If You Think Fentanyl Is Bad...

By Josh Bloom — January 17, 2017

The second to last thing the world needs now is a more efficient way to make fentanyl—the "super heroin" that is killing heroin addicts like never before. The very last thing we need is a list of fentanyl analogs that are strong that they make the drug itself look like cotton candy, and procedures for how to make them. But, get have both in one PLOS paper [1].

"An Efficient, Optimized Synthesis of Fentanyl and Related Analogs"

Carlos A. Valdez, Roald N. Leif, and Brian P. Maye; PLOS, September 2014 | Volume 9, Issue 9

In my first career in drug discovery research, I spent 27 years attempting to maximize the potency (1) of molecules against a given target (2,3). Yet, even I was stunned by what organic chemists were able to do to enhance the potency of an already-powerful drug. The numbers you will see below appear to be unimaginable, but they are all real—because of the power of synthetic organic chemistry.

First, let's look at the relative potency of heroin and fentanyl. The photo speaks for itself (4).
As bad as that looks consider the following:

By simply replacing the hydrogen atom (red circle) in fentanyl with what is called a carbomethoxy group (blue circle), you now have carfentanil, which is 20-times more potent than fentanyl and 1000-times more than morphine (5). To put this in perspective, the estimated lethal dose of fentanyl is about one milligram, so a lethal dose of carfentanil would be 50 micrograms (0.050
milligrams). Unless you're Superman, you cannot even see 50 micrograms. To help visualize this, one poppy seed weighs about 0.3 milligrams (300 micrograms). So, a lethal dose of carfentanil would be approximately one-sixth the weight of a poppy seed.

But carfentanil isn't even the most potent fentanyl analog out there. That honor belongs to a satanic derivative called ohmefentanyl. (Although it would not be unreasonable to call it Oh My! fentanyl).

Ohmefentanyl—one scary dude. Values are relative to morphine

Two simple modifications—the addition of one methyl group and one hydroxyl group (blue circles)—makes the molecule 6.3 times more potent than carfentanil, 126-times more so than fentanyl, and 6,300 times more than morphine. This is just nuts. Doing the math (5), the estimated lethal dose of ohmefentanyl is 0.16 micrograms, which means that one poppy seed's worth (300 micrograms) of ohmefentanyl is enough to kill 1900 people. Another way of looking at it is even scarier: One ounce of the stuff (28 grams, 28,000,000 micrograms) would be enough to kill 175 million people—half the population of the United States (7).

And, not only is it easy to make, but the paper tells you how to do so (!):
Fentanyl (4)

N-[1-(2-phenylethyl)-4-piperidinyl]aniline (14) (1.35 g, 4.8 mmol) was dissolved in methylene chloride (40 mL) in a 100 mL round bottom flask equipped with a small stir bar and was treated with diisopropylethylamine (DIPEA, 1.68 mL, 1.24 g, 9.6 mmol, 2.0 equiv.). The solution was cooled with an ice bath and treated dropwise with propionyl chloride (0.83 mL, 0.88 g, 9.6 mmol, 2.0 equiv.). The resulting mixture was stirred for 2 h at ambient temperature. The mixture was transferred to a separatory funnel and partitioned (CH₂Cl₂//H₂O). The organic phase was washed with brine (NaCl/H₂O, 1×50 mL), satd. NaHCO₃ (1×50 mL), dried over anhydrous Na₂SO₄ and evaporated in vacuo at 40°C to give a yellow oil that was purified by flash column chromatography (3:7 → 7:3 EtOAc/hexanes) to furnish fentanyl (4) as a light yellow oil (1.53 g, 95%). Rf = 0.28 (1:1 EtOAc/hexanes); ¹H NMR (600 MHz, CDCl₃) δ 7.48–7.37 (m, 3H), 7.33–7.27 (m, 2H), 7.25–7.17 (m, 3H), 7.13–7.05 (m, 2H), 4.88–4.71 (br, 1H), 3.83–3.47 (br, 2H), 3.20–3.09 (br, 2H), 3.09–2.99 (br, 2H), 2.82–2.70 (br, 2H), 2.13–1.99 (br, 4H), 1.94 (q, J = 7.4, 2H), 1.01 (t, J = 7.4, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 174.0, 138.1, 137.0, 129.9, 129.8, 129.0, 128.9, 128.7, 127.0, 59.1, 52.6, 50.7, 31.3, 28.4, 28.0, 9.5; HRMS (CI) m/z calcd for C₂₂H₂₈N₂O [M⁺]: 336.2202; found 336.2201; Anal. Calcd for C₂₂H₂₈N₂O: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.42; H, 8.05; N, 8.62.

General procedure for synthesis of fentanyl and derivatives.

And the optimal reaction conditions:

### Table 1. Optimization steps for the synthesis of fentanyl (4); *isolated yield; †alkylation in the synthesis of thiofentanyl derivatives; ‡reductive amination.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Synthetic Step</th>
<th>Reagents/Conditions</th>
<th>T (°C)</th>
<th>Yield* (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Alkylation</td>
<td>PhCH₂CH₂Br, C₂H₅CO₂H, DMF</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>Alkylation</td>
<td>PhCH₂CH₂Br, C₂H₅CO₂H, CH₂CN</td>
<td>80</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>R-OMs (19) C₂H₅CO₂H•DMF</td>
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<td>62</td>
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<tr>
<td>4</td>
<td>R-OMs (19) C₂H₅CO₂H•CH₂CN•</td>
<td>80</td>
<td>83</td>
<td></td>
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<tr>
<td>5</td>
<td>RA†</td>
<td>NaOAc, CH₂Cl₂, AcOH</td>
<td>25</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>NaCNBH₃, CH₂Cl₂, AcOH</td>
<td>25</td>
<td>64</td>
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<tr>
<td>7</td>
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<td>84</td>
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<tr>
<td>10</td>
<td>Acylation</td>
<td>Propionyl anhydride, pyridine</td>
<td>25</td>
<td>94</td>
</tr>
<tr>
<td>11</td>
<td>Acylation</td>
<td>Propionyl chloride, pyridine</td>
<td>25</td>
<td>95</td>
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<tr>
<td>12</td>
<td>Acylation</td>
<td>Propionyl chloride, DIPEA, CH₂Cl₂</td>
<td>25</td>
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</table>

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I recently wrote about the power of organic synthesis, which was responsible for ensuring that Taxol—a very important cancer drug that treats ovarian and other difficult cancers—could be made in the quantities required to ensure that it was available to all. The natural source—the bark of the Pacific yew tree—could not possibly provide enough drug. But, chemists figured out a way to make it. Without this hugely important advance, a drug that has saved thousands of lives would not be in pharmacies. Synthetic organic chemistry has much power, and this power can be used for good or evil.

These drugs are truly evil.

Notes:

(1) Drugs that are more potent will usually require a lower therapeutic dose. Lower doses of any given drug (or chemical) are less likely to have side effects.

(2) There are a number of ways to do this. The most commonly used strategy is using structure-activity relationships. The concept is simple. Organic chemists make (usually) systematic, single changes in the structure of a promising looking molecule and the new molecule is tested. If it is more potent, then you know you've hit a sweet spot, and focus on that particular portion of the molecule by directing efforts to synthesize a similar molecule that may be even better. This iterative process is the way most drugs have been discovered.

(3) There are a number of other methods used to discover and optimize potential drugs, all of which are performed at the very beginning of the drug discovery process—lead identification and optimization. Another commonly used method for lead optimization is the use of x-ray crystallography to "see" the atomic structure of the molecular target—the enzyme or receptor to be inhibited. A molecule that has some activity in *in vitro* (outside of the body) tests can then be soaked with the target, and (if you're lucky) will form a protein crystal with the molecule trapped at the binding site. The crystal is then bombarded with x-rays, and the image formed (after some heavy duty computing) reveals the chemical structure of the target protein at the atomic level. These images can be visualized in 3D. It is then possible to perform docking experiments with hypothetical molecules, which helps guide chemists in deciding what to synthesize next. This method is called computer assisted (or aided) drug design (CADD).

A novel and very clever technique for identifying discovery leads is being used to test chemical compounds at Harvard. Dr. Chris Gerry explains how a DNA-based screen works:

"Another method for finding interesting compounds uses large collections of molecules that each attached to a unique piece of DNA. Performing experiments with many compounds at once is typically very expensive because each experiment must be physically separated one another. DNA, however, can act as a "barcode" that identifies the structure of that compound, even when it's present in..."
tiny amounts or in a complex mixture of other molecules. As a result, this technology can often expedite the search for compounds that interact with therapeutically relevant proteins, nucleic acids, or other biological macromolecules.”

Chris Gerry, Ph.D., Harvard University.

(4) It should be perfectly obvious why opioid addicts are dying in record numbers. Even a small error in weighing out fentanyl can easily result in a fatal overdose.

(5) I don’t know what happened to my brain. When I write an article that contains math, I get it wrong approximately 100% of the time, which is pointed out be readers. C’mon. I can take it.

(6) These relative potencies are based on in vitro tests, which may or may not represent the relative potency in humans. For example, although ohmefentanyl is 6,300-times more potent than morphine in "test tubes," it is not necessarily 6,300-times more so than morphine in an animal or human. Each fentanyl analog will have its own set of pharmacokinetic factors, such as absorption and metabolism, which also govern how deadly it will be.

(7) How these guys managed to make ohmefentanyl without killing themselves is beyond me. No matter how careful you are, one will be always be exposed to chemical that is used. Not only did they have to synthesize it, but they also had to purify it, weigh it, put it a vial, analyze it, and clean the glassware.

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