
The Increasing Trend in Designer Fentanyls: A Synthetic Perspective

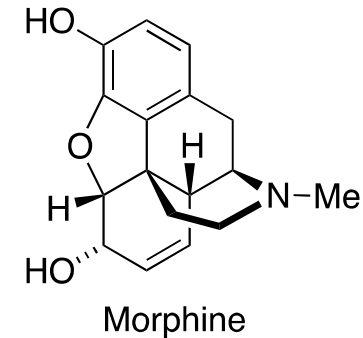
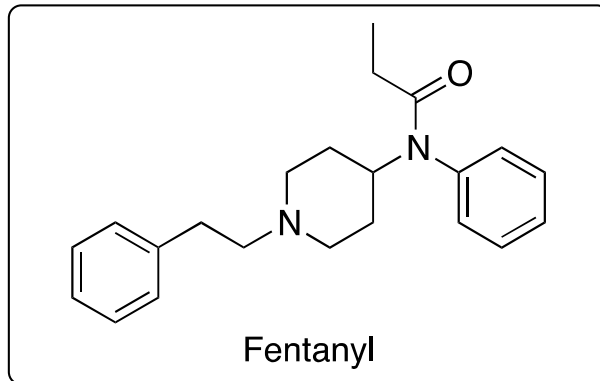


Matthew J. Connolly, PhD.

London, November 2018

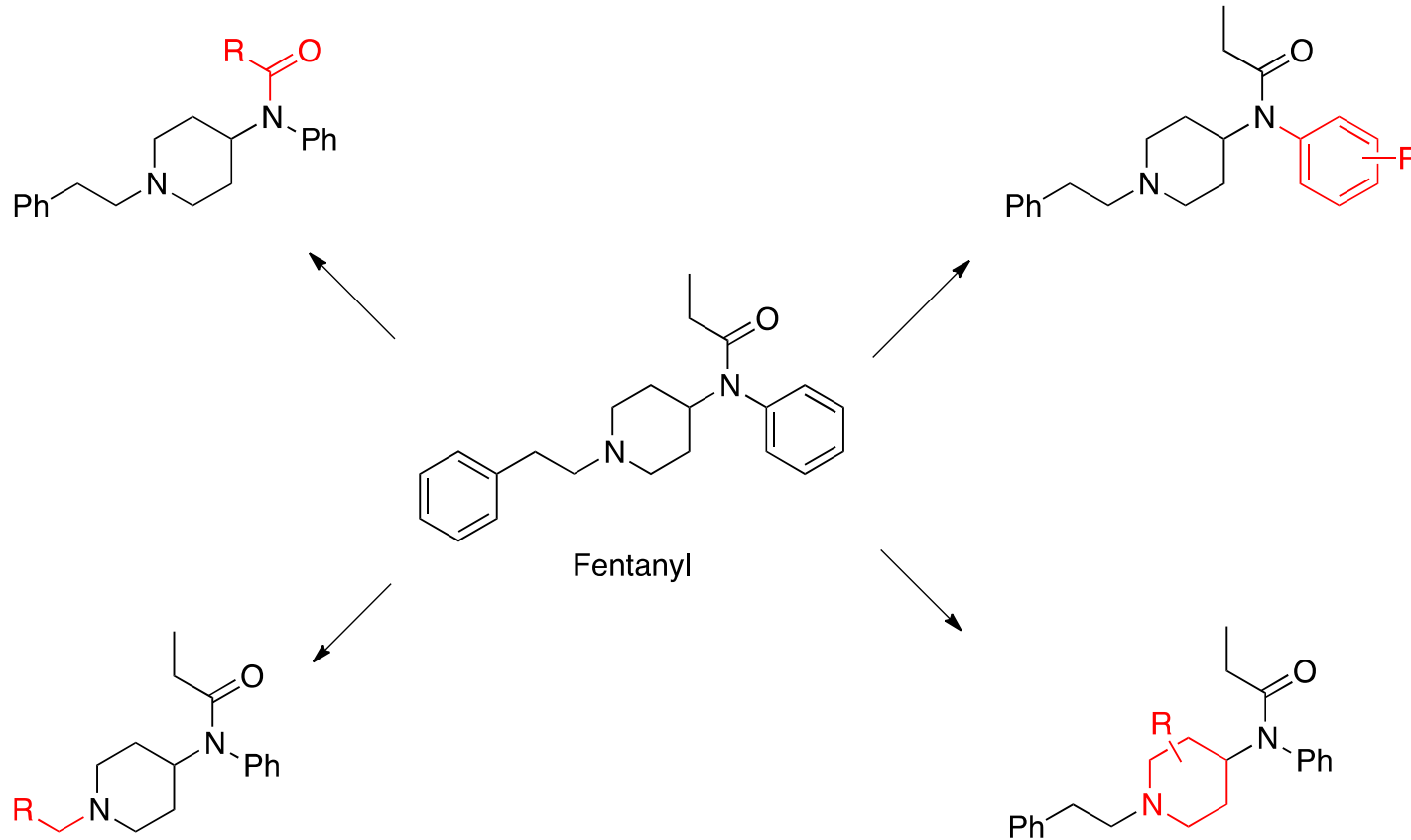


Fentanyl



- Fentanyl is a strong opiate-like painkiller, commonly used in anesthetic procedures in hospitals (where dosage is carefully calculated according to body mass on a case-by-case basis, due to the high overdose potential).
- From a chemical perspective, it is far, far simpler than morphine.
- It is also 50-100 times stronger than morphine.
- Perhaps unsurprisingly, due to the synthetic facility of its derivatives and high overdose potential, it is amongst the fastest growing narcotic threats at the moment.

Fentanyl Derivatives

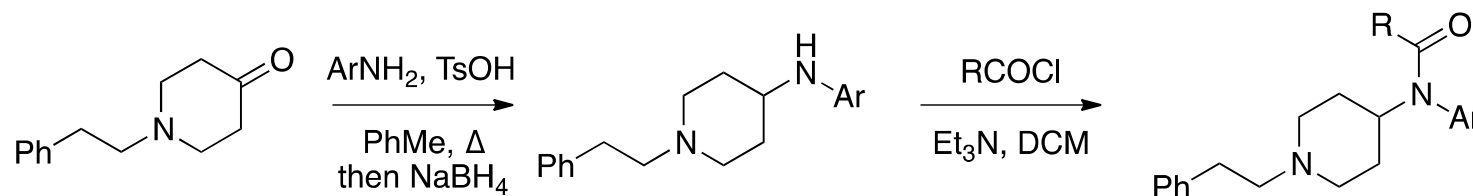


- And, of course, any combination of the above....!

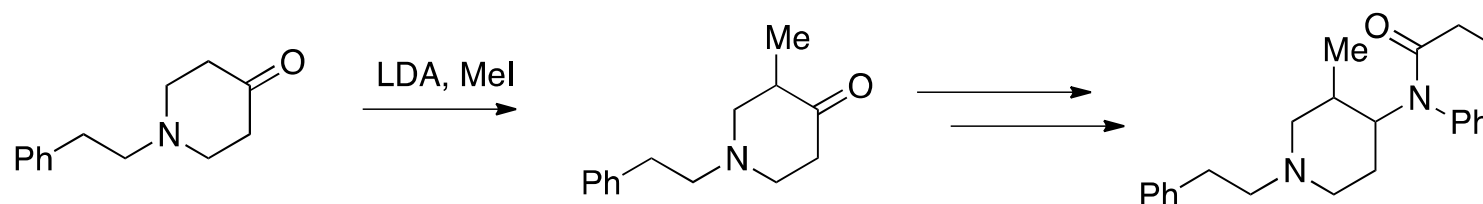
Synthesis



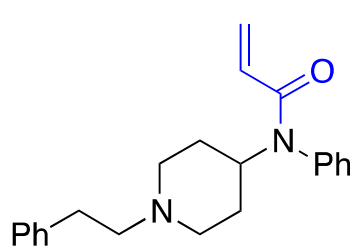
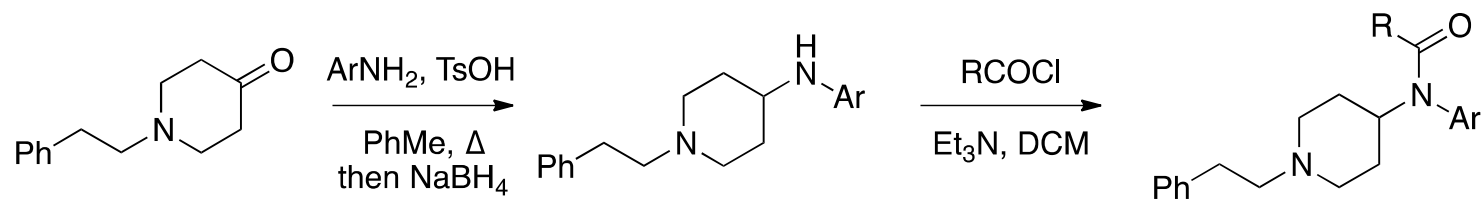
- Two step synthesis from commercial material (available in bulk).
- Both steps simple and amenable to large-scale synthesis.



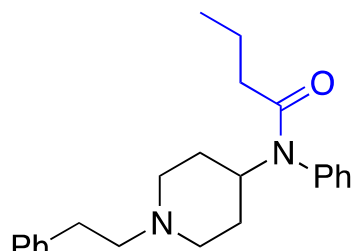
- Potential for variation of both the *N*-Aryl group and acyl group by this method
- 3-Methyl fentanyl (longer biological half-life) can also be produced in a single additional step. A range of derivatives can be produced in an analogous way to above.



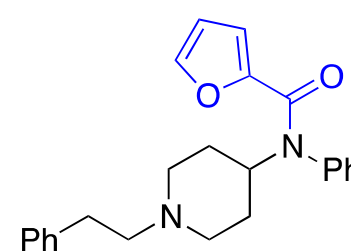
Commonly Encountered Designer Fentanyls



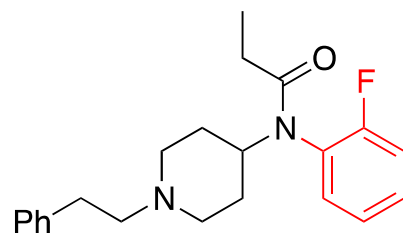
Acrylyl fentanyl



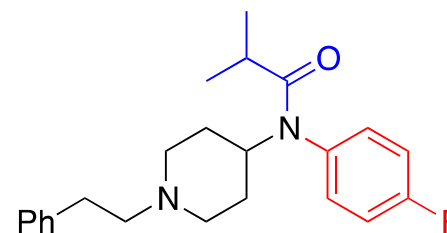
Butyryl fentanyl



Furanyl fentanyl (FuF)



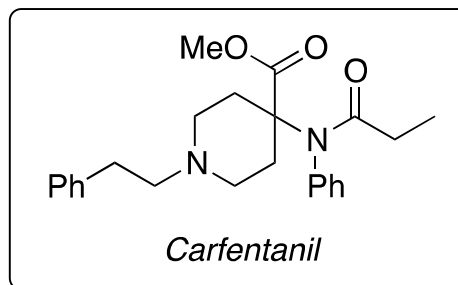
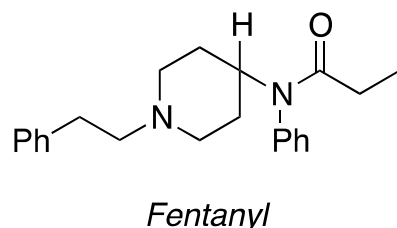
2-Fluorofentanyl



4-Fluoroisobutyrylfentanyl (4-FiBF)

- Each prepared in two simple steps from the same starting material.

Carfentanil



- Carfentanil is an extremely potent synthetic opiate, with a potency approximately 10,000 times that of morphine. Very difficult to weigh out an accurate dose.
- It is not approved for medical usage on humans and is only used as a tranquilizer for large animals.
- Used illicitly, often in combination with other opiates, such as heroin. Many fatalities have been reported.
- Worries over potential usage as a chemical weapon.
- Was used as an aerosol by Russian forces to end the 2002 Moscow theater hostage crisis. All 40 hostage takers died, as well as 180 of the hostages.

Should we be Worried?



ASIA
Lethal Opiates Delivered By Mail From China, Killing Addicts In The U.S.
March 11, 2017, 6:03 AM ET
Heard on Weekend Edition Saturday
AIRUN RATH

A drug lethal enough to be used as a chemical weapon — called carfentanil — has made its way into the illicit opiate trade.

Carfentanil is an opiate 10,000 times more powerful than morphine. And since last summer, it's been killing addicts and confounding first responders across the country.

USA

Carfentanil, a deadly drug used to tranquillise elephants, has been detected in Sydney

DECEMBER 20, 2016 5:21PM

One of the world's deadliest drugs has been discovered inside Australia's borders for the first time.

Gavin Fernando, news.com.au @GavinDFernando

ONE of the world's deadliest drugs has been discovered inside Australia's borders for the first time.
Australian Border Force officials recently detected a package containing carfentanil in a Sydney mail centre, *The Daily Telegraph* reports.

The news in colour

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Australia

SPREDNING KUNNE BLITT KATASTROFALT:
15-åringens dødsdop kunne ført til flere hundre dødsfall

ESTREMT POTENT: Dødsdop er karfentanil, stoffet dion 15 år gamle gutten i Oslo fikk i seg og døde av i mars i år. Få milligram kan ta livet av flere hundre mennesker. Foto: AP

Politiet etterforsker om 15-åringen som ble funnet død på gutterommet etter å ha fått i seg det ekstremt dødelige stoffet karfentanil hadde planer om å selge dødsdopet videre.

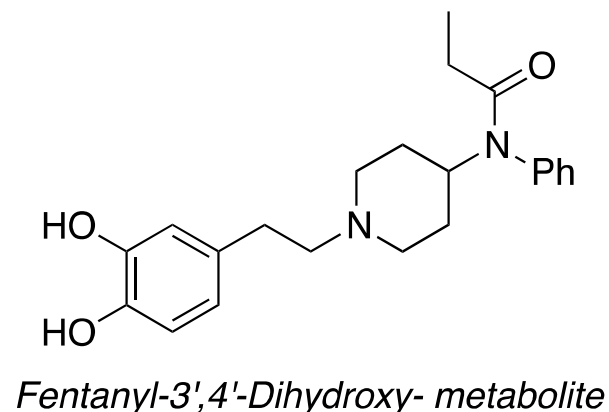
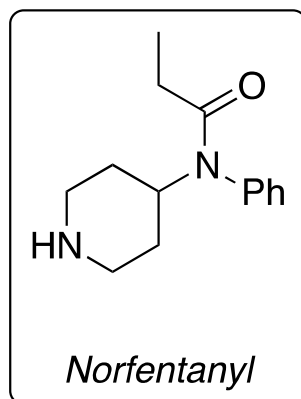
Mari Hvetlum og Roar Dalmo Møhlbak 20.04.2017 (Oppdatert: 20.04.2017)

Norway

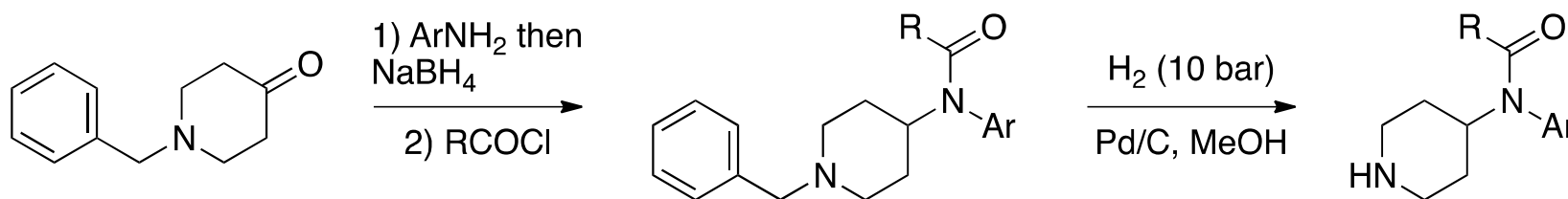
- Both fentanyl and carfentanil have led to a significant number of deaths worldwide.
- Designer fentanyls are largely untested *in vivo*, leading to difficulty in predicting strength and dosage.
- Easy access to a range of carfentanil analogues has potential to make things worse, with some analogues predicted to be more potent than carfentanil (by structure-activity relationship).

Fentanyl Metabolites

- The same simple, late-stage diversification strategy allows easy access to a number of common fentanyl metabolites, useful for forensic labs.

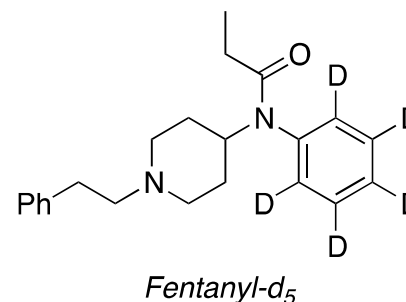
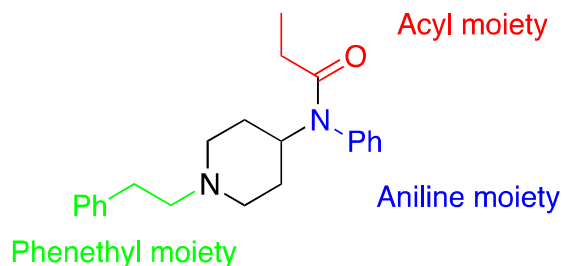


- For example, the synthesis of norfentanyl analogues (R and Ar represent generic and variable groups):



Internal Standards

- Most deuterated fentanyl-type internal standards include deuteration on either the aniline or acyl moiety.



- The labeled units are often lost in many fragmentation pathways during MS.

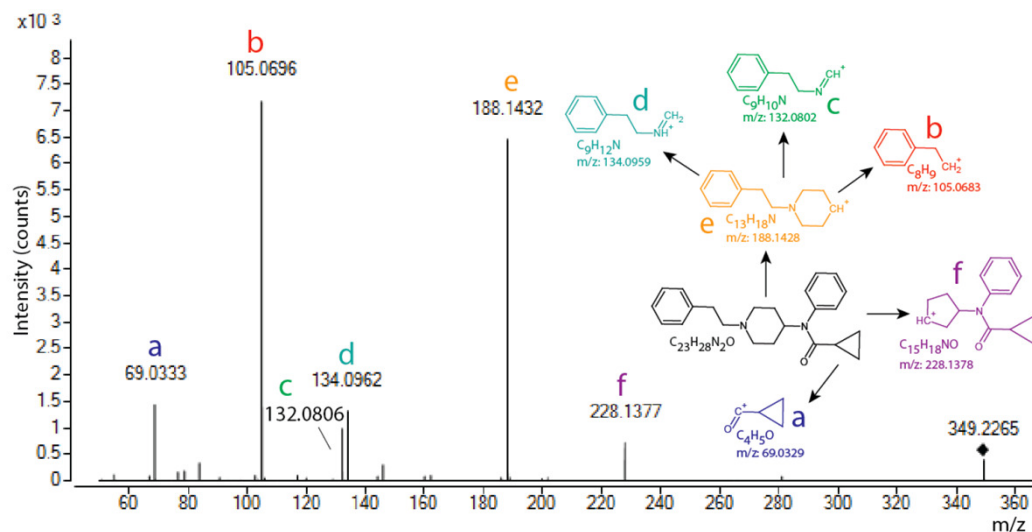
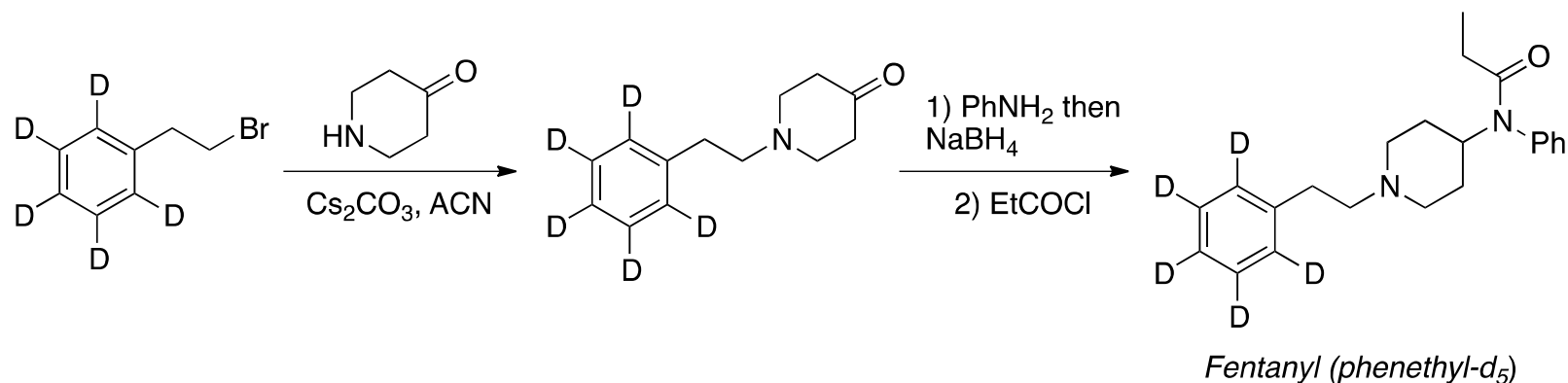


Figure 5. MS/MS-spectrum from Cyclopropylfentanyl with its proposed fragmentation pattern labelled a-f. For each fragment ion their monoisotopic mass is calculated. In black, the structure and molecular formula of Cyclopropylfentanyl is shown.

Internal Standards

- With this in mind, Chiron has recently used the same versatile route to develop Fentanyl (phenethyl-d₅), which is available in addition to regular Fentanyl-d₅.



- Should provide a standard with labeling in both the molecular ion and most major fragments.

Conclusions



- Fentanyl and carfentanil intoxication is a rapidly growing cause for concern around the world.
- Both are so potent that it is difficult to accurately measure the difference between an effective dose and lethal dose, without a calibrated analytical balance.
- Designer fentanyls largely untested *in vivo*, leading to uncertainty over dosage.
- Designer carfentanils have the same dosage uncertainty, coupled with much smaller dosages – more room for error.
- Simple, scalable, late-stage diversification routes available to synthesize new designer fentanyls, carfentanils, major metabolites and stable-isotope labeled internal standards.