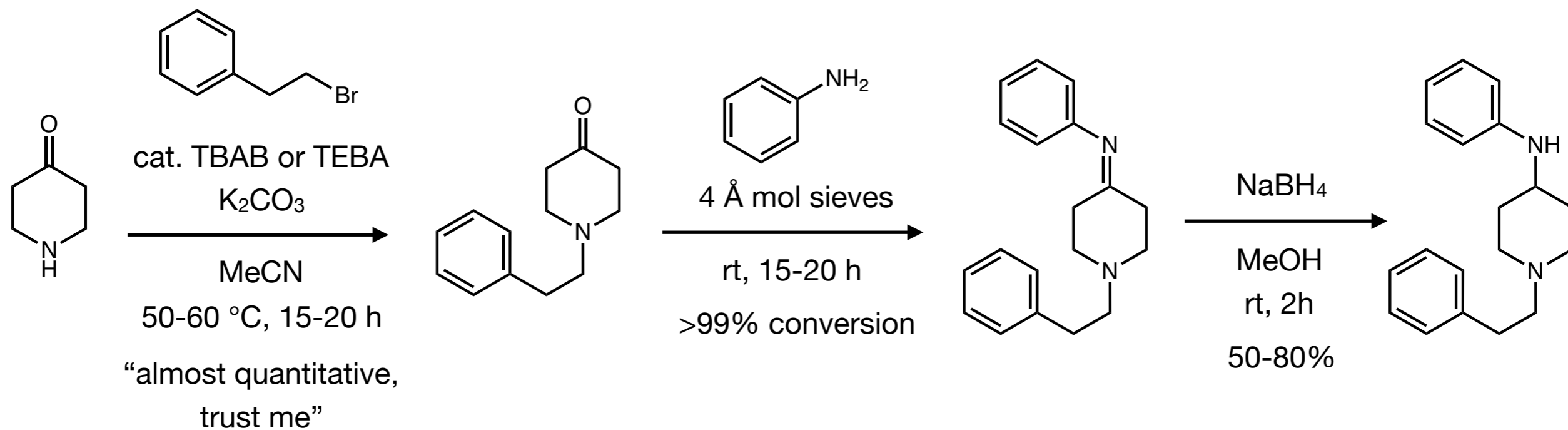
Fentanyl is a very interesting component for underground chemistry because one gram of pure fentanyl is equivalent of 100 g of very good street heroin.

## Siegfried synthesis of fentanyl (1998)

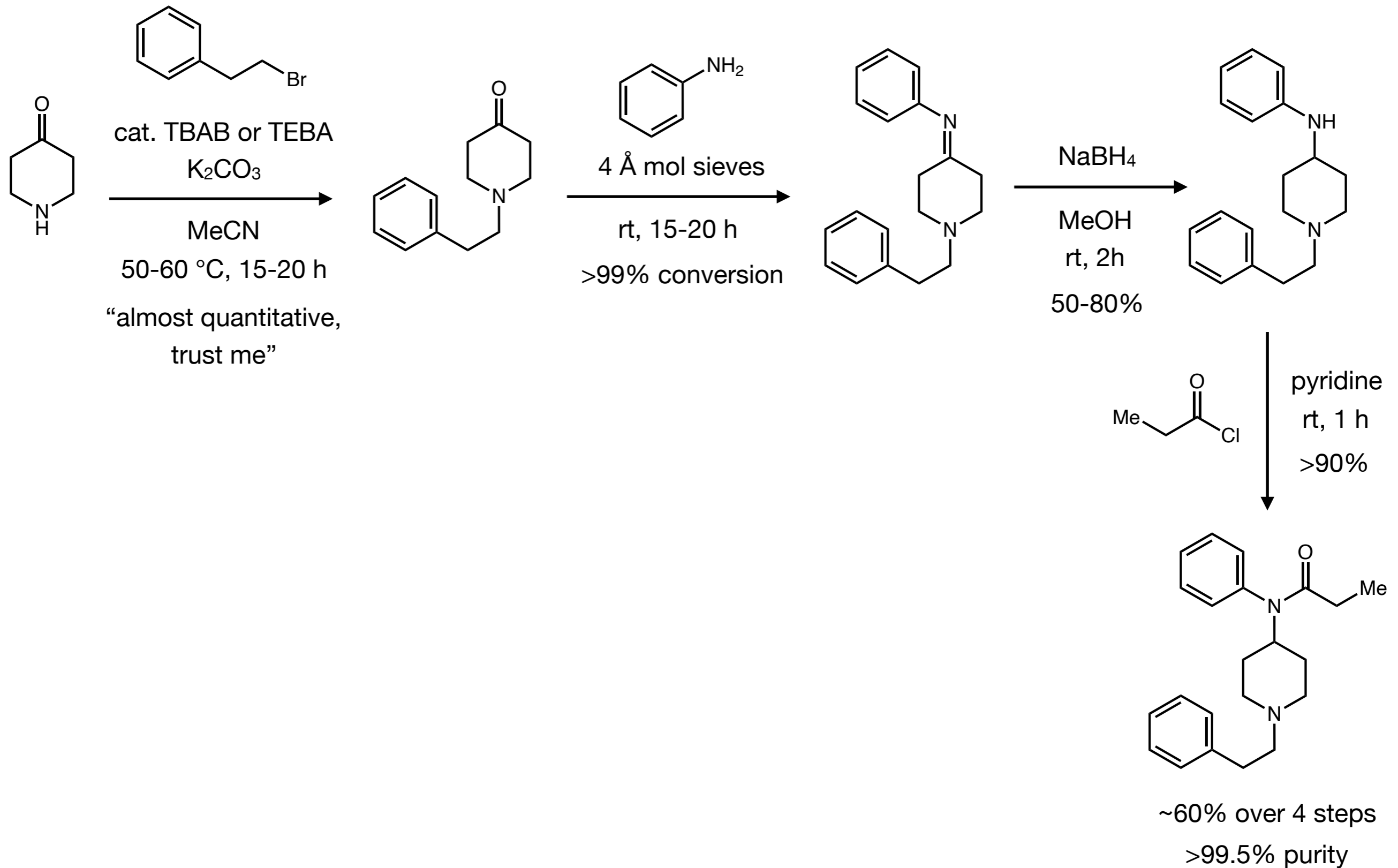




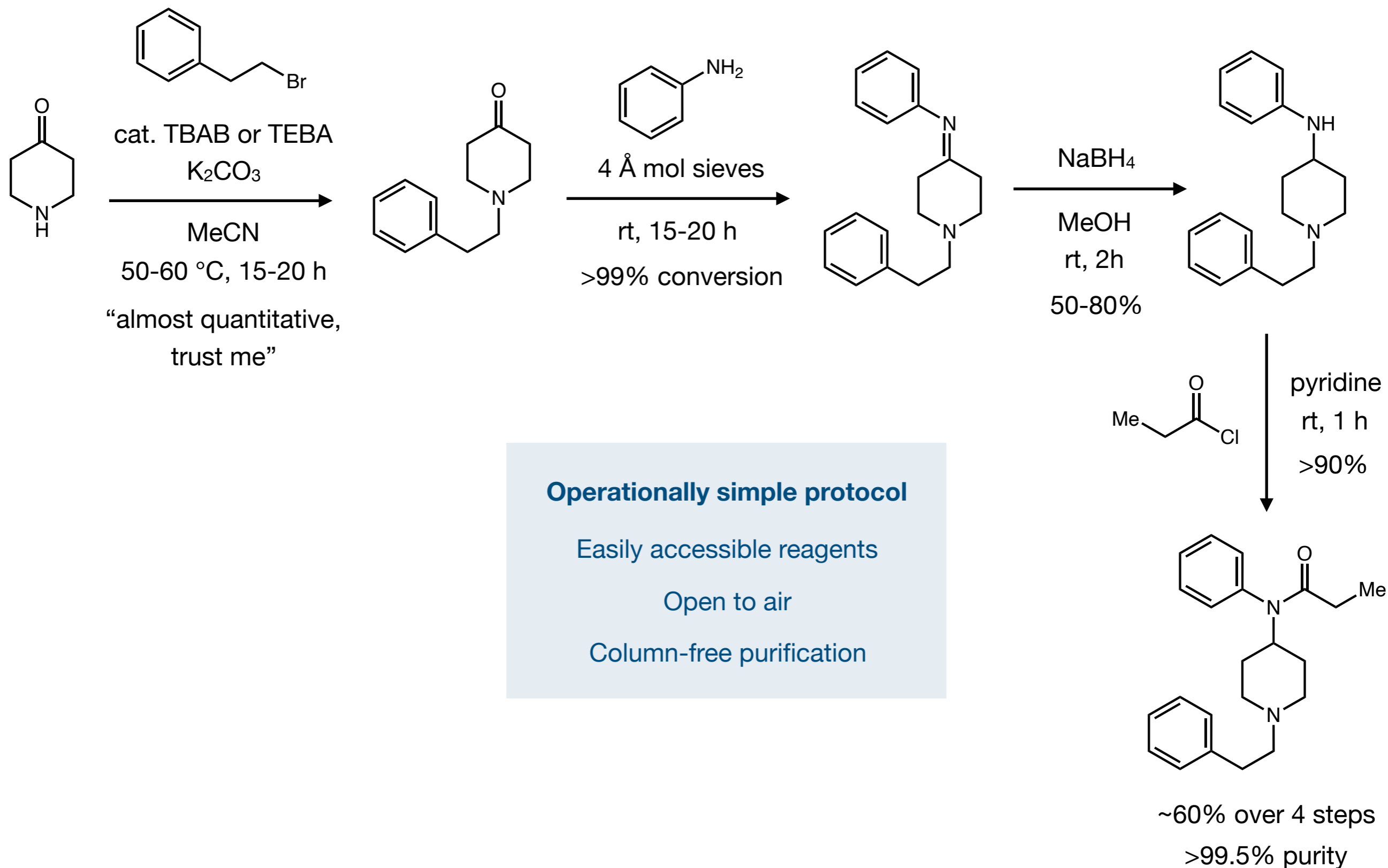
## Siegfried synthesis of fentanyl (1998)



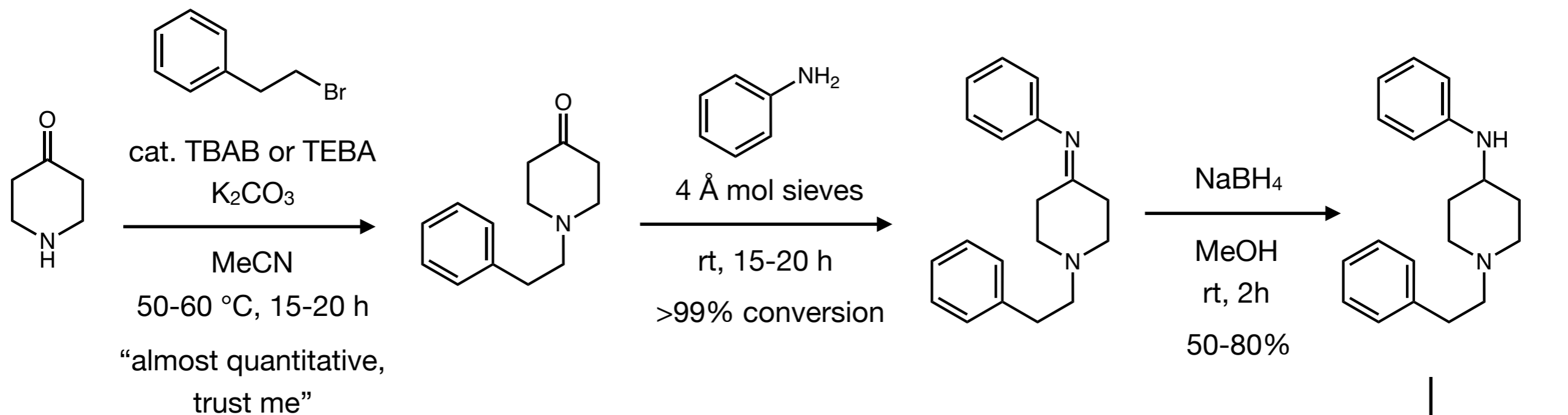
# Siegfried synthesis of fentanyl (1998)



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# Siegfried synthesis of fentanyl (1998)



**Operationally simple protocol**

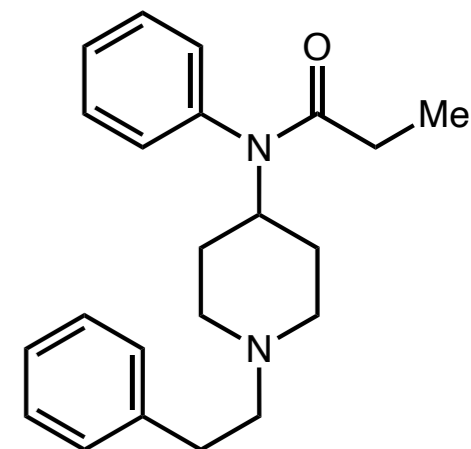
Easily accessible reagents

Open to air

Column-free purification



**"cooking"**



~60% over 4 steps

>99.5% purity

**Aspirational: a more practical approach to synthesizing fentanyl**



# *Gupta synthesis of fentanyl (2005)*

452 RESEARCH PAPER

JULY, 452-453

JOURNAL OF CHEMICAL RESEARCH 2005

## **A convenient one pot synthesis of fentanyl**

**Pradeep Kumar Gupta, Kumaran Ganesan, Ambuja Pande and Ramesh Chandra Malhotra\***

*Defence Research & Development Establishment, Gwalior (M. P.) India-474002*

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Fentanyl, N-(1-phenethyl-4-piperidyl) propionanilide, was prepared by performing three successive one pot reactions at room temperature.

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**Keywords:** fentanyl, one pot, three step, reductive amination, sodium triacetoxyborohydride

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452 RESEARCH PAPER

JULY, 452–453

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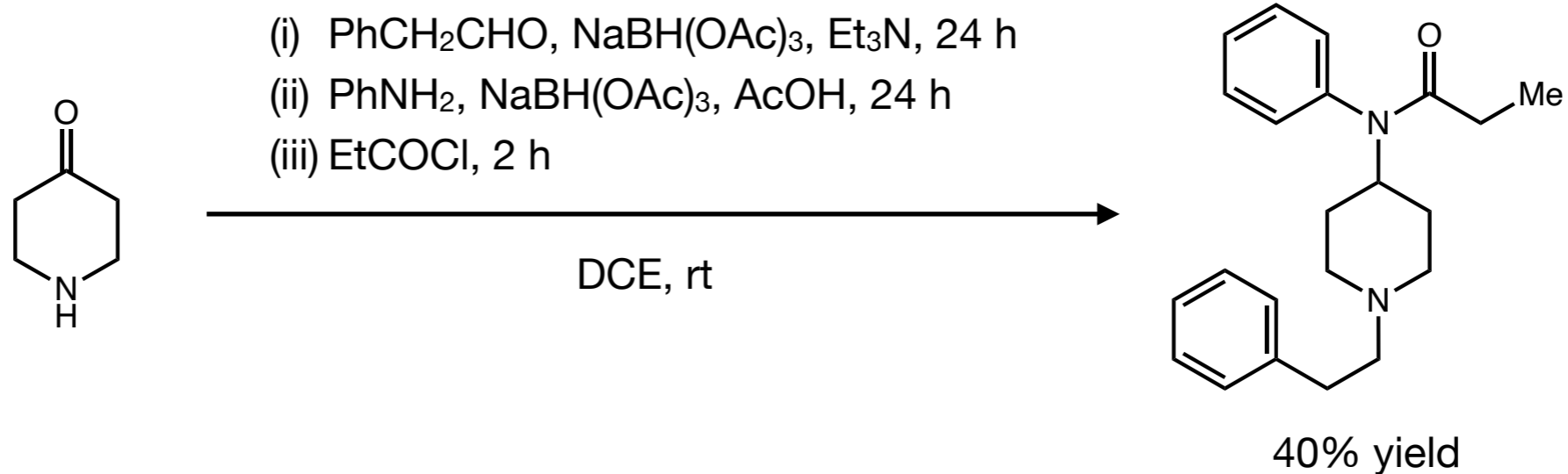
## A convenient one pot synthesis of fentanyl

Pradeep Kumar Gupta, Kumaran Ganesan, Ambuja Pande and Ramesh Chandra Malhotra\*

*Defence Research & Development Establishment, Gwalior (M. P.) India-474002*

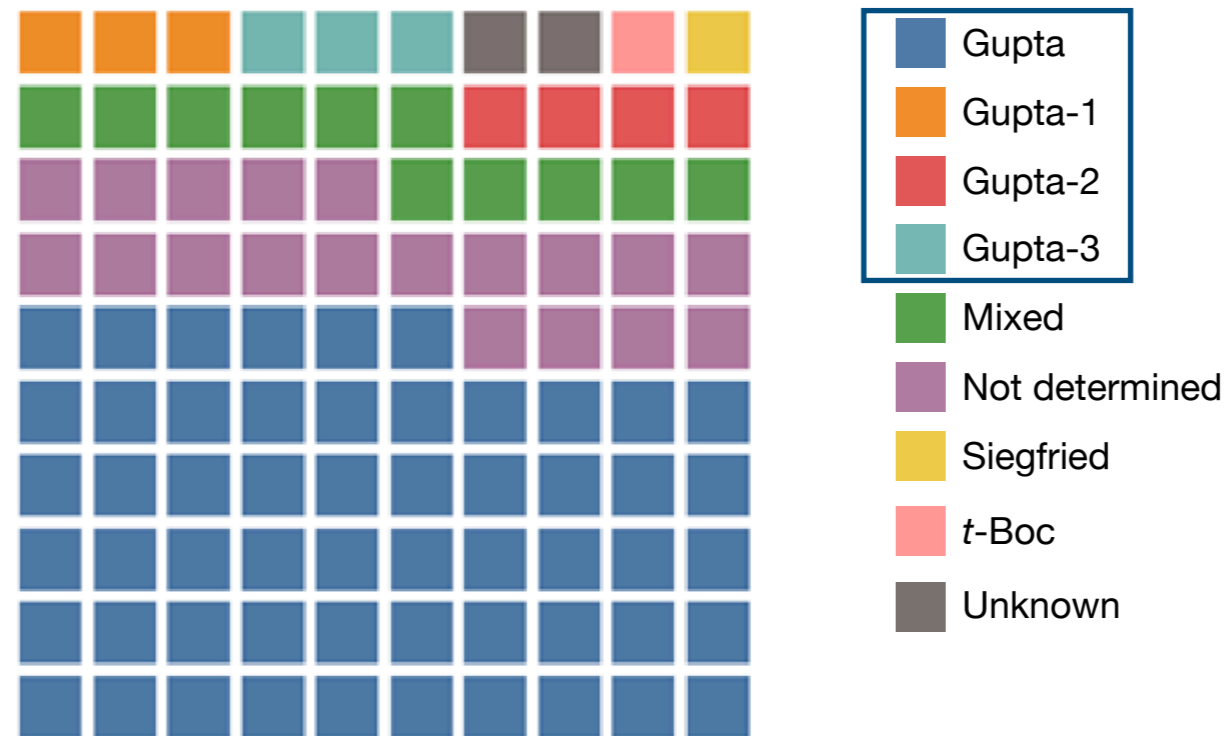
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## Gupta synthesis of fentanyl (2005)

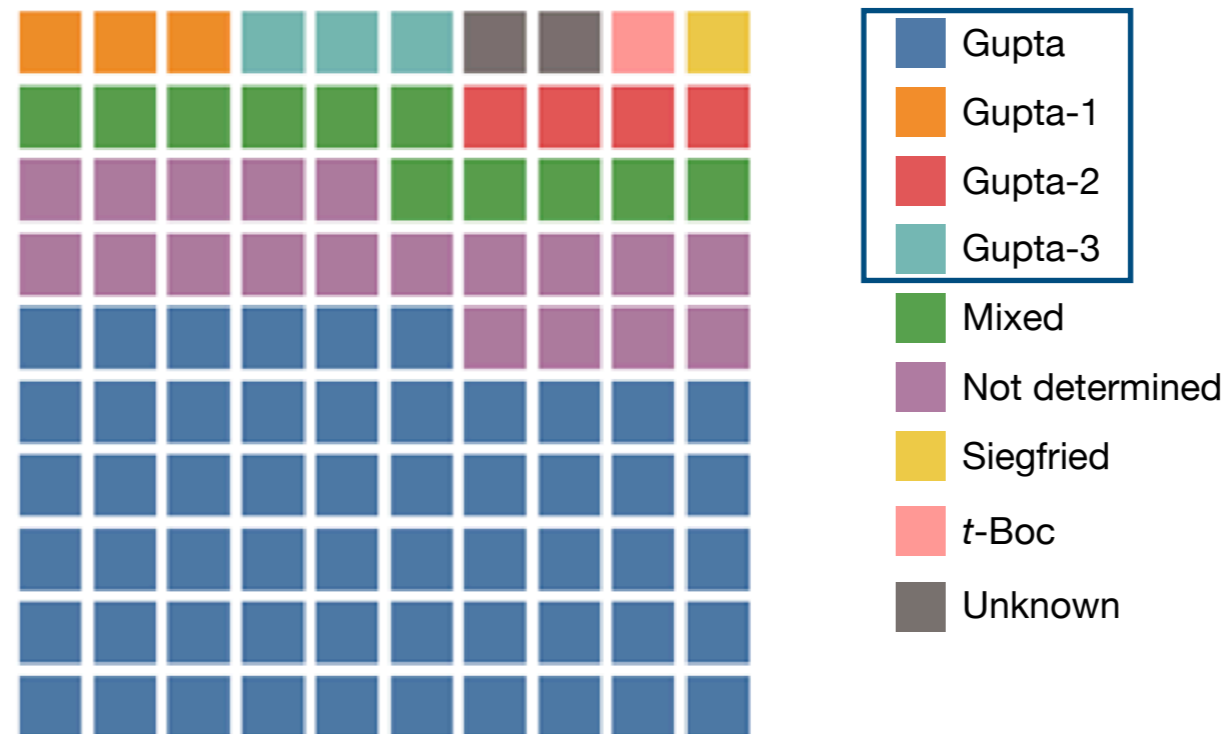
Fentanyl seized by the DEA in 2021



- **66%** of fentanyl seized by the DEA is produced via the Gupta Method or its variations

## Gupta synthesis of fentanyl (2005)

Fentanyl seized by the DEA in 2021

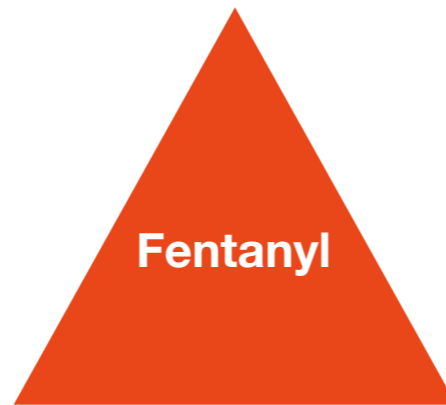


- **66%** of fentanyl seized by the DEA is produced via the Gupta Method or its variations
- **98%** of all fentanyl and fentanyl analogues trafficked were **illicitly manufactured**

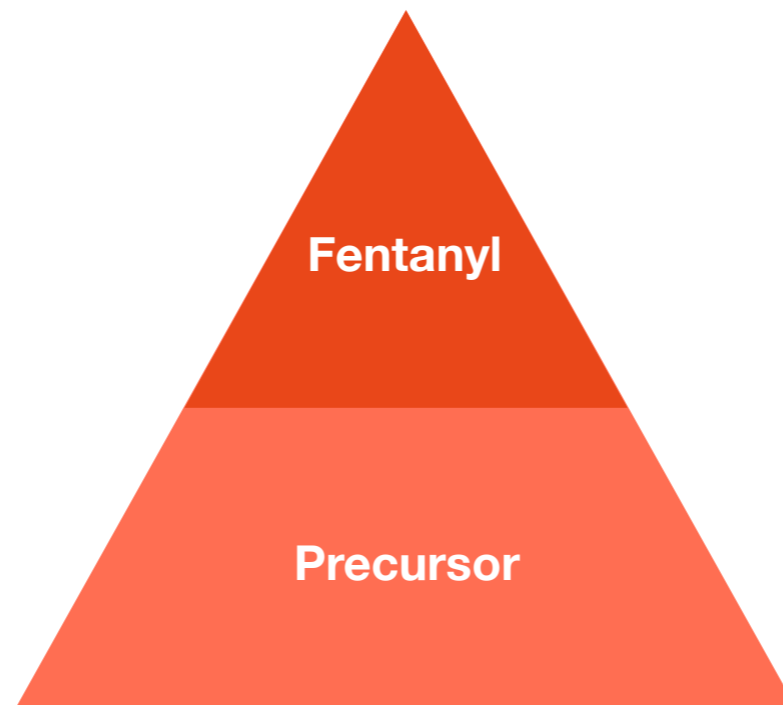
**A more proactive approach is needed to address the fentanyl crisis**



## *Actions to prevent fentanyl production*

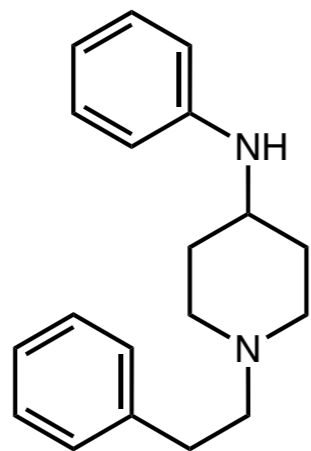
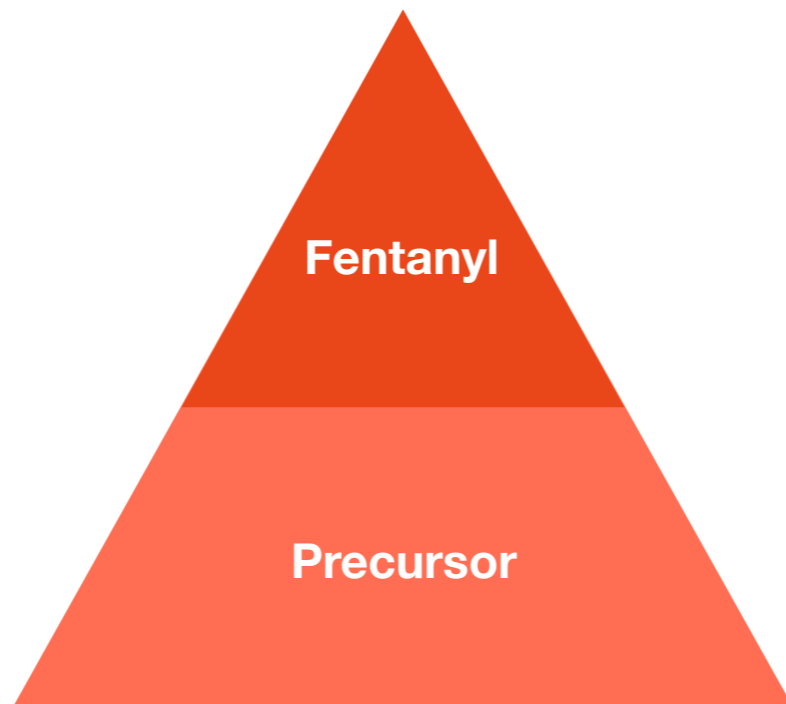


## *Actions to prevent fentanyl production*



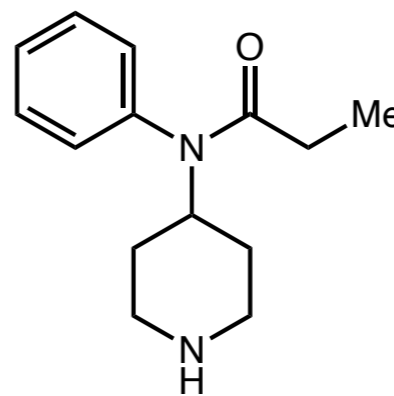
Chemicals used to produce the drug in one step

## *Actions to prevent fentanyl production*



**4-ANPP**

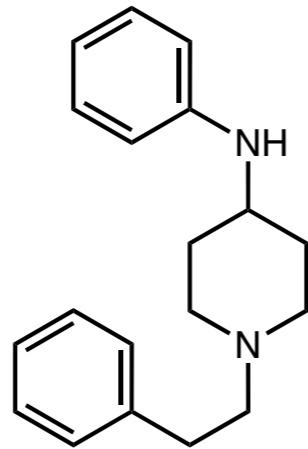
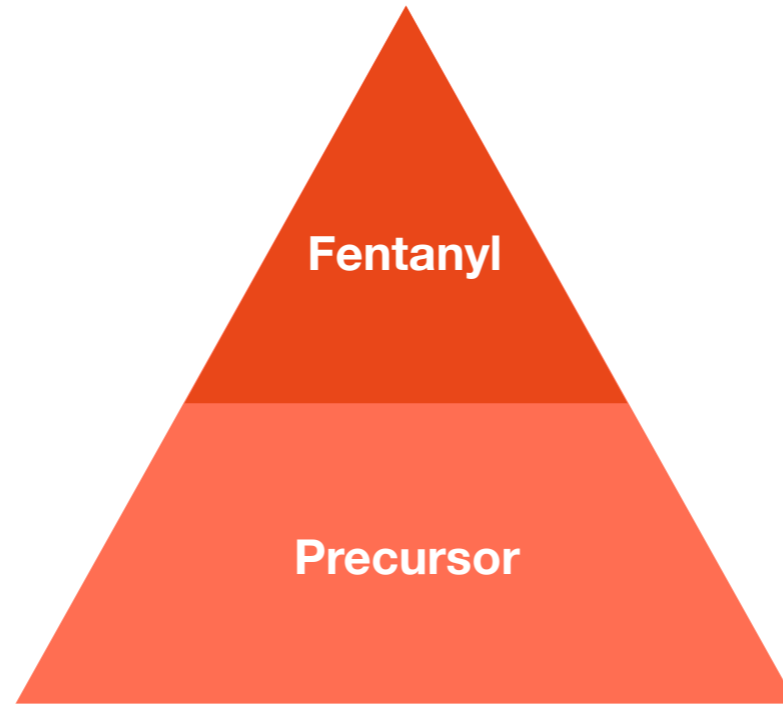
Gupta, Siegfried



**norfentanyl**

Janssen

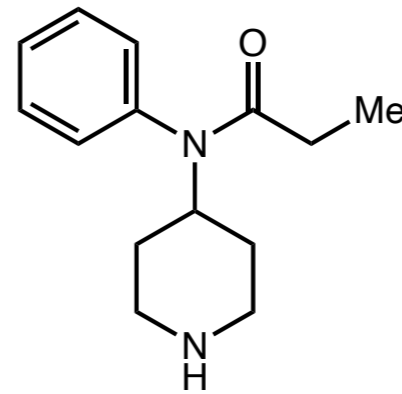
# Actions to prevent fentanyl production



**4-ANPP**

Gupta, Siegfried

Schedule II since 2010

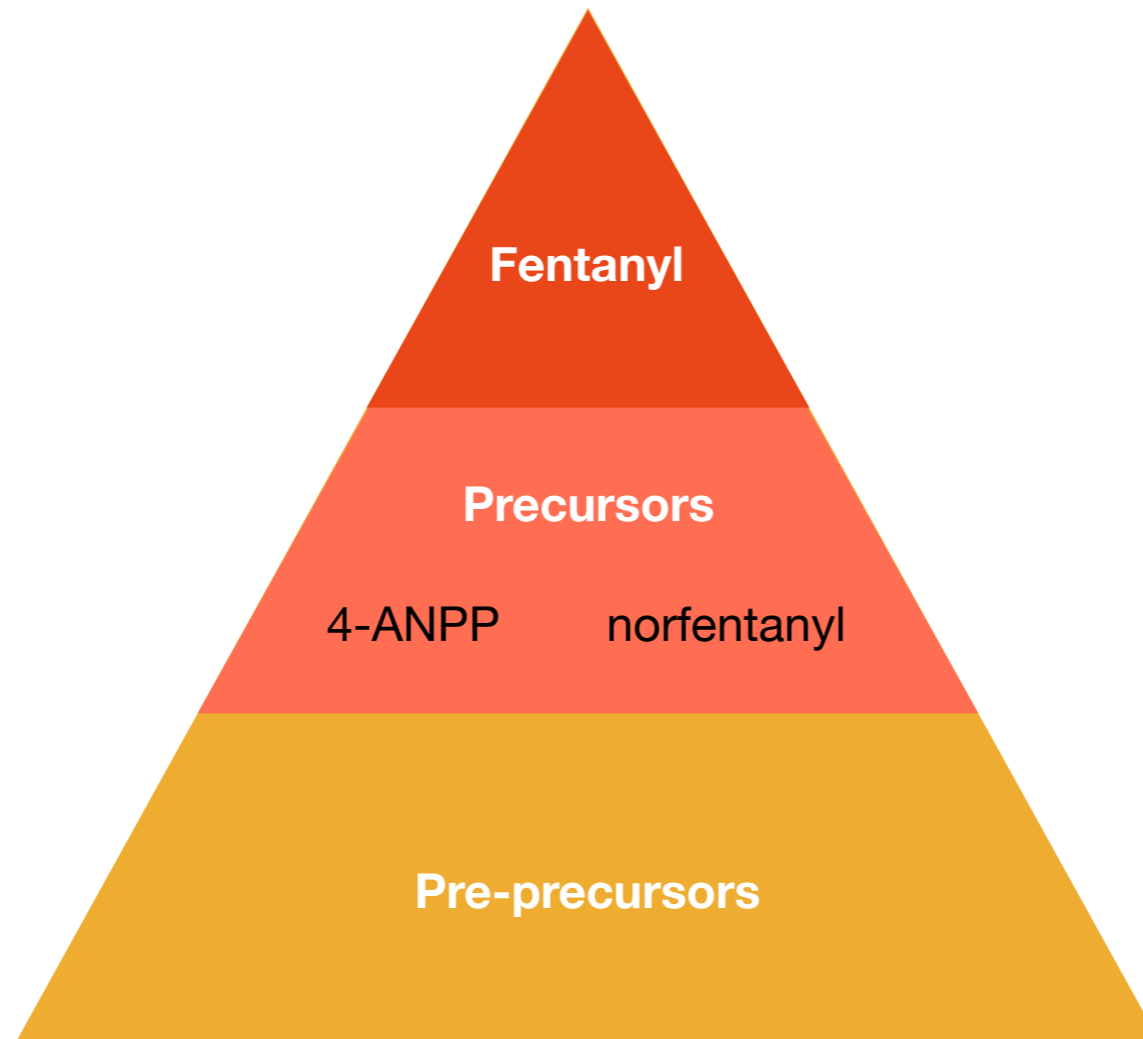


**norfentanyl**

Janssen

Schedule II since 2020

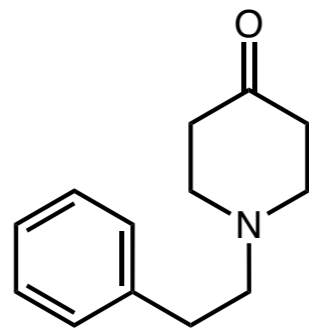
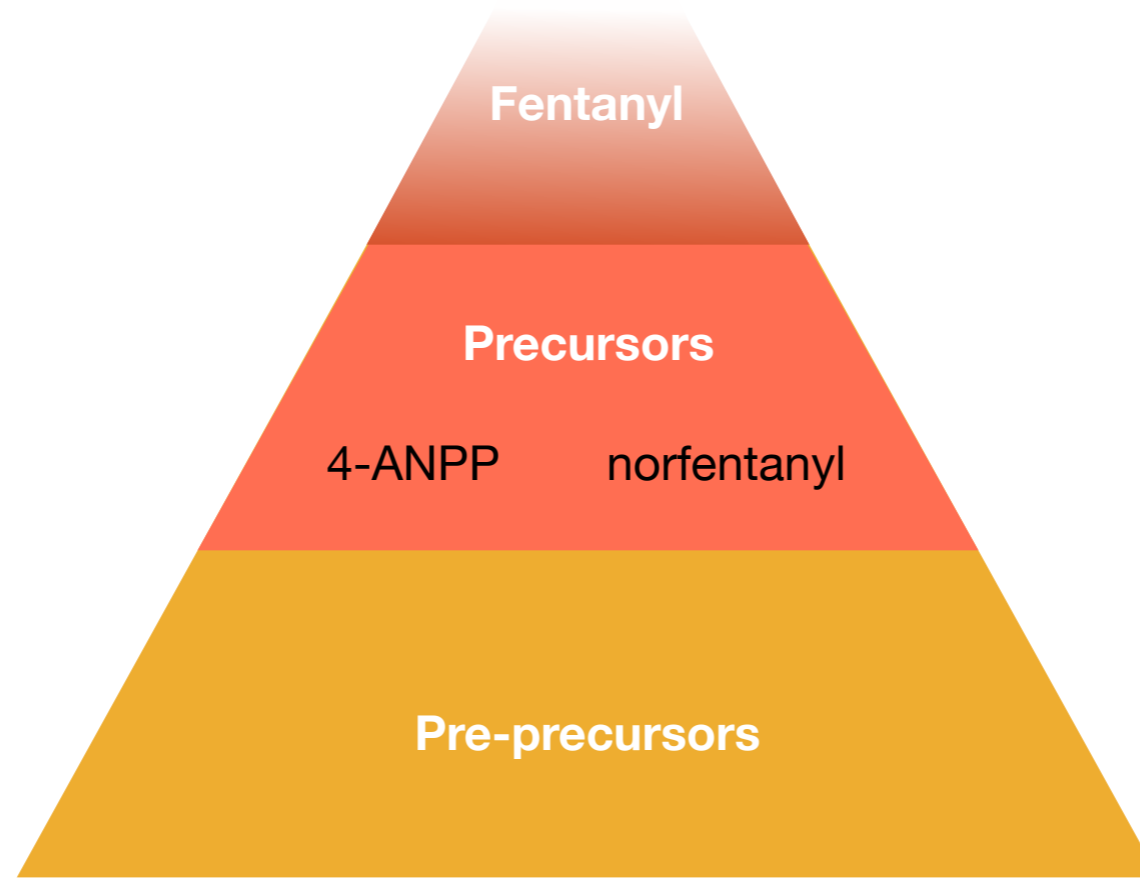
# *Actions to prevent fentanyl production*



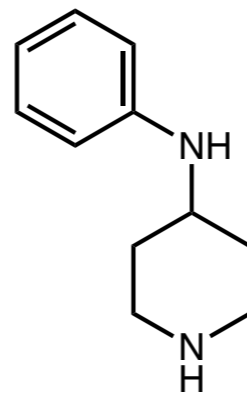
Chemicals that require additional steps to produce the drug



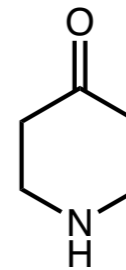
# Actions to prevent fentanyl production



**NPP**

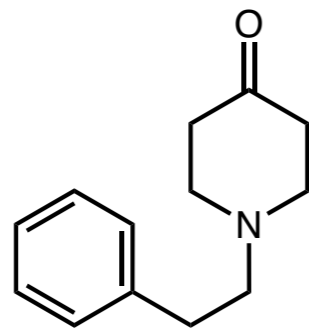
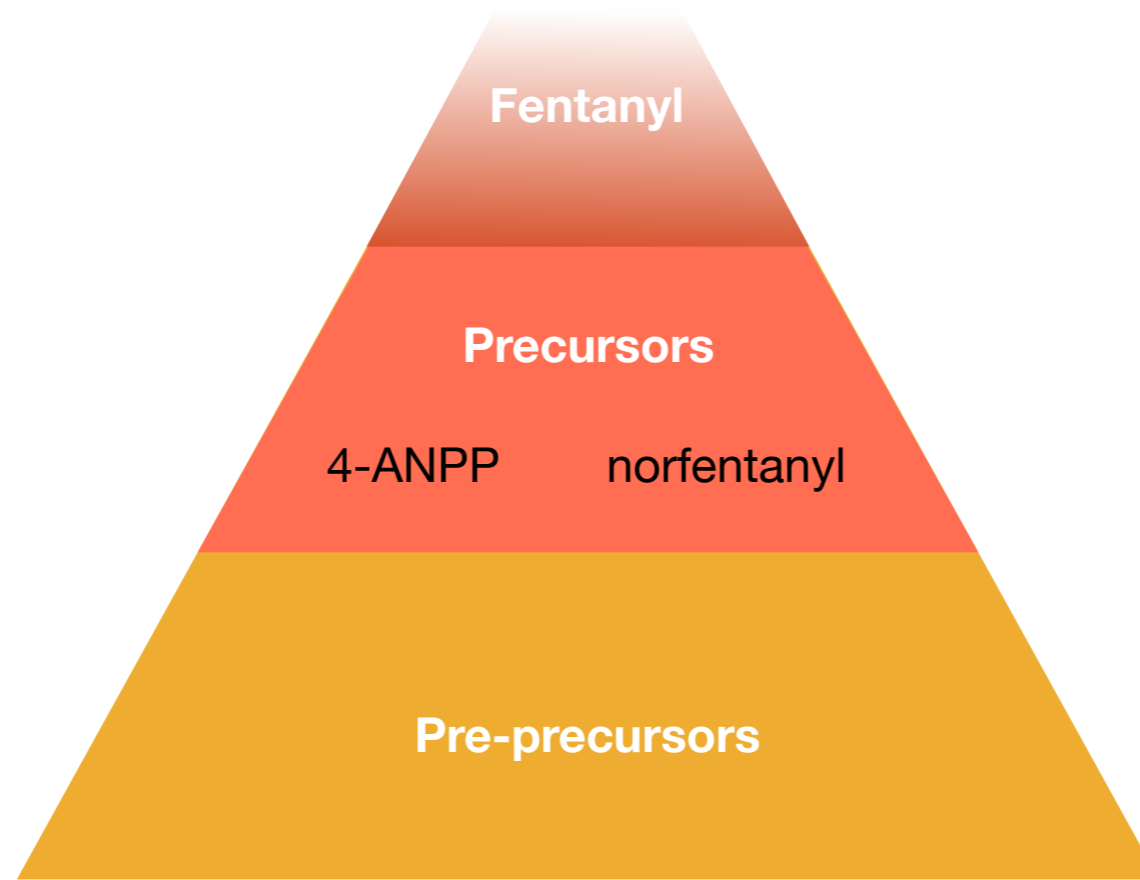


**4-AP**



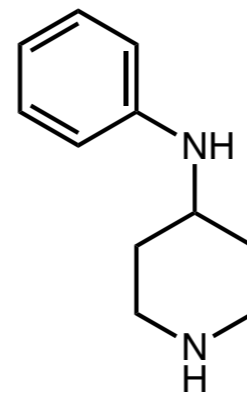
**4-piperidone**

# Actions to prevent fentanyl production



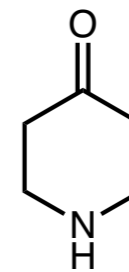
**NPP**

List I since 2007



**4-AP**

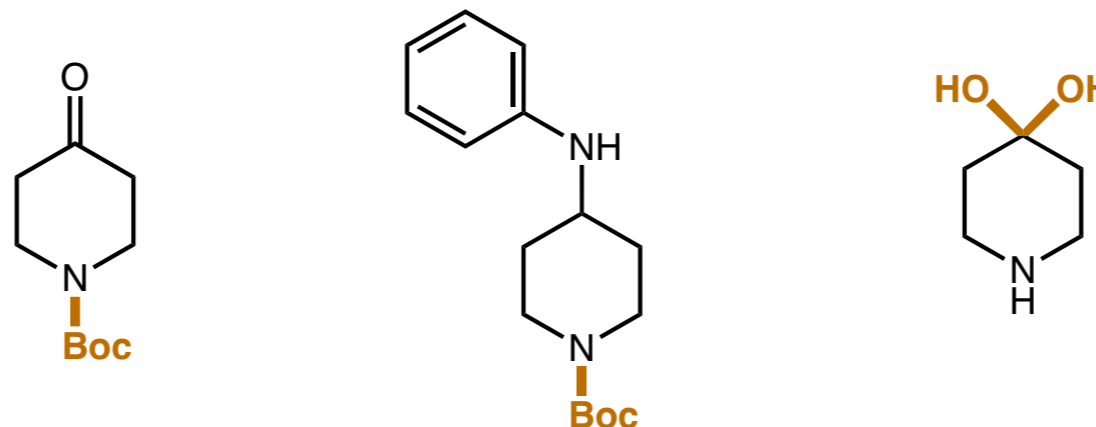
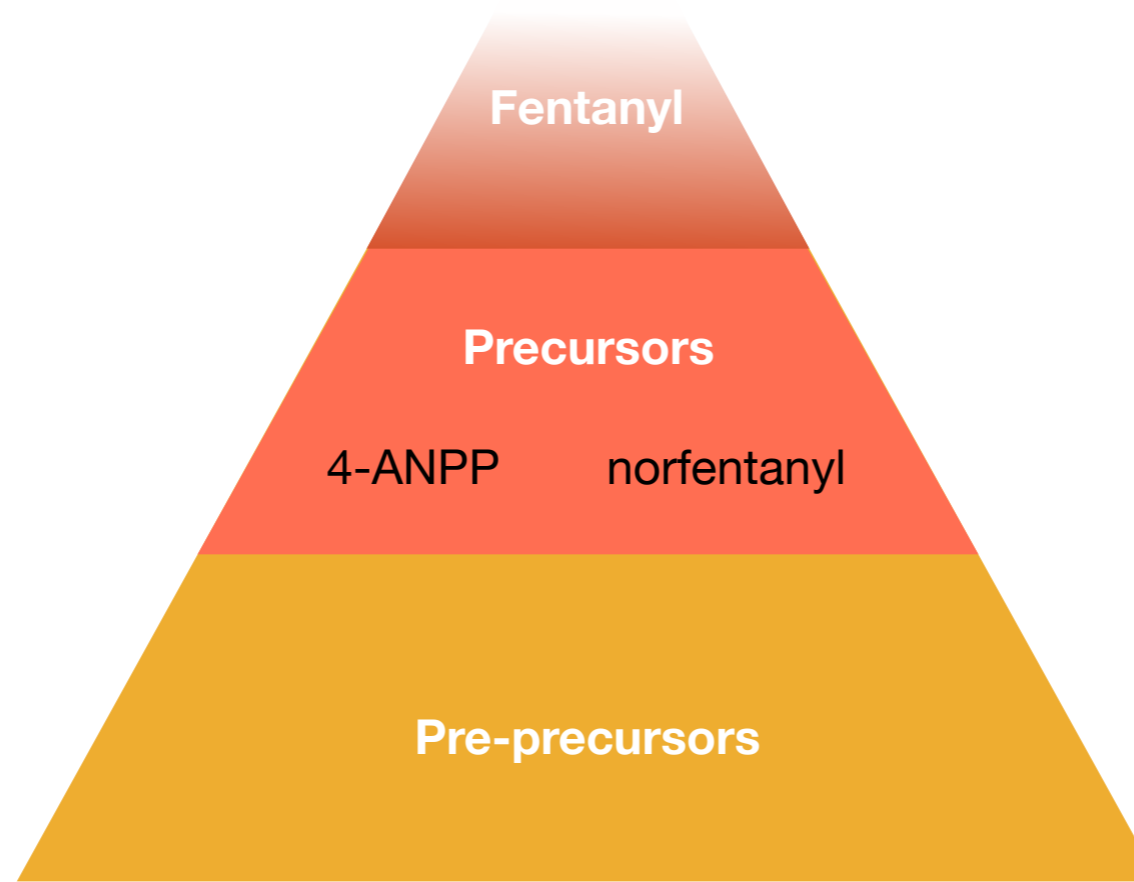
List I since 2020



**4-piperidone**

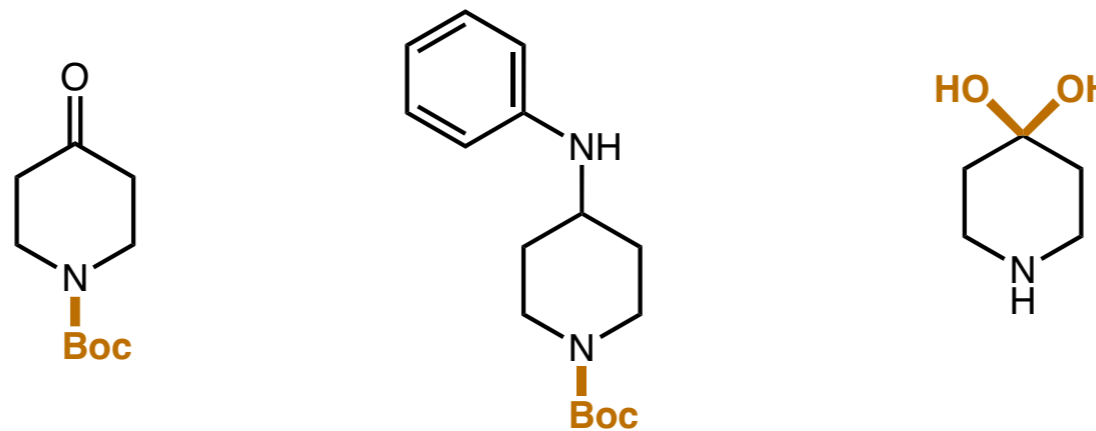
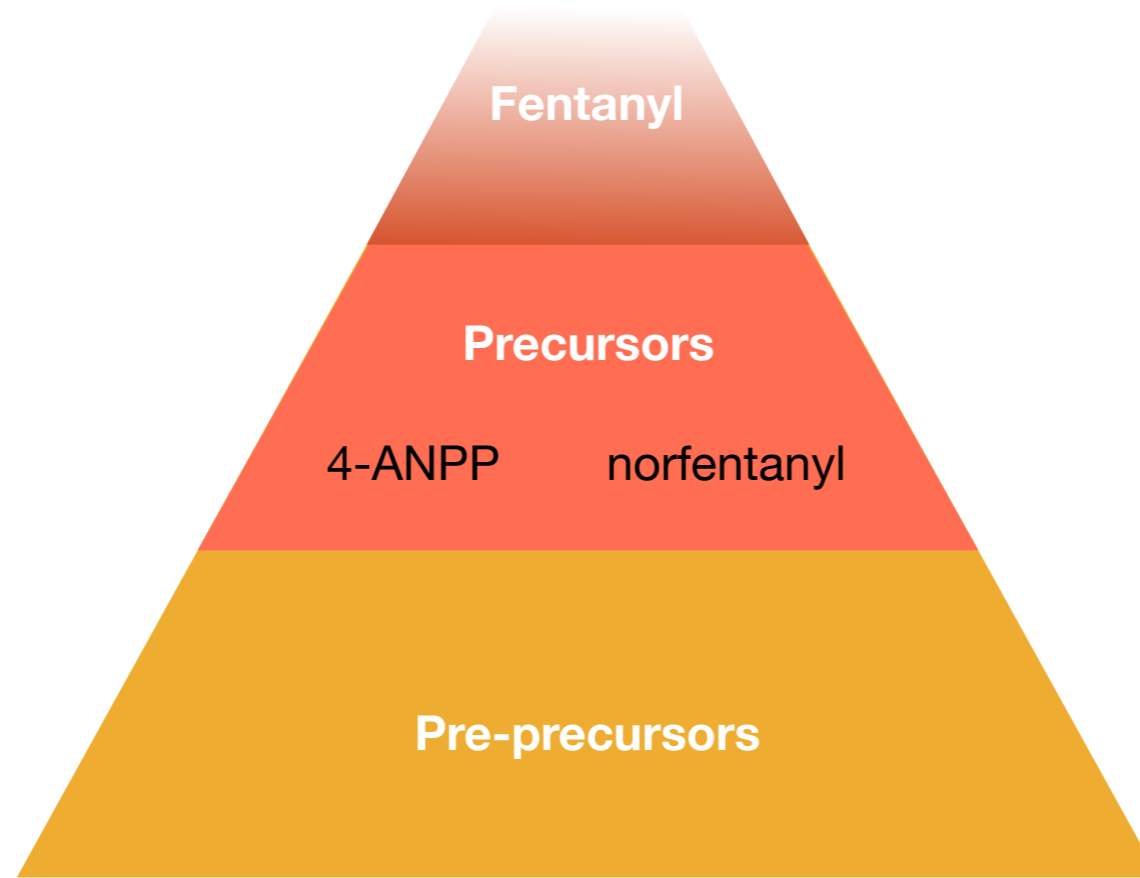
List I since 2023

# Actions to prevent fentanyl production



**“masked precursors”**

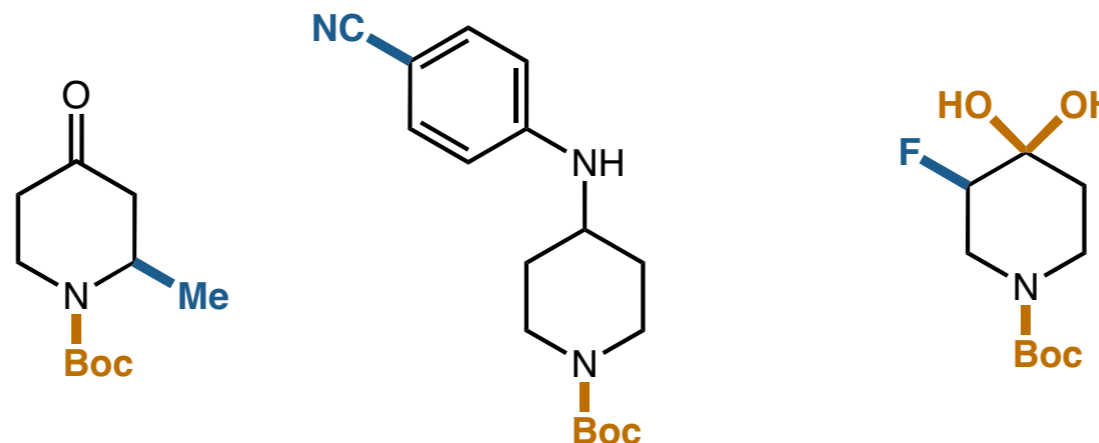
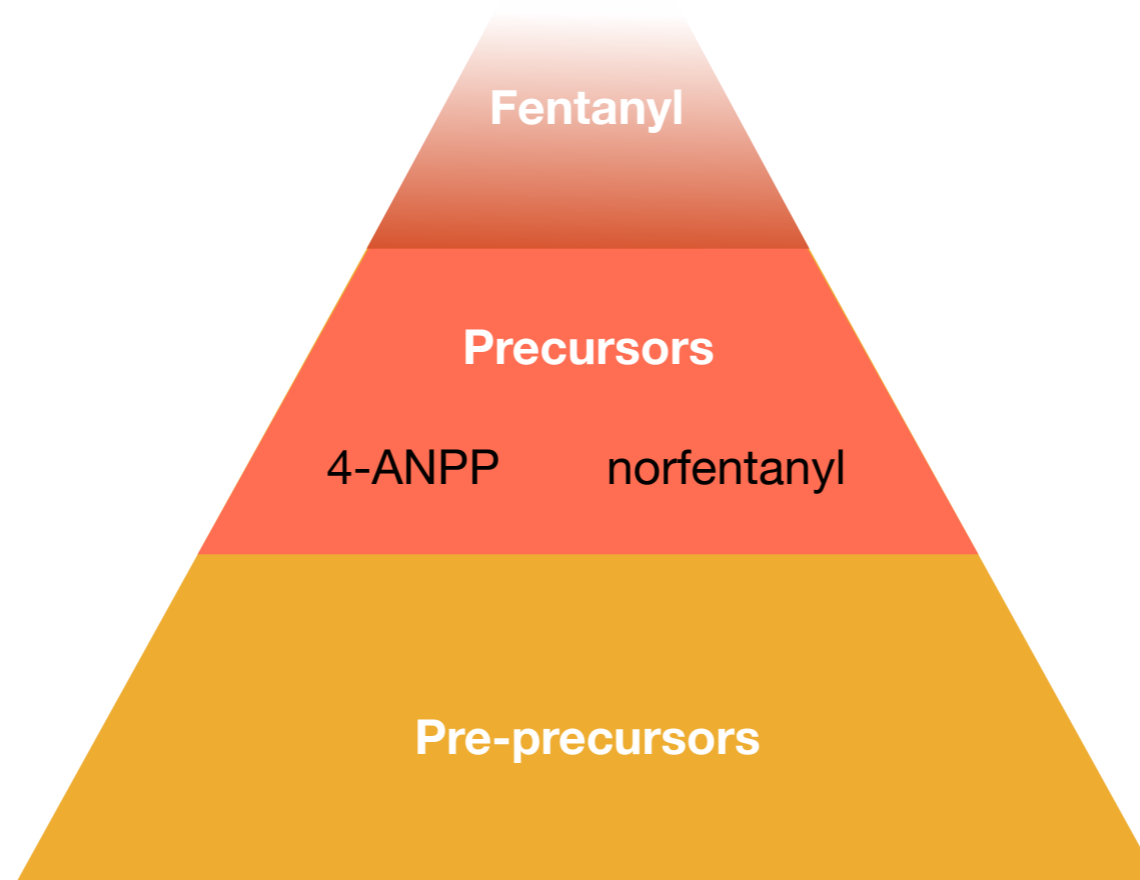
# Actions to prevent fentanyl production



Categorized as List I chemicals since 2023

**“masked precursors”**

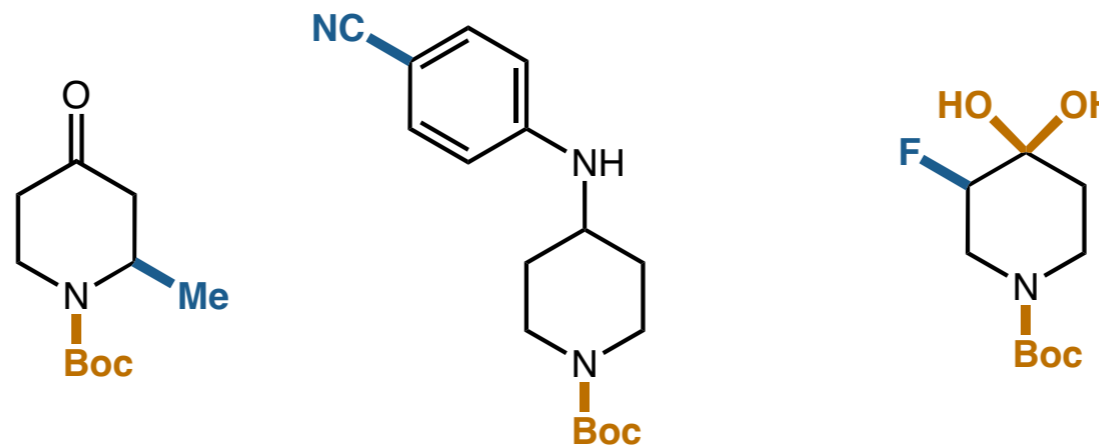
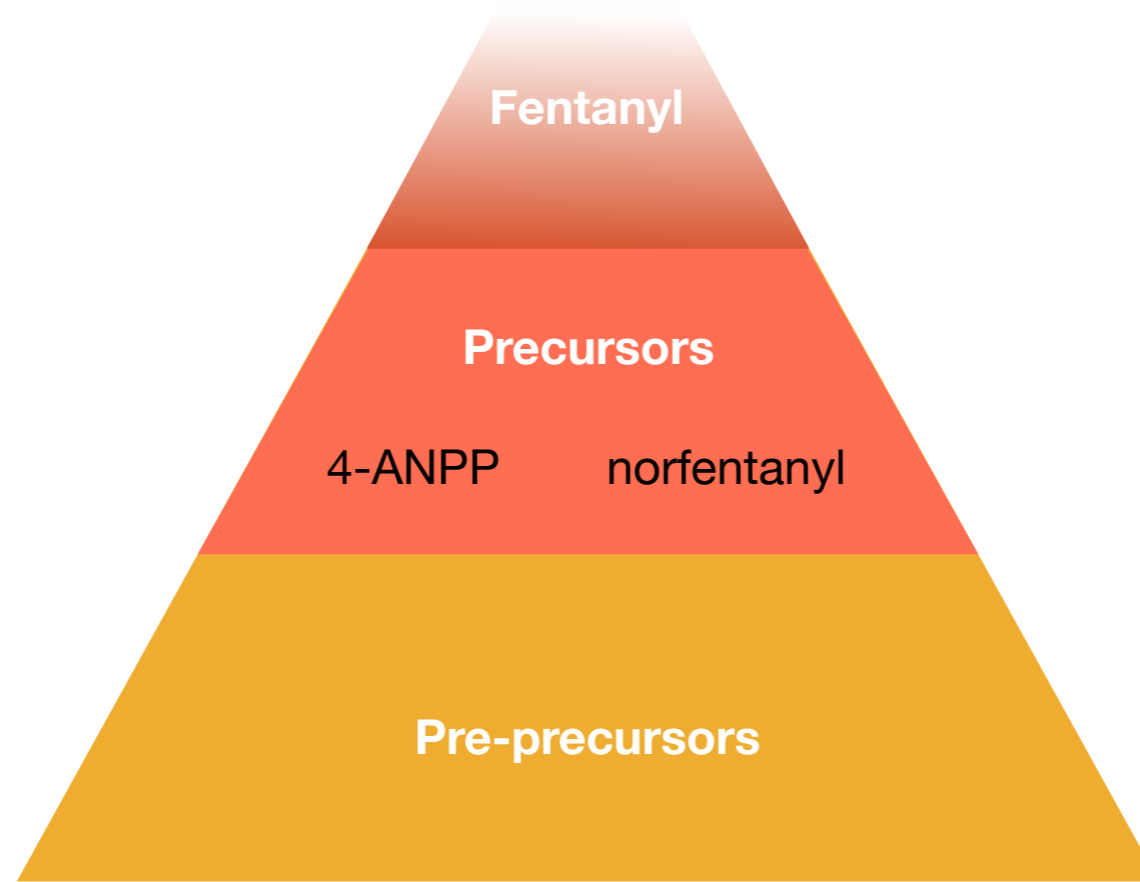
# Actions to prevent fentanyl production



“designer precursors”



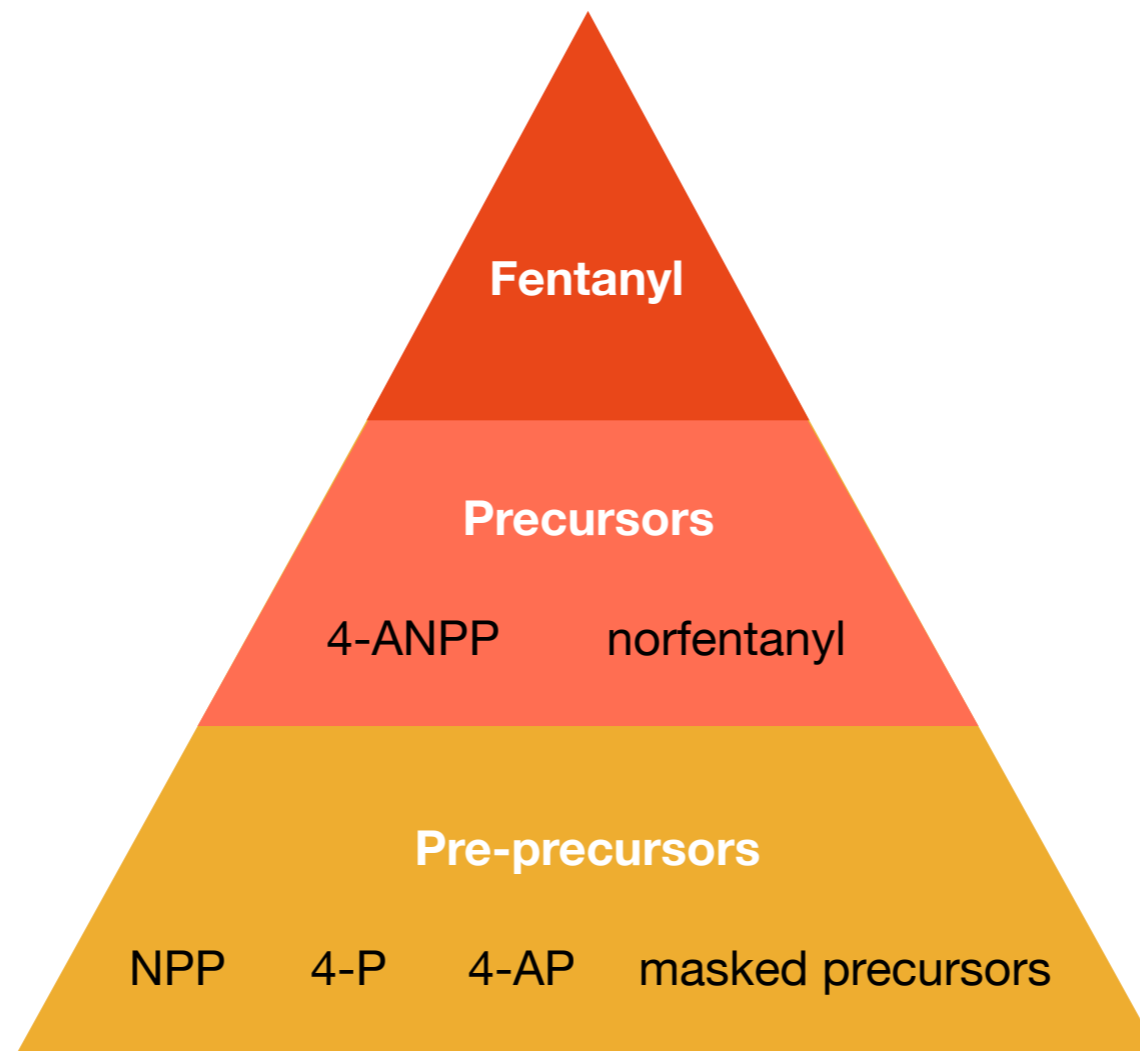
# Actions to prevent fentanyl production



Not currently regulated

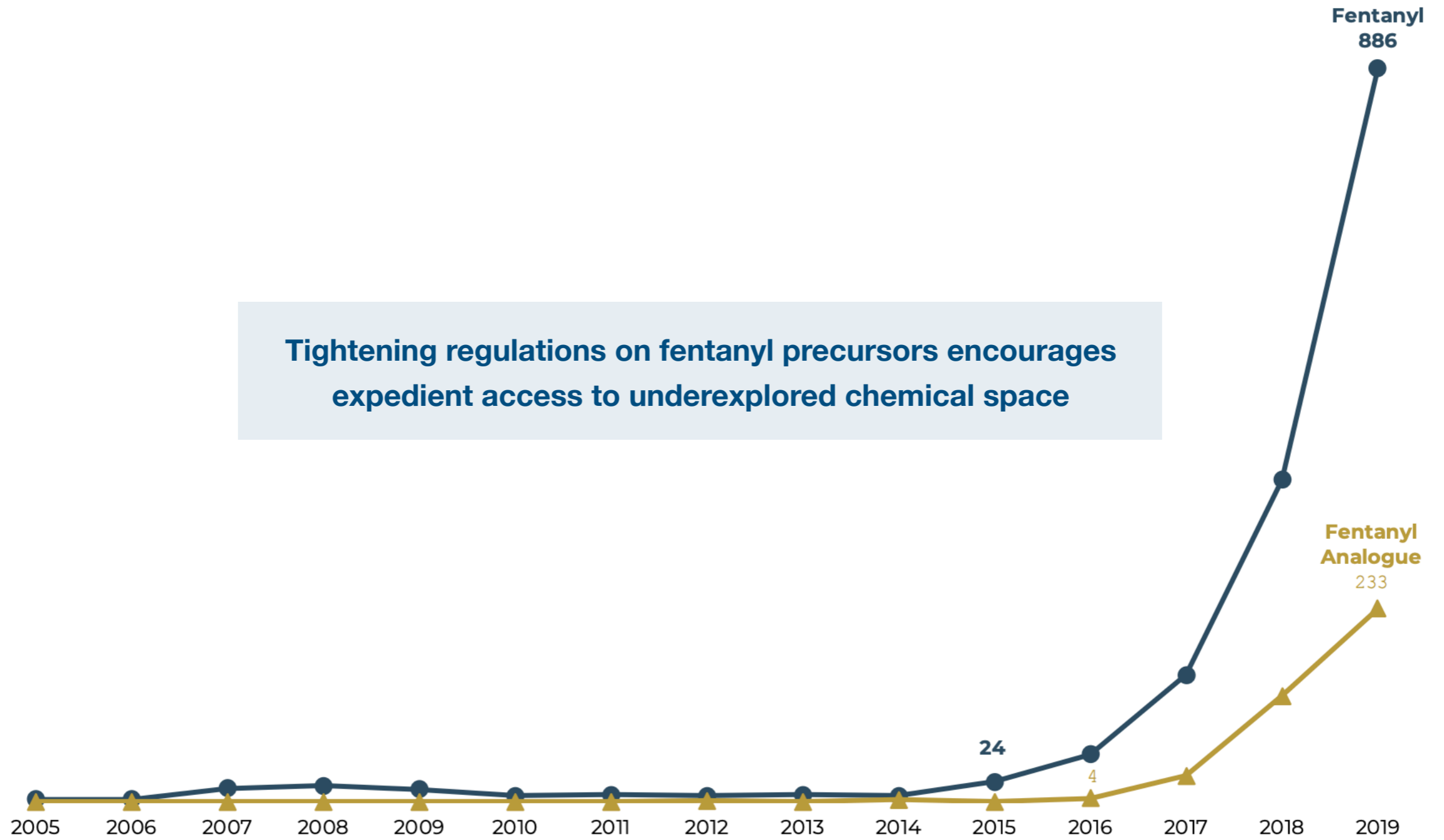
**“designer precursors”**

*Actions to prevent fentanyl production*



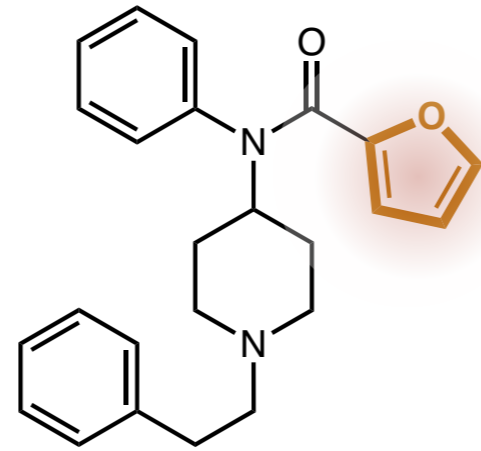
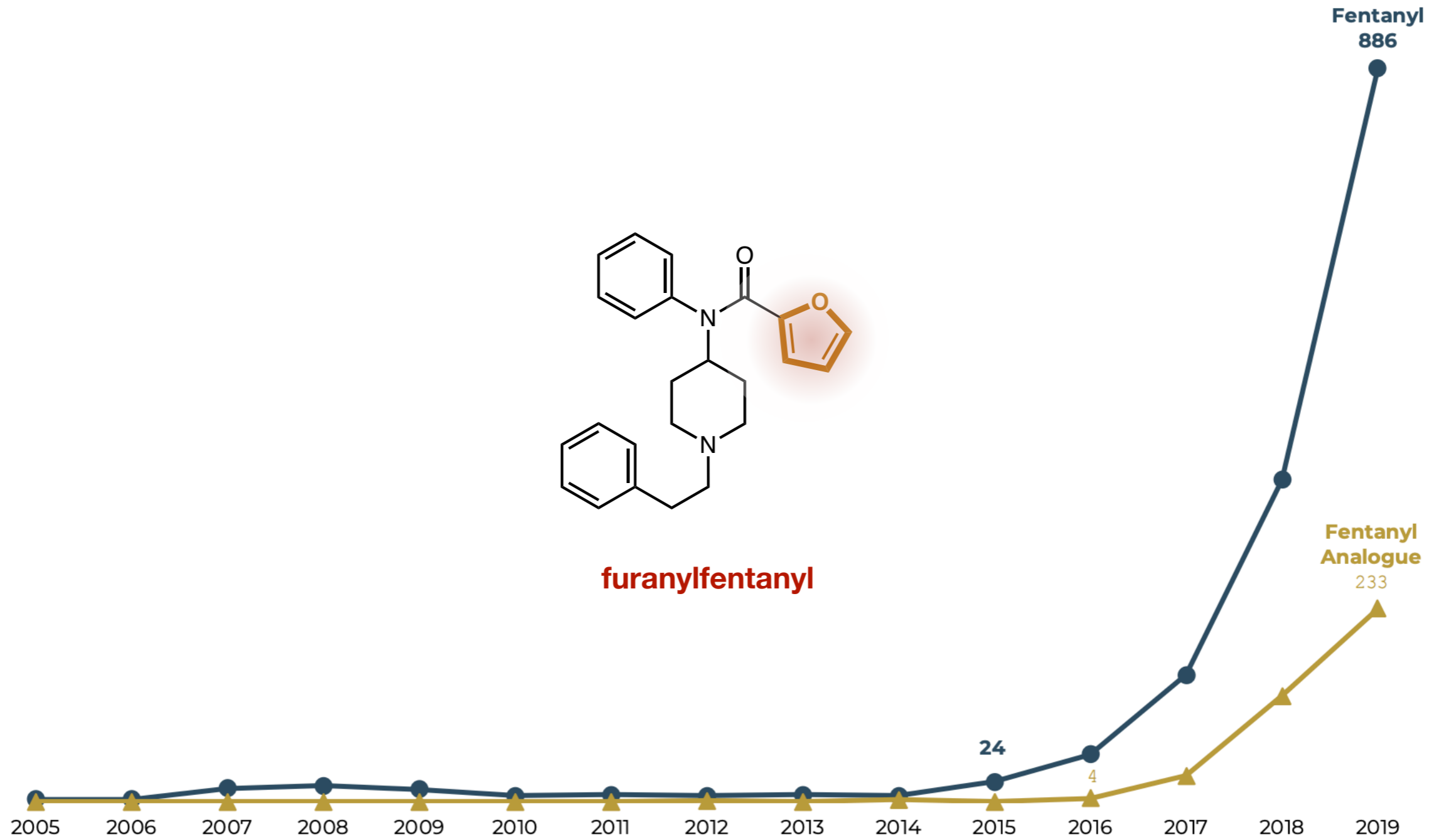
**Tightening regulations on fentanyl precursors encourages expedient access to underexplored chemical space**

2016



Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

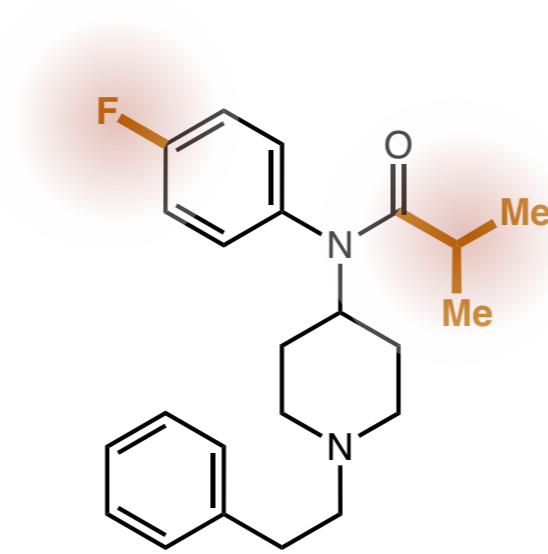
2016



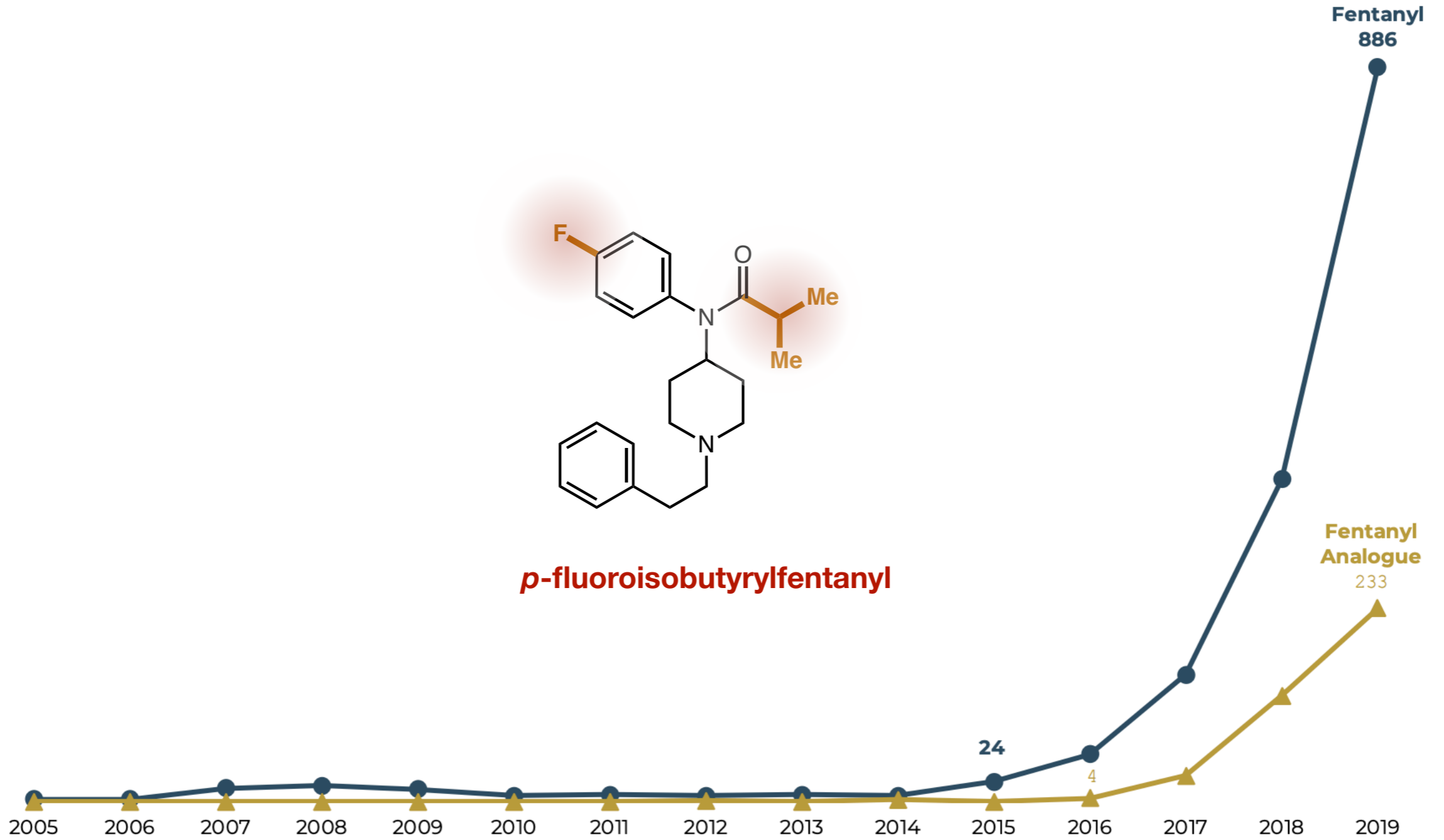
**furanylfentanyl**

Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

2016



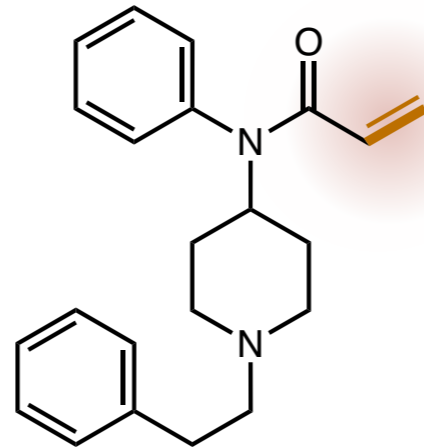
*p*-fluoroisobutyrylfentanyl



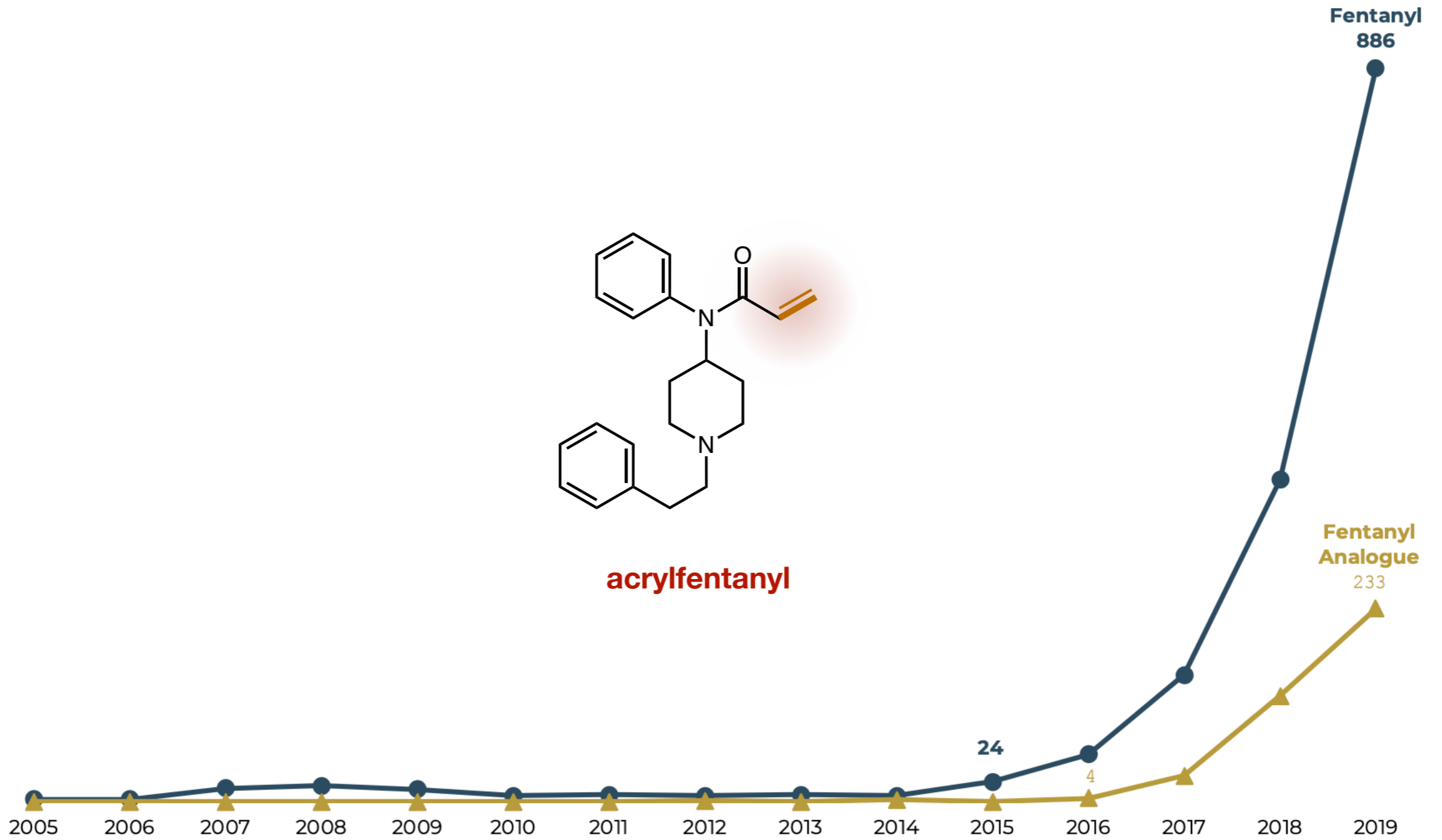
Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time



2016

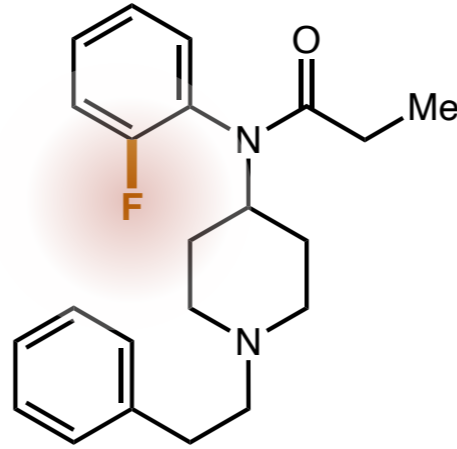


acrylfentanyl

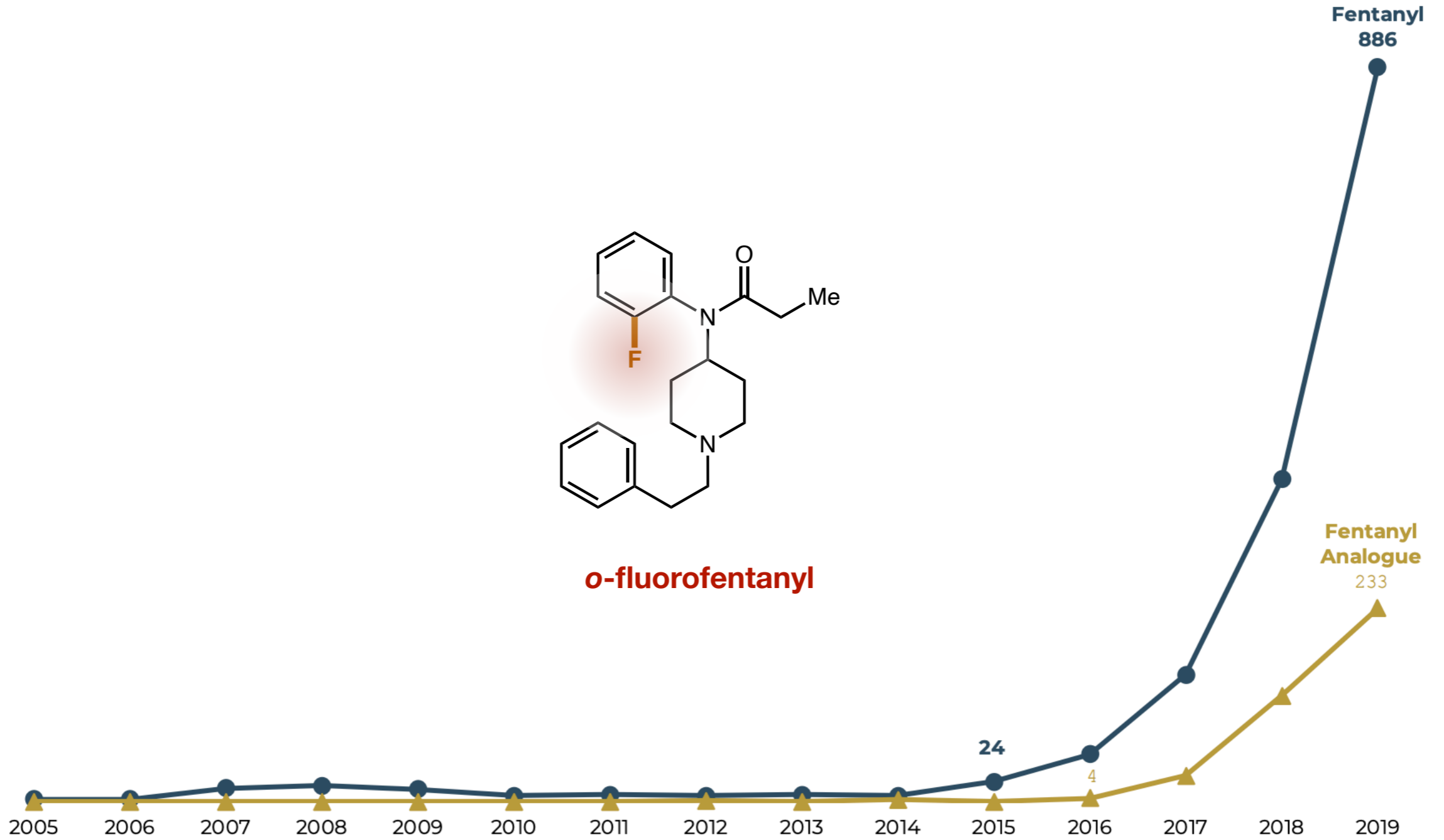


Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

2016

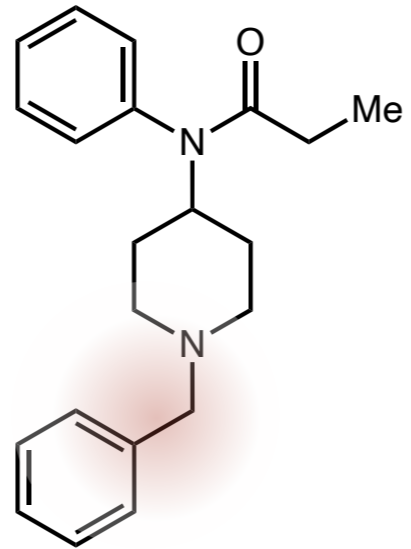


**o-fluorofentanyl**

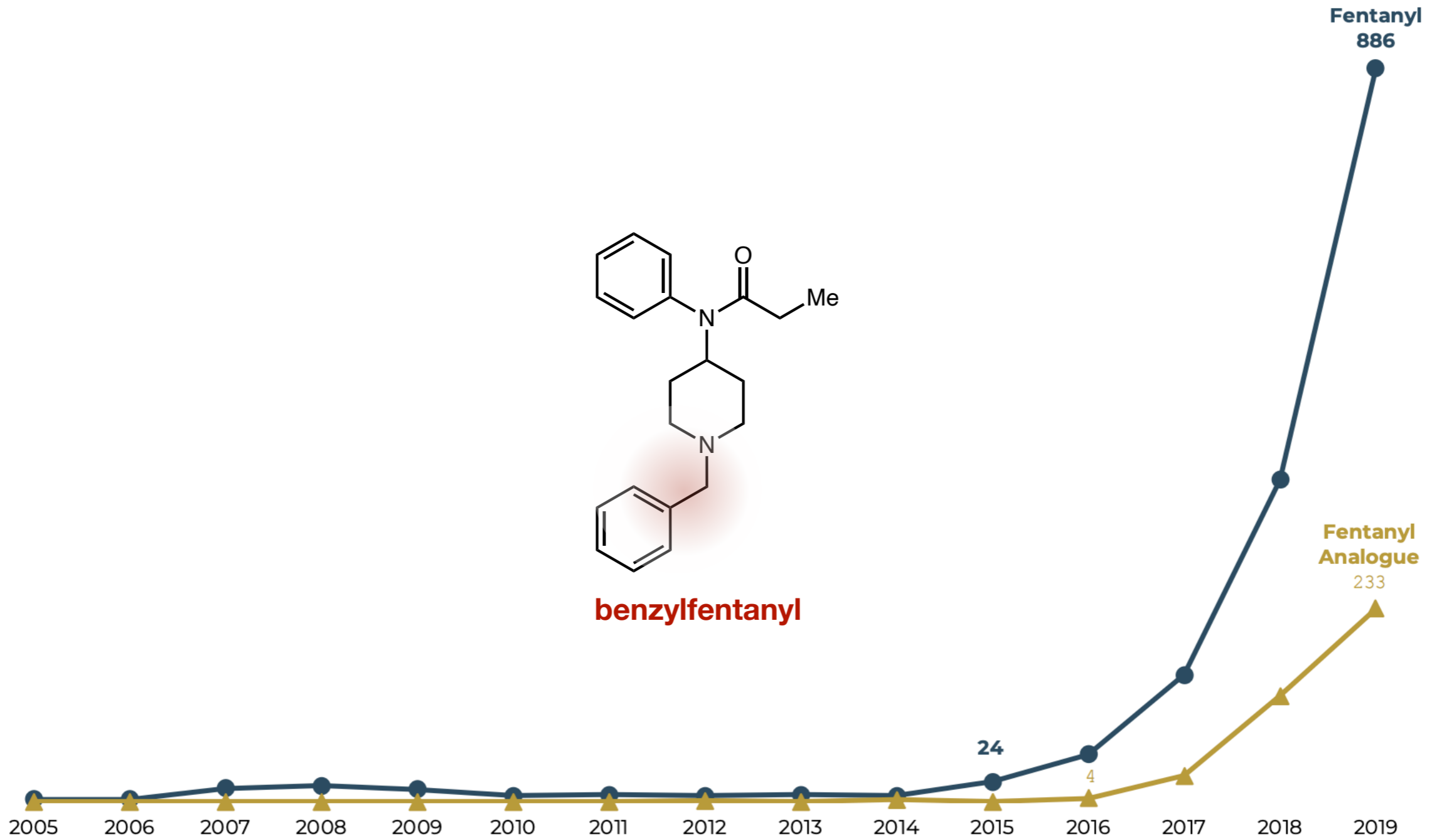


Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

2016

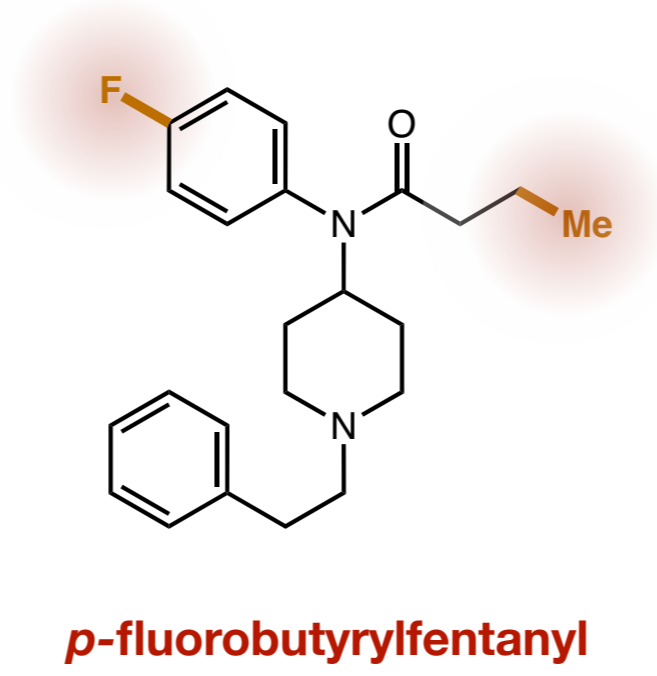
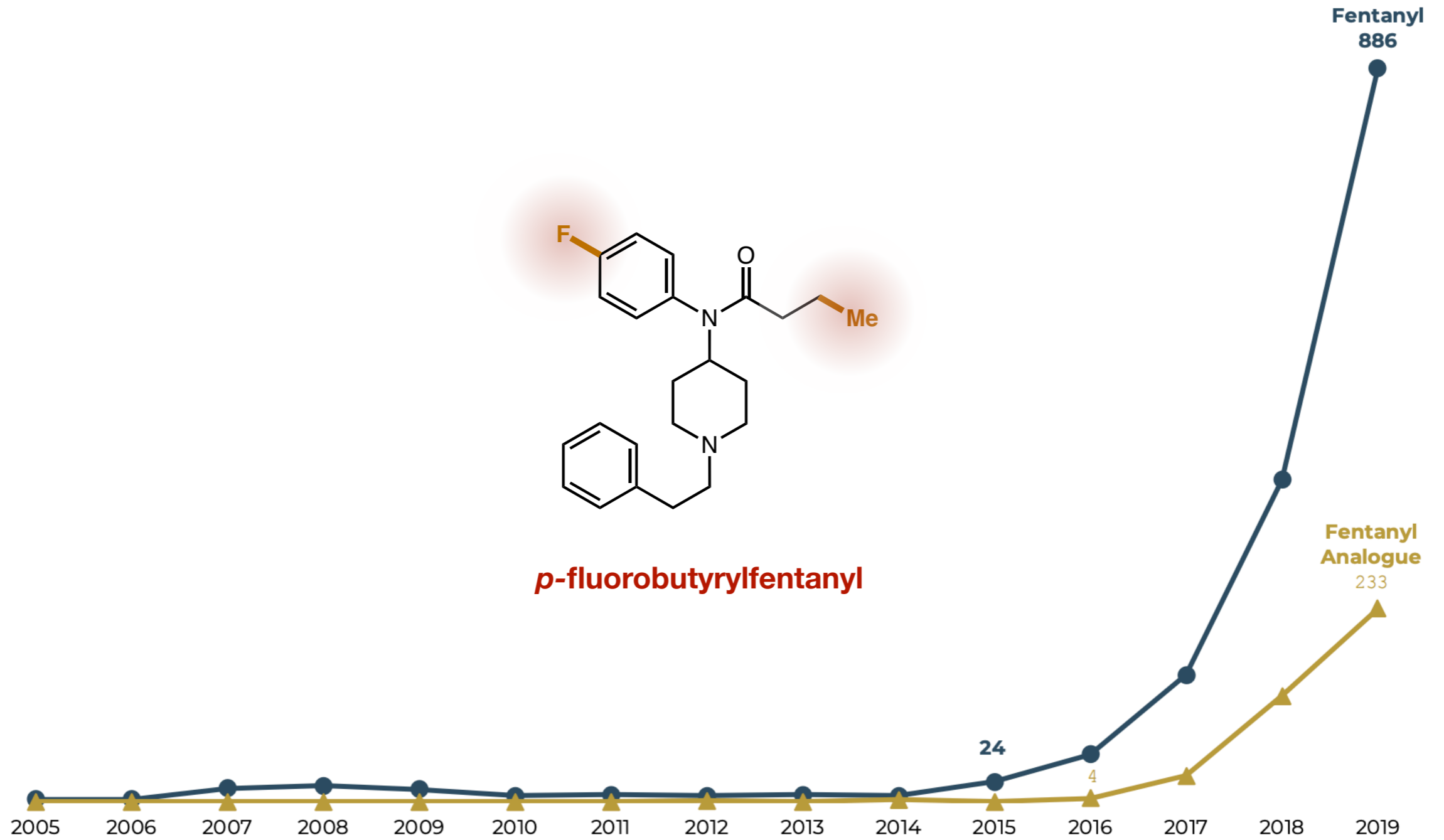


**benzylfentanyl**



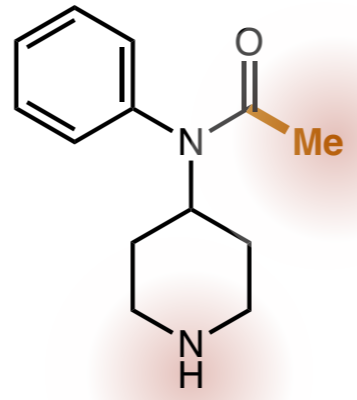
Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

2016

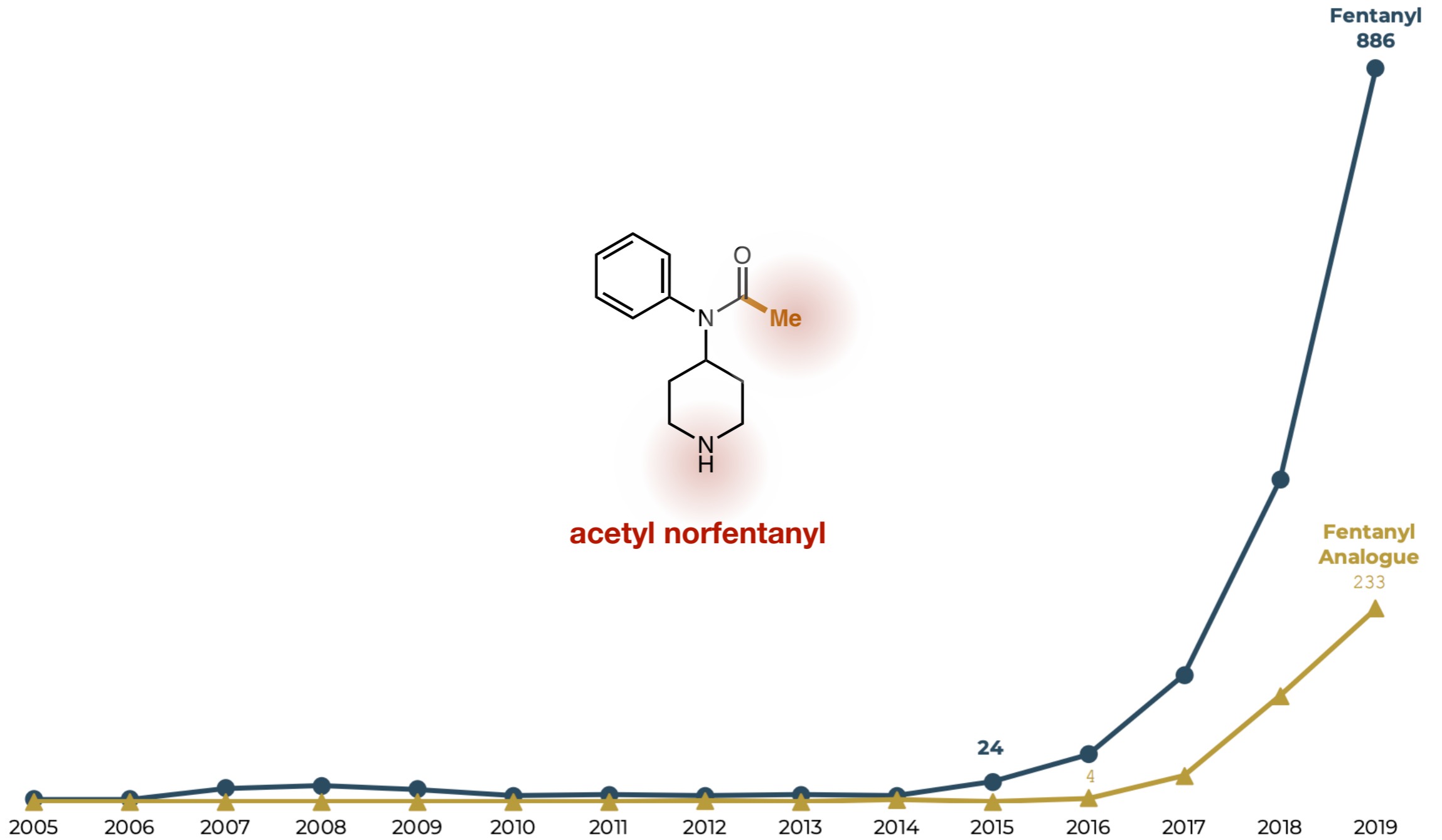


Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

2016

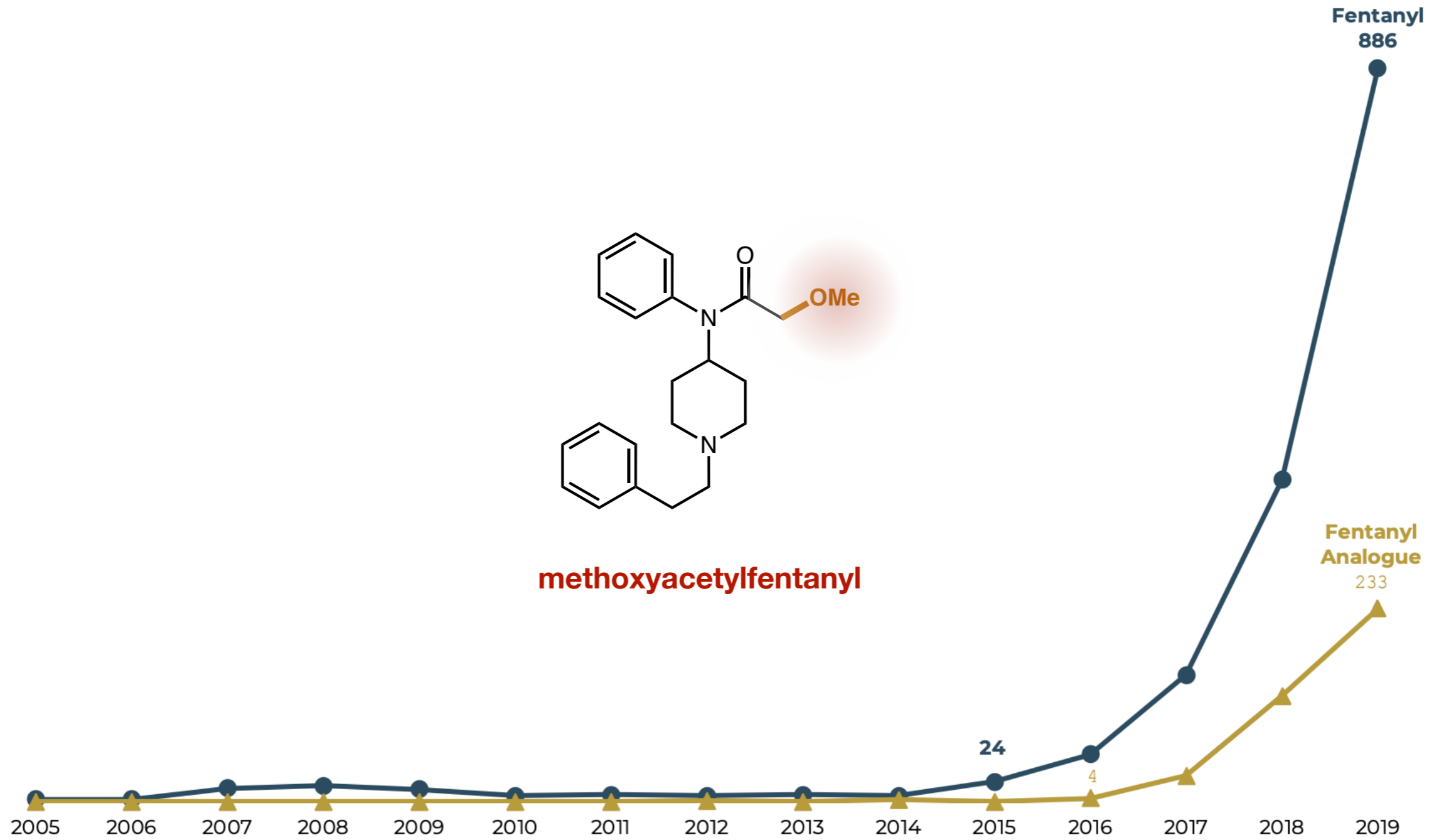


acetyl norfentanyl



Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

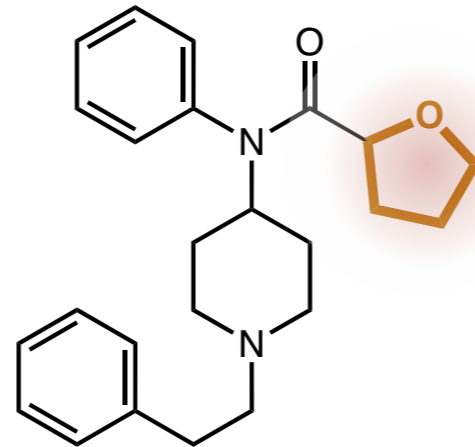
2017



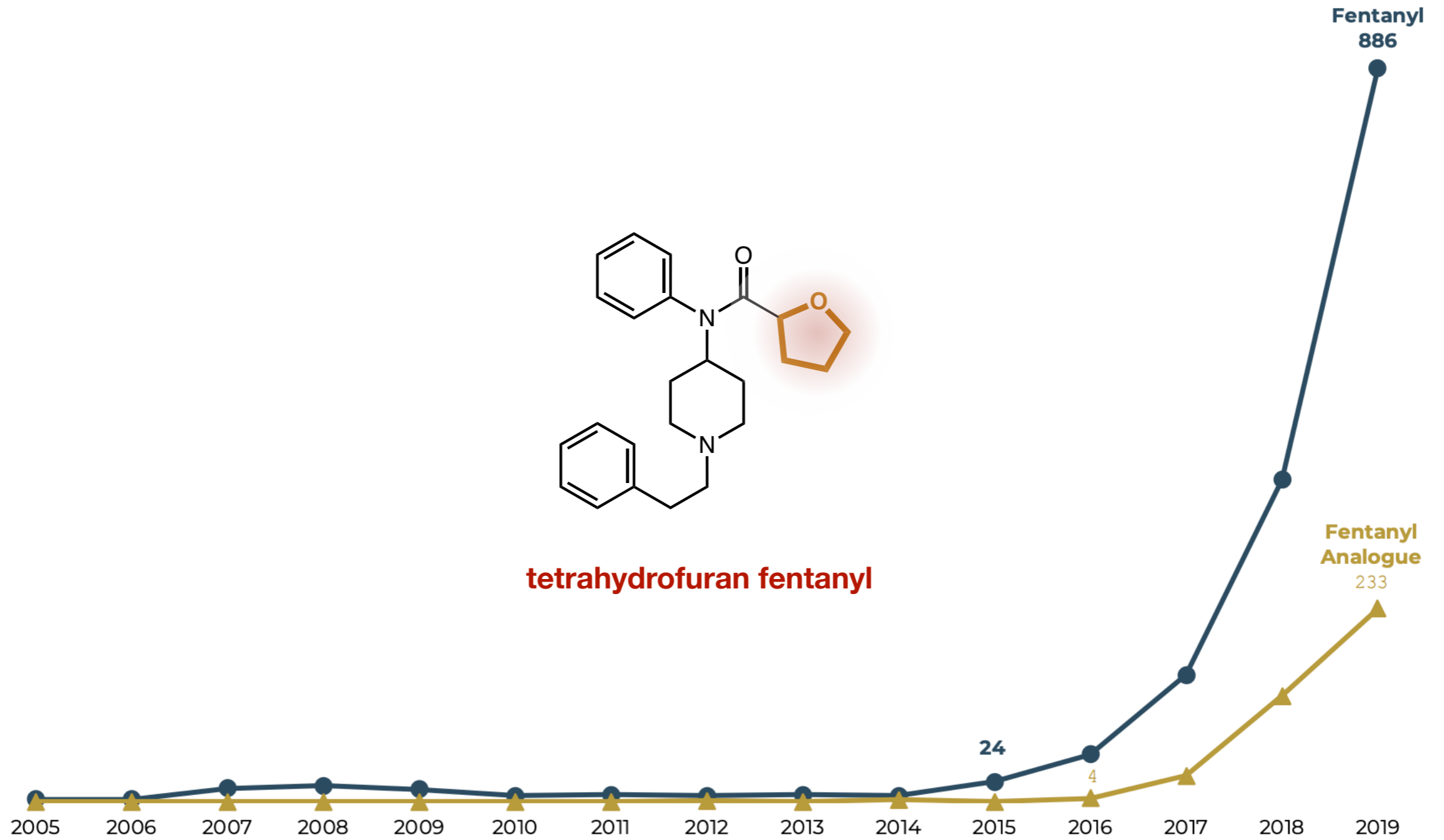
Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time



2017

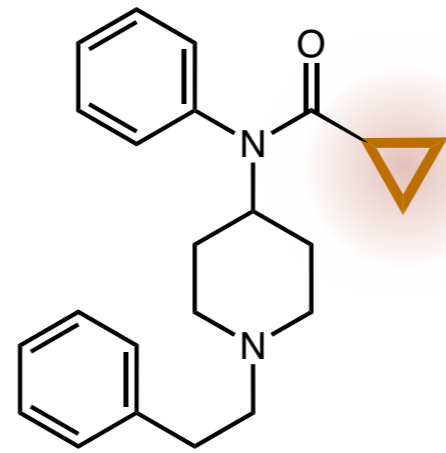
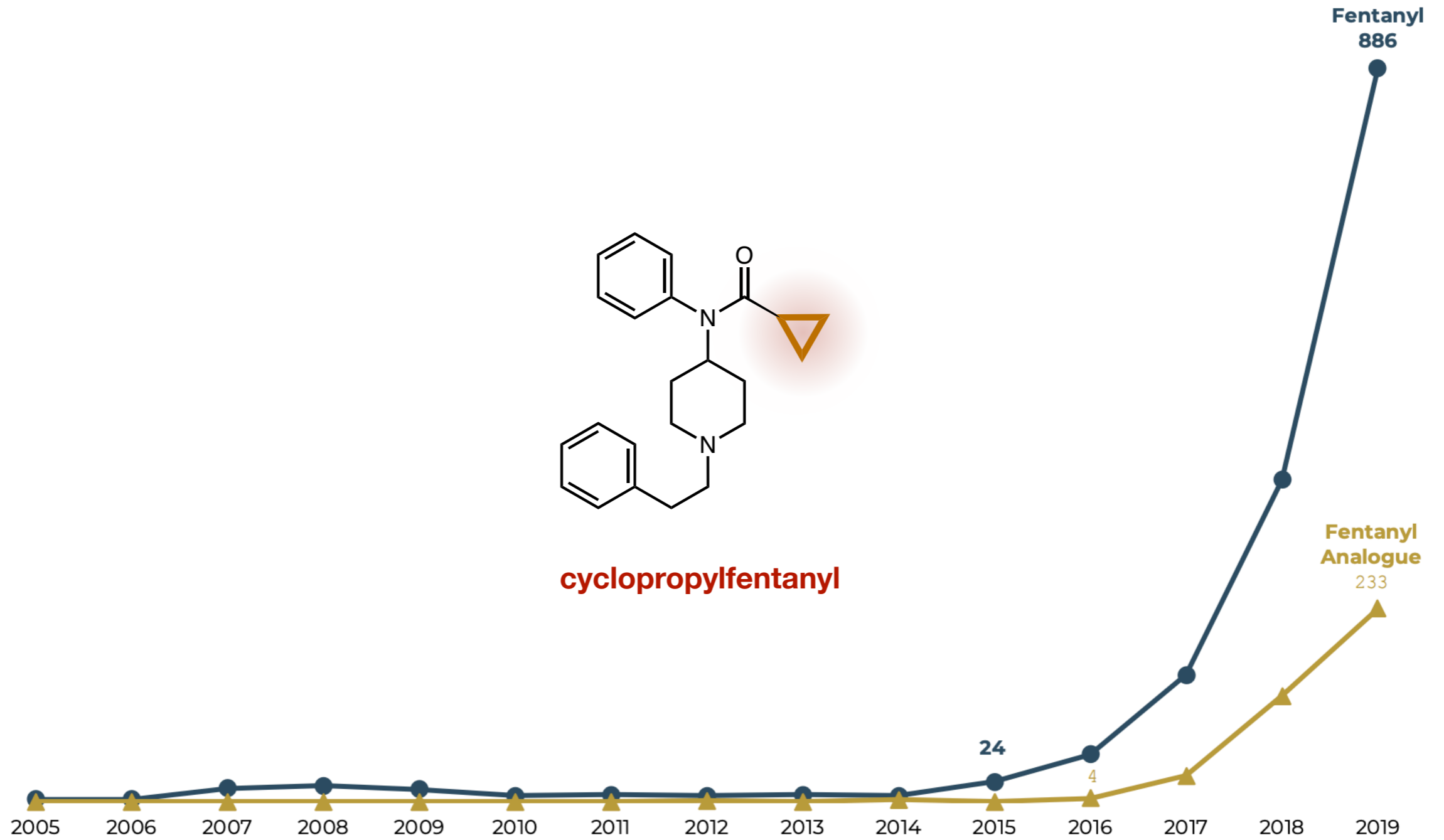


**tetrahydrofuran fentanyl**



Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

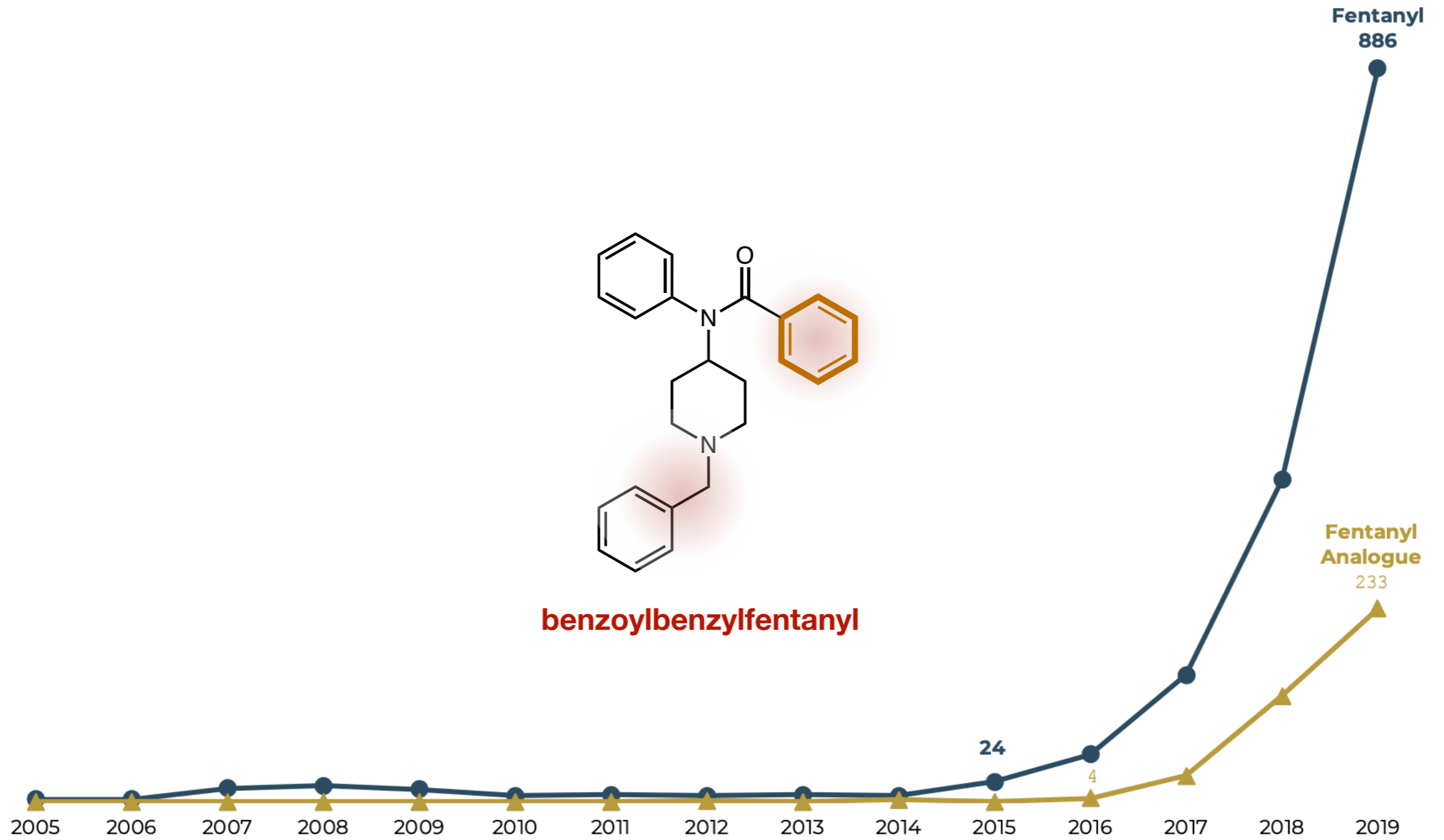
2017



**cyclopropylfentanyl**

Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

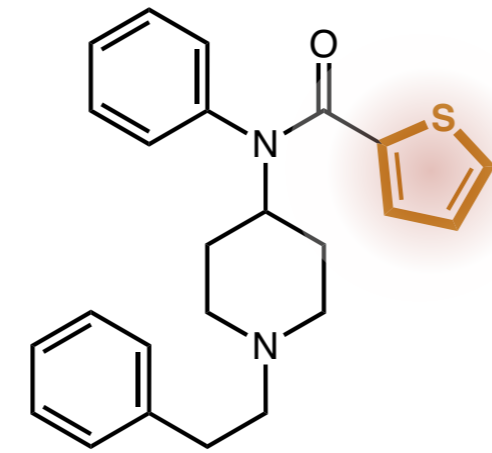
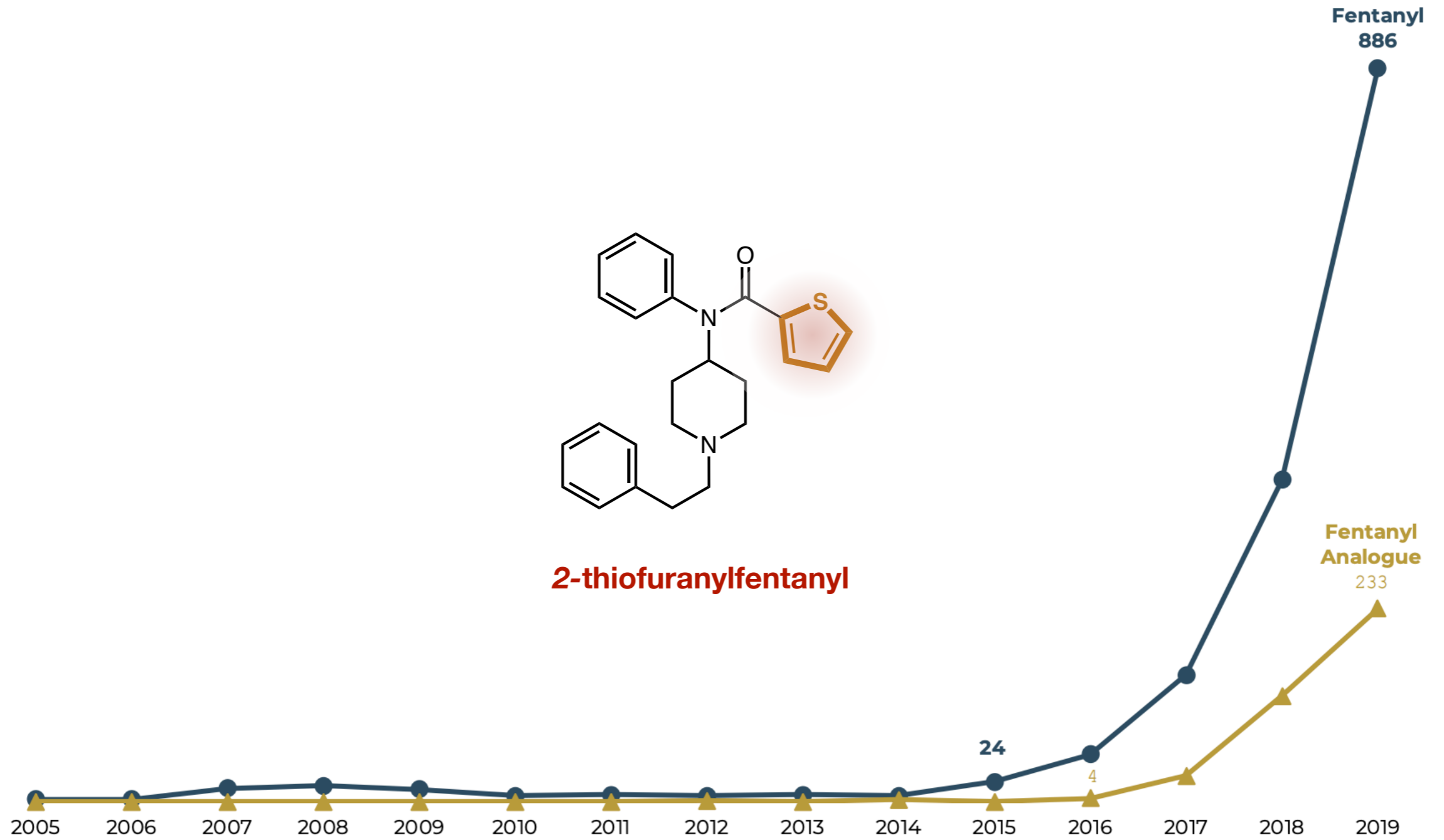
2017



benzoylbenzylfentanyl

Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

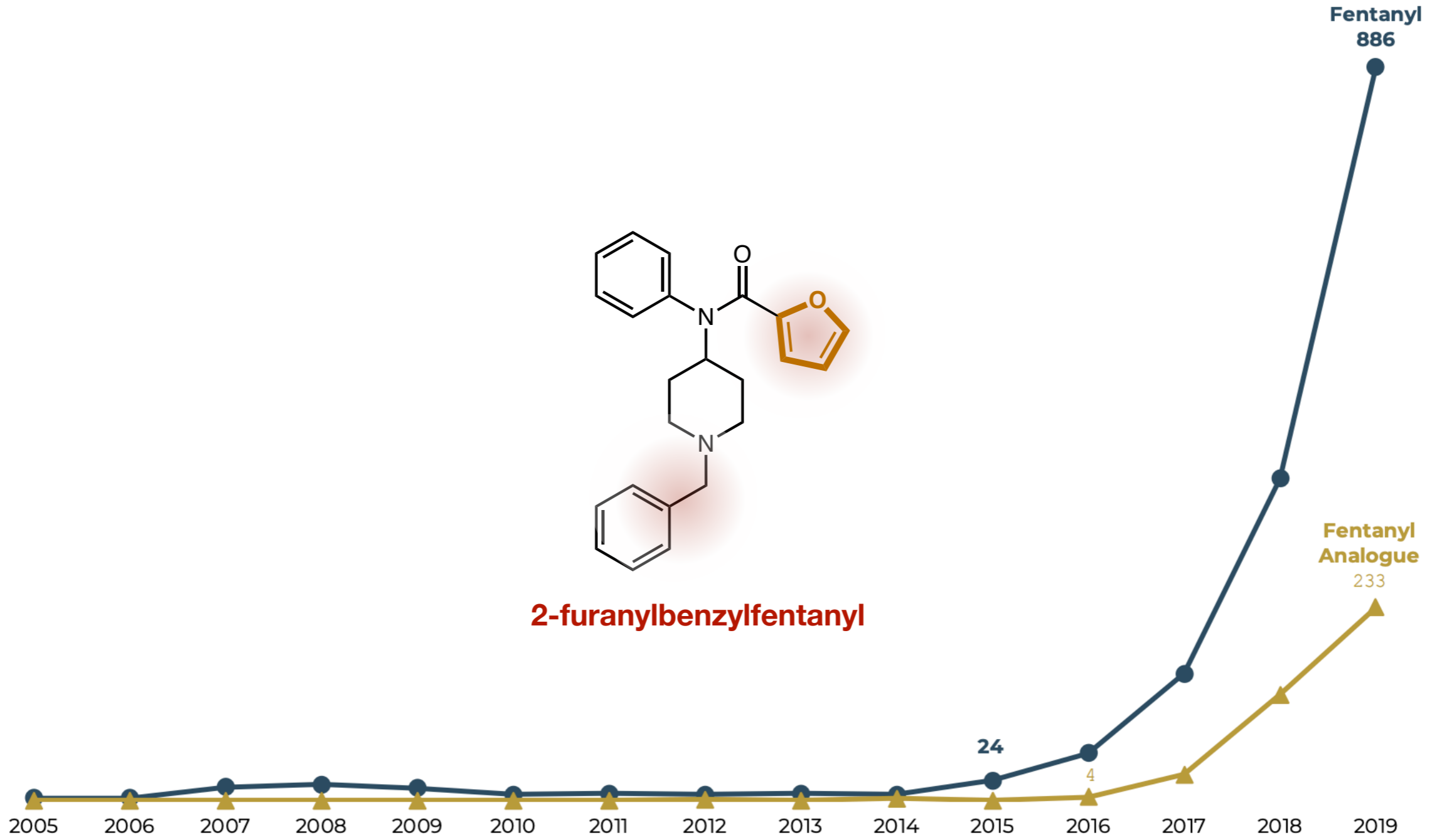
2017



2-thiofuranylfentanyl

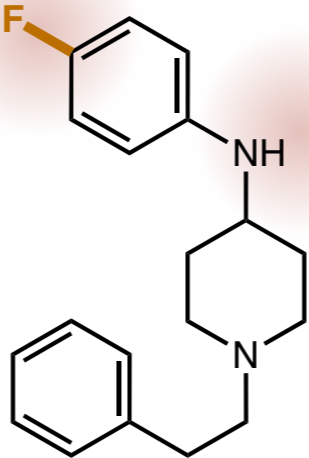
Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

2018

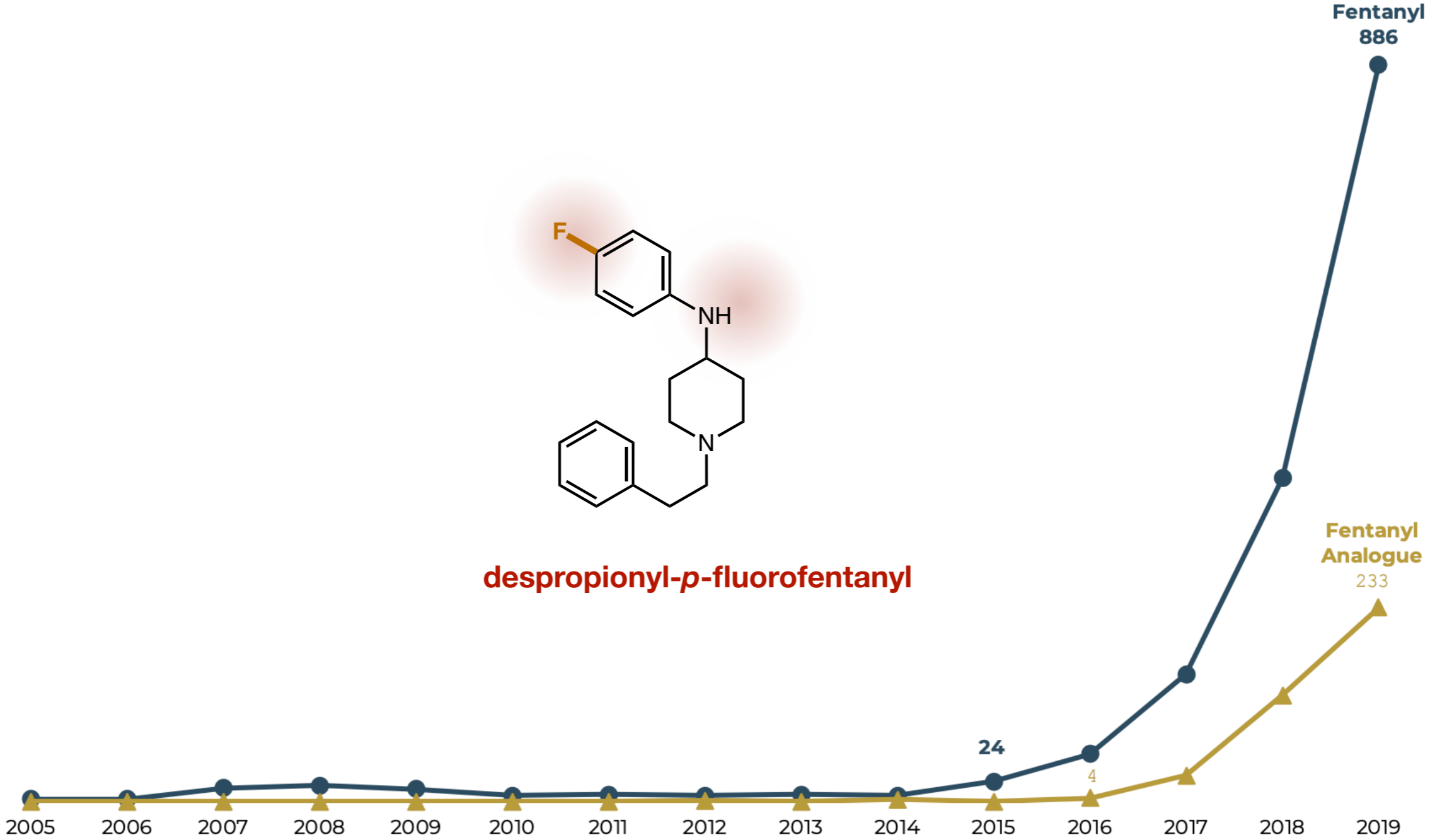


Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

2018



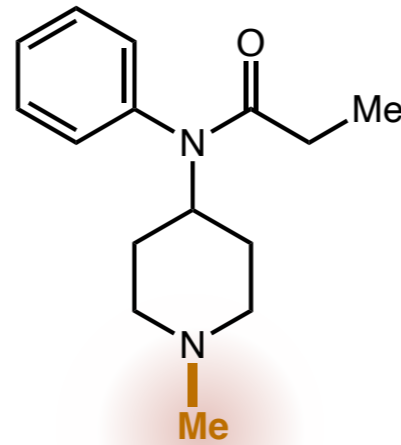
despropionyl-*p*-fluorofentanyl



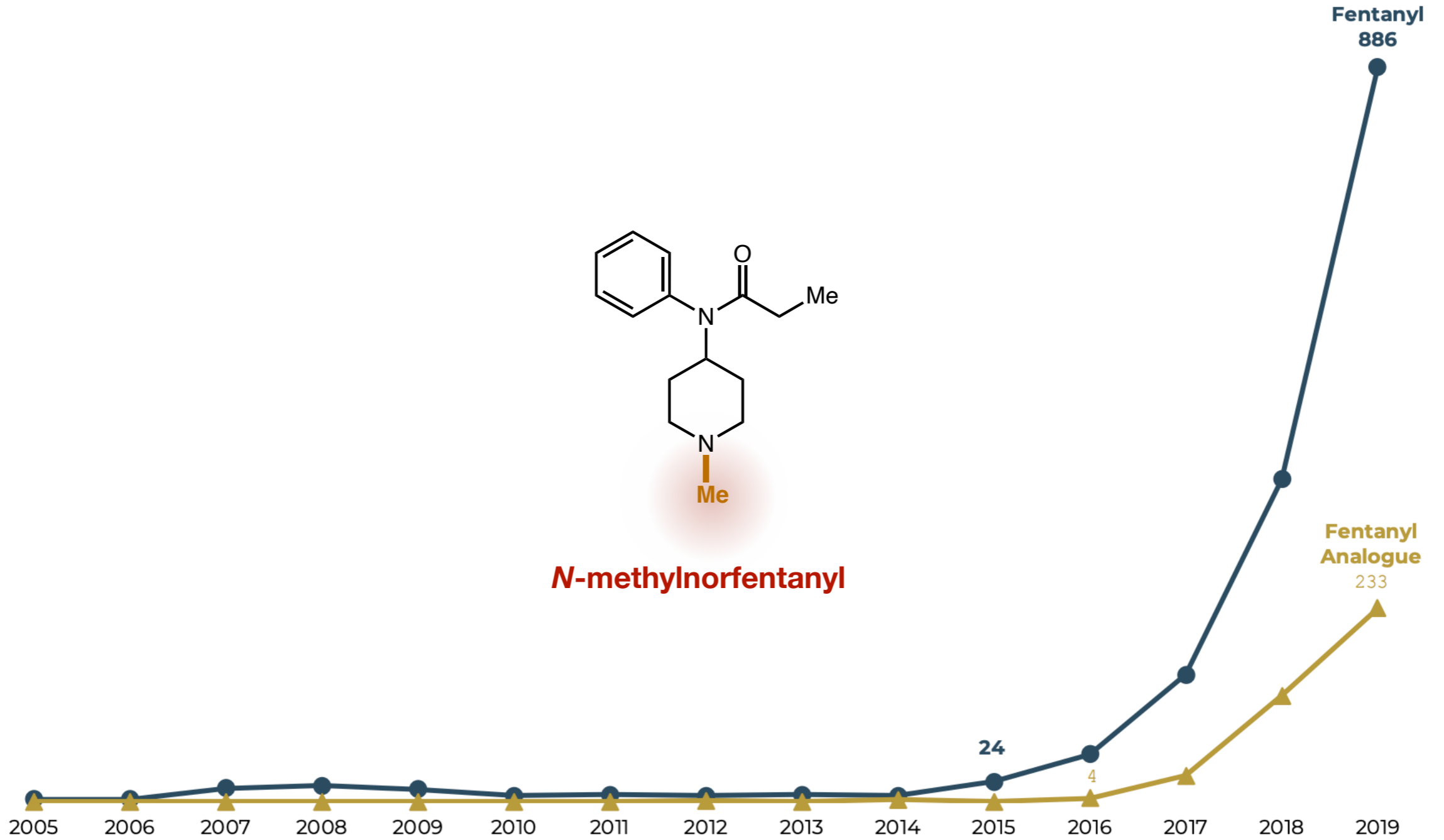
Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time



2018

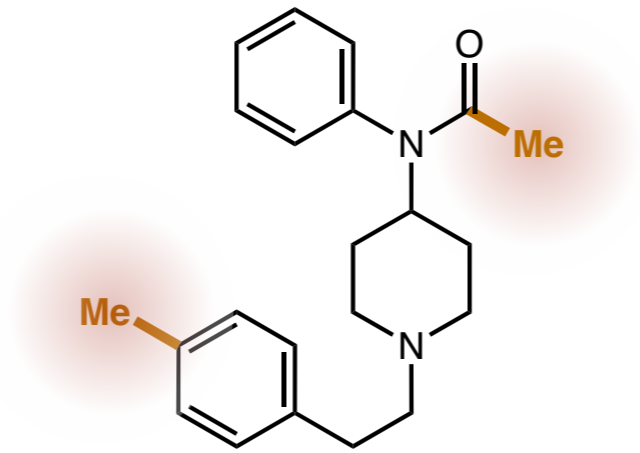


**N-methylnorfentanyl**

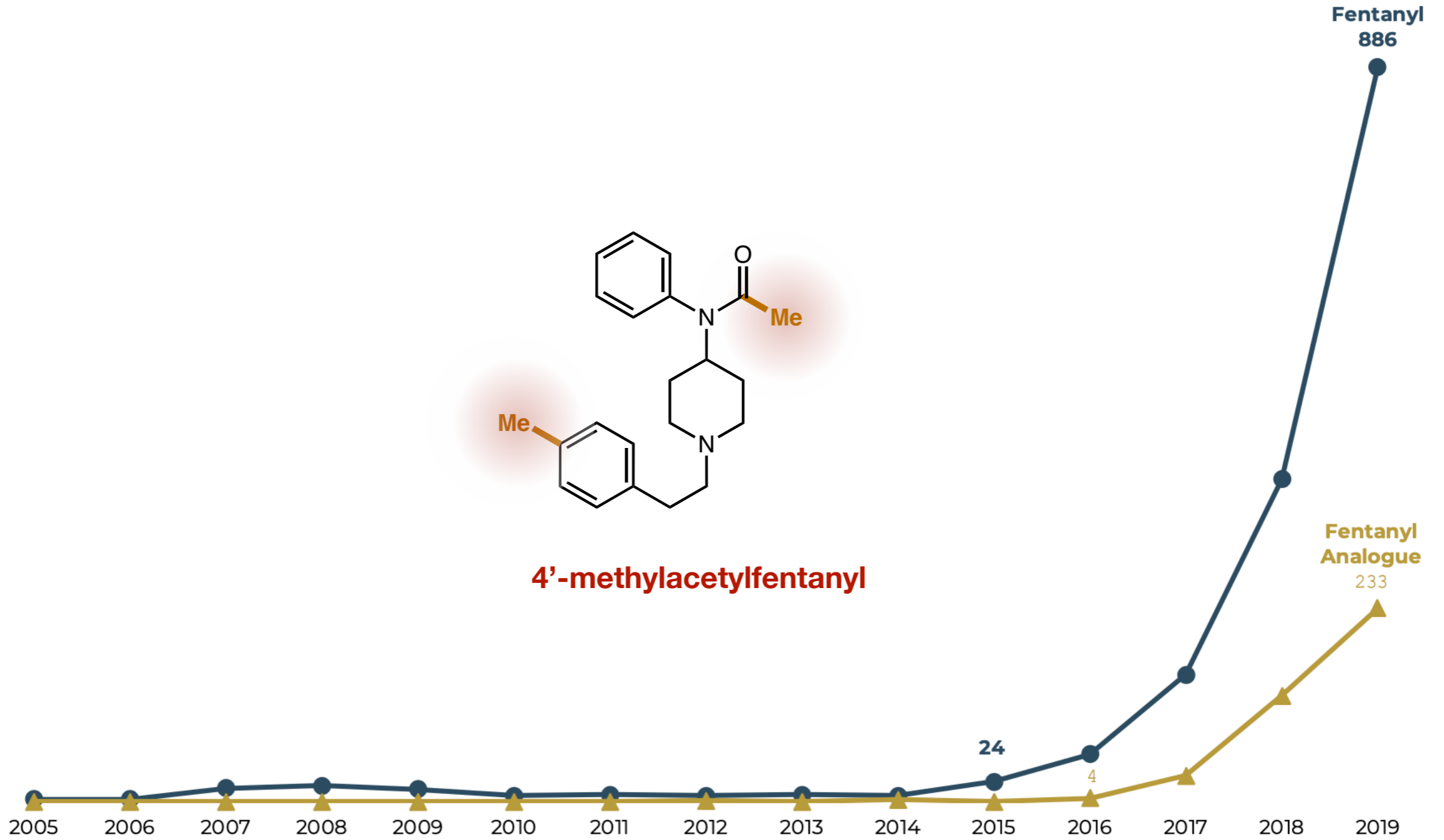


Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

2018

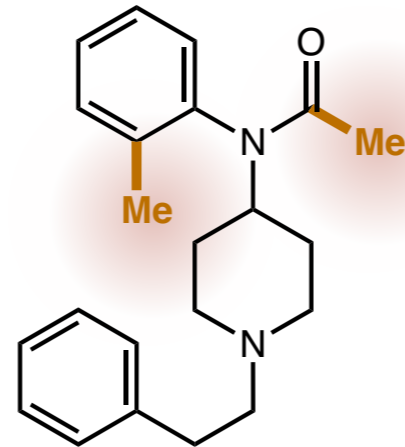
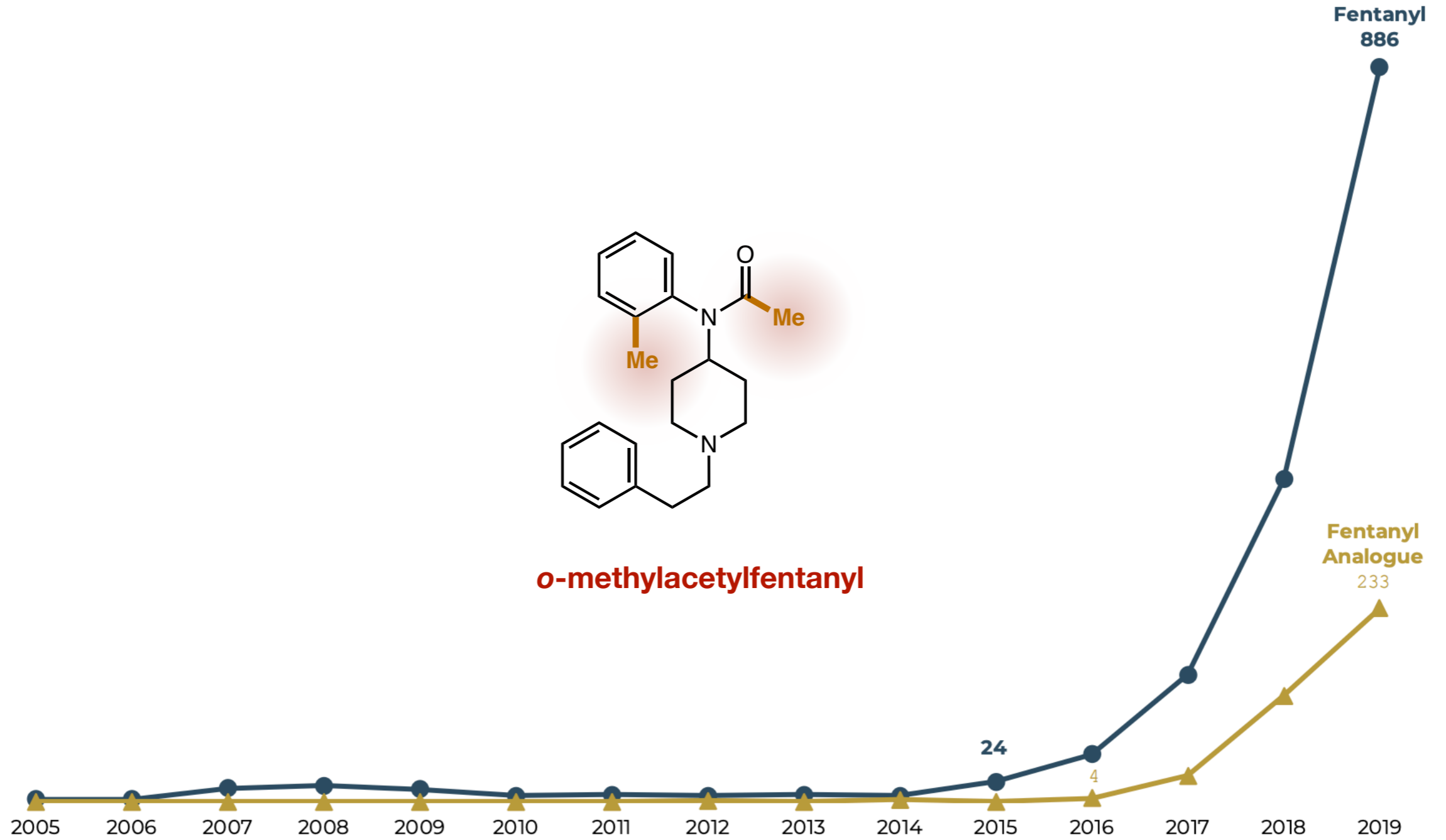


4'-methylacetylfentanyl



Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

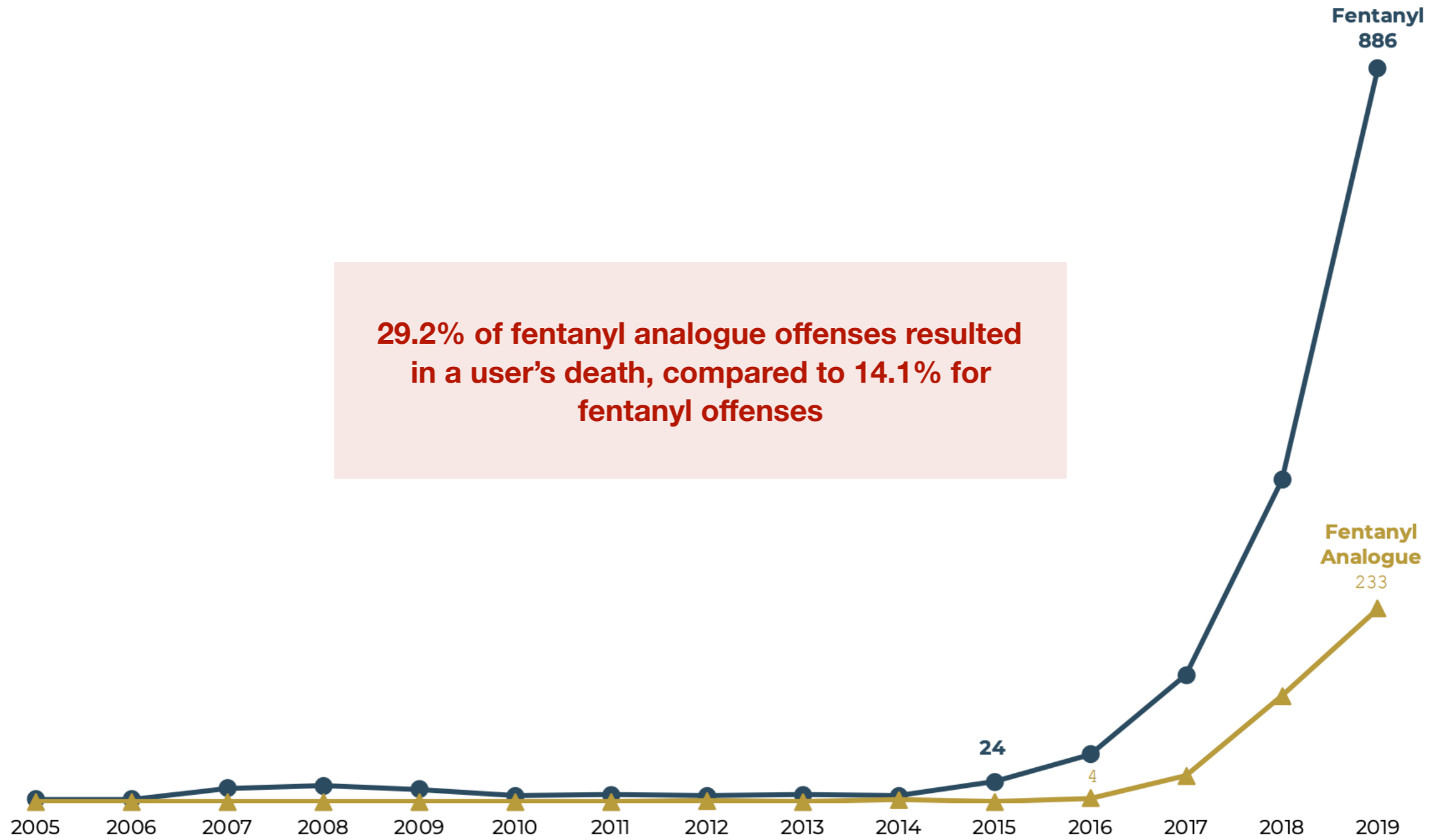
2018



**o-methylacetylfentanyl**

Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

2018



Number of Federal Fentanyl and Fentanyl Analogue Trafficking Offenders Over Time

*Emergency scheduling of all fentanyl analogs by the DEA (2018)*

**83 FR 5188**

Places all fentanyl-related substances that are not currently listed in any schedule of the Controlled Substances Act (CSA) and their isomers, esters, ethers, salts and salts of isomers, esters, and ethers in schedule I.

## *Emergency scheduling of all fentanyl analogs (2018)*

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**1**

voided the requirement of scientific and medical evaluation for pharmacological similarity



## *Emergency scheduling of all fentanyl analogs (2018)*

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**1**

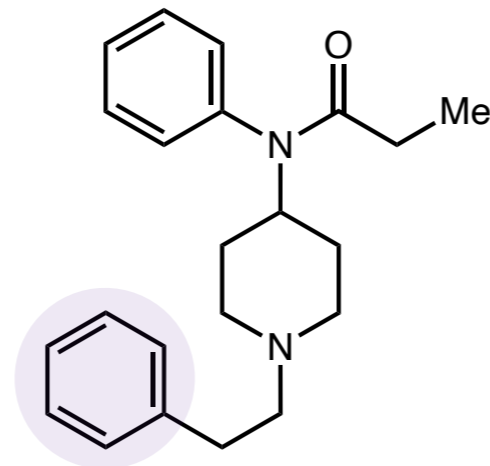
voided the requirement of scientific and medical evaluation for pharmacological similarity

**2**

“fentanyl-related substance” is defined purely by **chemical structure**

## *Emergency scheduling of all fentanyl analogs (2018)*

2 “fentanyl-related substance” is defined purely by **chemical structure**

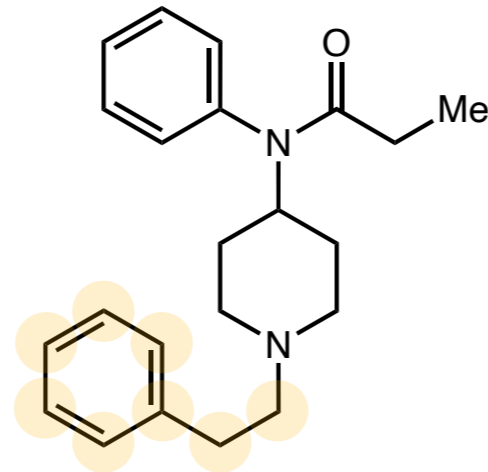


(A) replacement of the phenyl portion of the phenethyl group by any monocycle, whether or not further substituted in or on the monocycle

## *Emergency scheduling of all fentanyl analogs (2018)*

2

“fentanyl-related substance” is defined purely by **chemical structure**

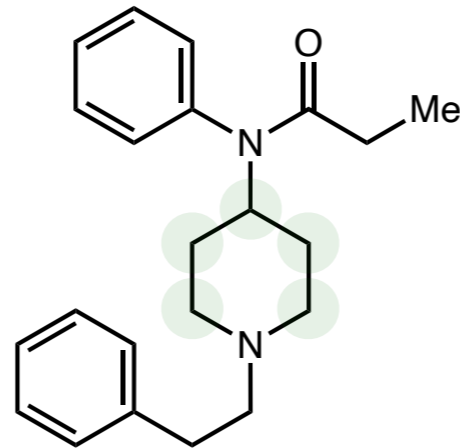


(B) substitution in or on the phenethyl group with alkyl, alkenyl, alkoxy, hydroxyl, halo, haloalkyl, amino or nitro groups

## *Emergency scheduling of all fentanyl analogs (2018)*

2

“fentanyl-related substance” is defined purely by **chemical structure**

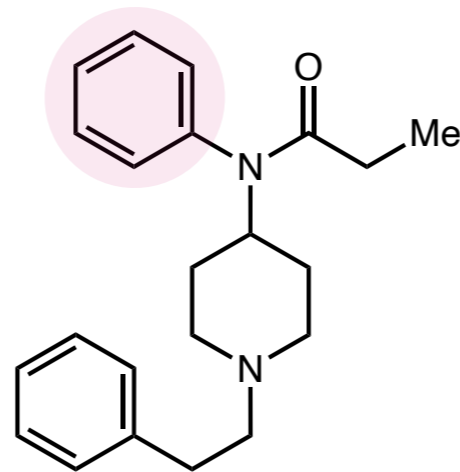


(C) substitution in or on the piperidine ring with alkyl, alkenyl, alkoxy, ester, ether, hydroxyl, halo, haloalkyl, amino or nitro groups

## *Emergency scheduling of all fentanyl analogs (2018)*

2

“fentanyl-related substance” is defined purely by **chemical structure**

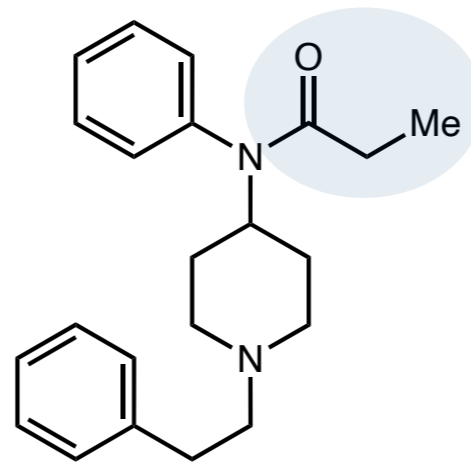


(D) replacement of the aniline ring with any aromatic monocycle whether or not further substituted in or on the aromatic monocycle

## Emergency scheduling of all fentanyl analogs (2018)

2

“fentanyl-related substance” is defined purely by **chemical structure**



(E) replacement of the *N*-propionyl group by another acyl group.



2024

HEALTH

## **'Historic' drop in U.S. overdose deaths accelerates as fentanyl crisis eases**

NOVEMBER 14, 2024 · 3:47 PM ET

2024

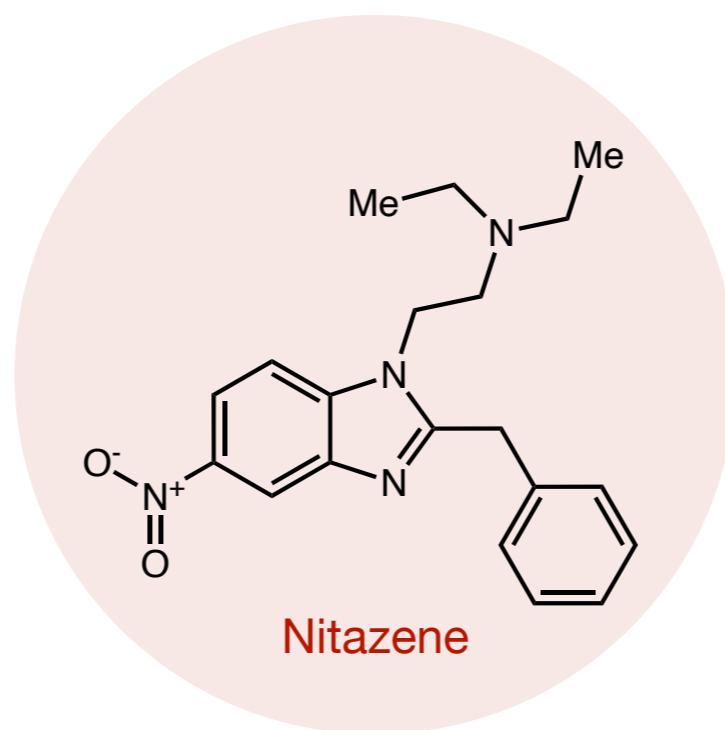
## **New class of opioids that may be more potent than fentanyl emerges globally**

**Nitazenes, synthetic opioids, could create latest drug crisis as scientists rush to find how to detect them in drug supply**

*Today*

## New class of opioids that may be more potent than fentanyl emerges globally

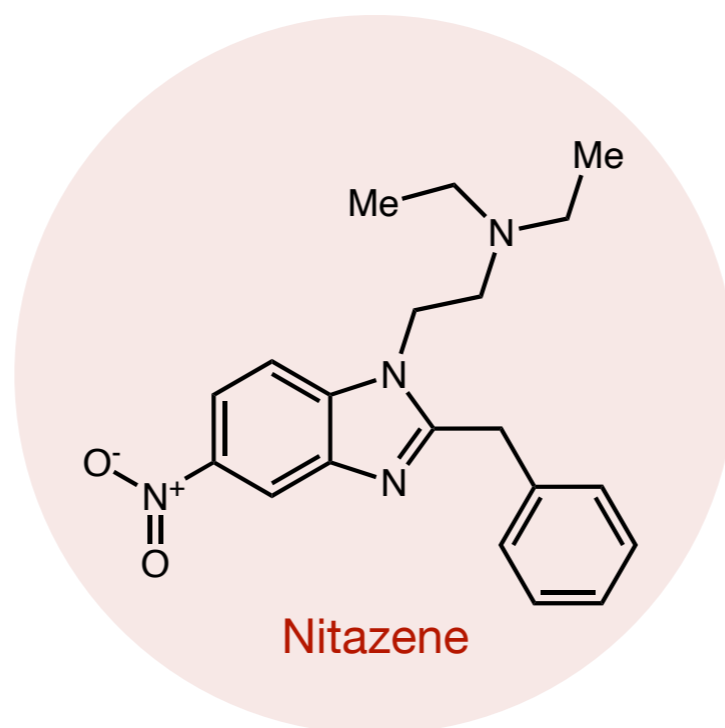
Nitazenes, synthetic opioids, could create latest drug crisis as scientists rush to find how to detect them in drug supply



*Today*

## New class of opioids that may be more potent than fentanyl emerges globally

Nitazenes, synthetic opioids, could create latest drug crisis as scientists rush to find how to detect them in drug supply

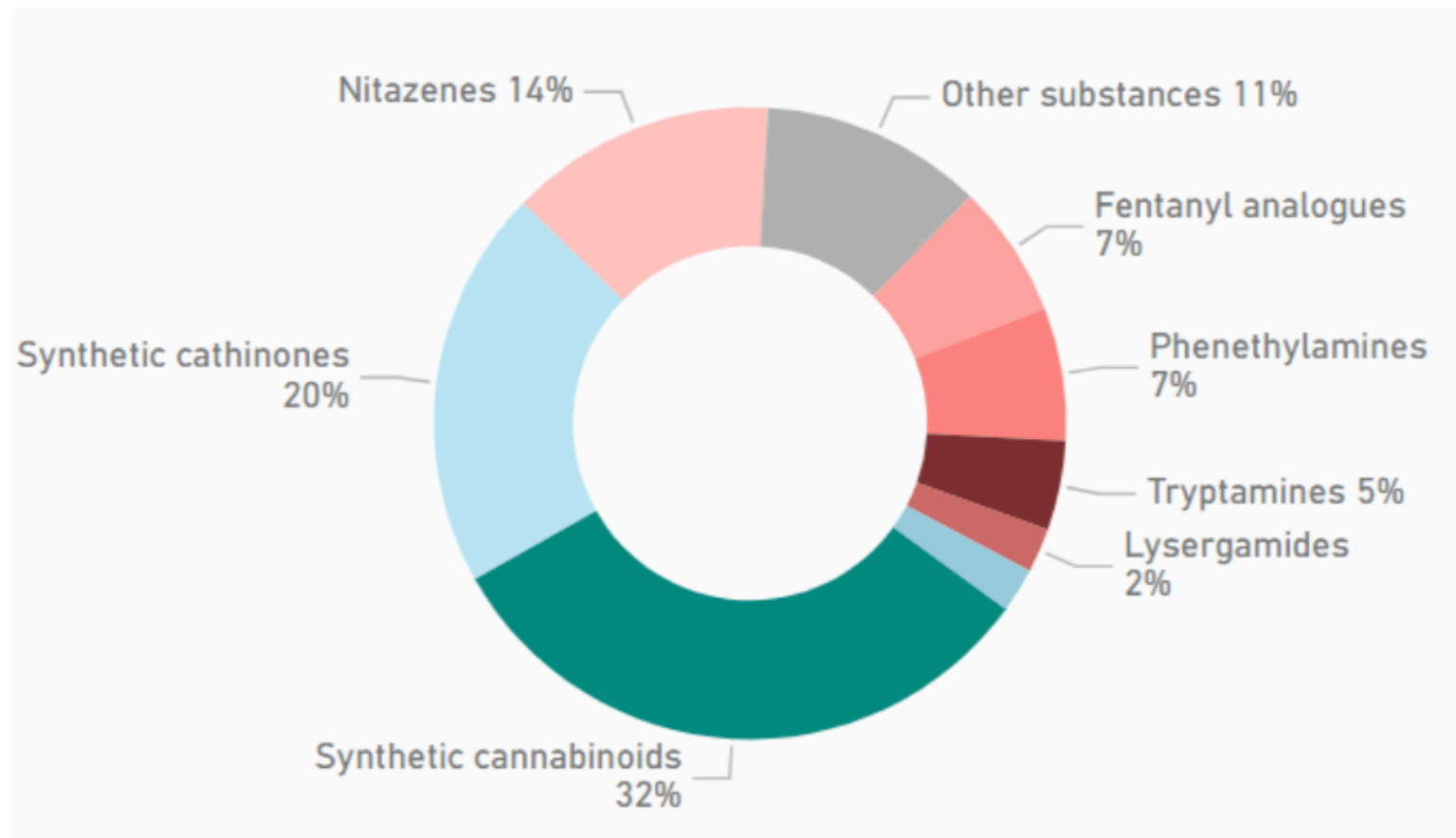


**16 new analogs** reported since its appearance in 2019

Today

## New class of opioids that may be more potent than fentanyl emerges globally

Nitazenes, synthetic opioids, could create latest drug crisis as scientists rush to find how to detect them in drug supply



New nitazene analogs are synthesized at a **faster rate** than new fentanyl analogs

## *The future of designer drugs*

**How can we better combat designer drugs?**



# *Rapid identification of novel designer drugs via machine learning*



**Michael Skinnider**

Princeton University

- DarkNPS

## *Rapid identification of novel designer drugs via machine learning*



**Michael Skinnider**

Princeton University

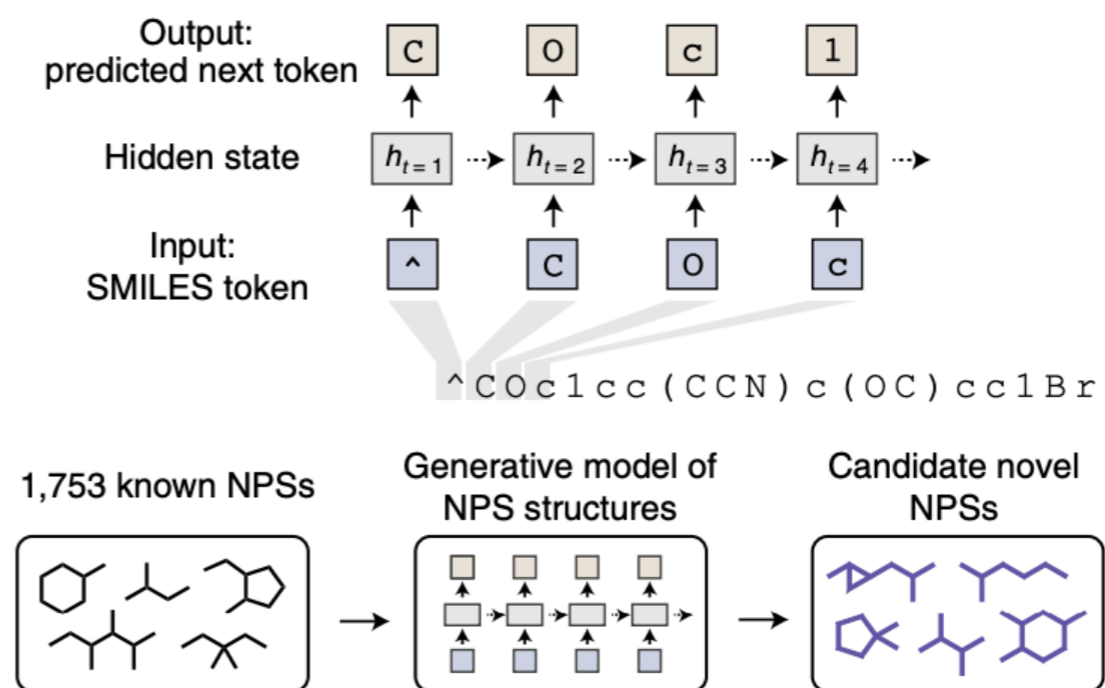
- DarkNPS
- Elucidates the chemical structure of an unidentified designer drug using only MS data

# Rapid identification of novel designer drugs via machine learning



**Michael Skinnider**  
Princeton University

- DarkNPS
- Elucidates the chemical structure of an unidentified designer drug using only MS data

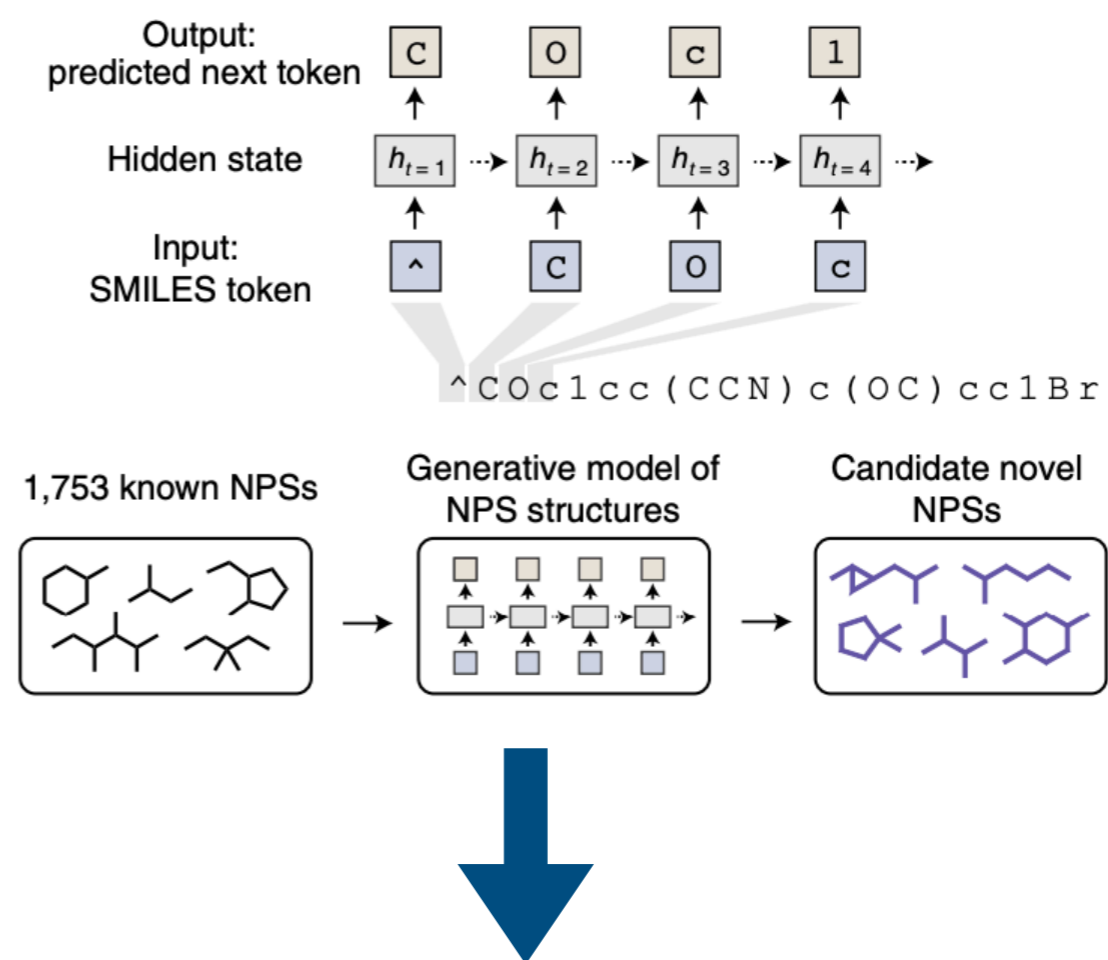


# Rapid identification of novel designer drugs via machine learning



**Michael Skinnider**  
Princeton University

- DarkNPS
- Elucidates the chemical structure of an unidentified designer drug using only MS data



**51% accuracy** for 40 new designer drugs

**70% top-three accuracy, 85% top-ten accuracy**

## *Conclusions and final thoughts*



## *Conclusions and final thoughts*



**Chemists will always be one step ahead of the law**

# Synthesis of Fentanyl under Continuous Photoflow Conditions

Felipe C. Braga, Tiago O. Ramos, Timothy J. Brocksom, and Kleber T. de Oliveira\*



Cite This: *Org. Lett.* 2022, 24, 8331–8336



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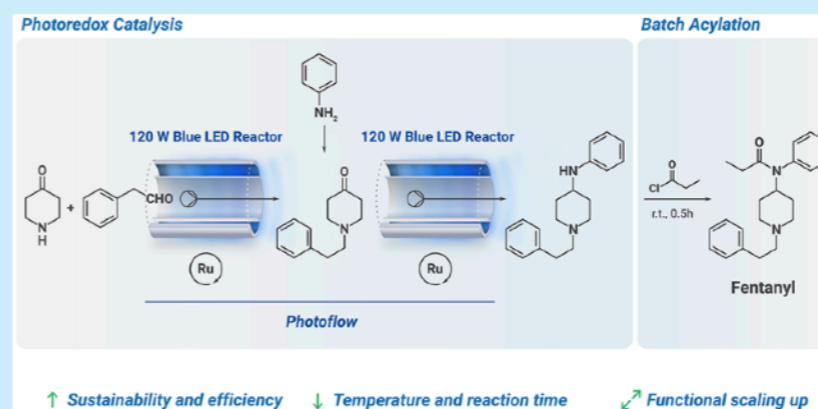
ACCESS |

Metrics & More

Article Recommendations

Supporting Information

**ABSTRACT:** An advantageous and original synthesis of fentanyl is described. This new approach includes two efficient continuous flow reductive aminations achieved via photoredox catalysis and a final batch acylation. A telescoped protocol for the two photocatalyzed steps is also presented, and overall, this protocol provides improved sustainability, significant efficiency, reduced temperatures and reaction times, and is functional for scaling up this relevant active pharmaceutical ingredient (API).





*Thank you!*

