STATEMENT OF

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BEFORE THE

UNITED STATES SENTENCING COMMISSION

FOR A PUBLIC HEARING ON FENTANYL AND SYNTHETIC CANNABINOIDS

PRESENTED

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Introduction

Acting Chair Pryor and Members of the Sentencing Commission, thank you for the opportunity to discuss the chemical structures of fentanyl and fentanyl analogues. The dramatic increase in trafficking and abuse of designer synthetic opioids, such as fentanyl and fentanyl analogues, has emerged during a time when the incidence of opioid abuse in the United States is already at alarming levels. The proliferation of fentanyl analogues mirrors the evolution of other novel psychoactive substances (NPS). Fentanyl and fentanyl analogues have a history of being trafficked as replacements for other opioids, such as heroin. In the 1970s and 1980s, fentanyl and fentanyl analogues appeared on the illicit drug market and overdoses were documented.[1]

Currently, traffickers are again exploiting available legitimate research information on structure activity relationships, making small changes to the chemical structure of fentanyl and distributing these fentanyl analogues in the illicit drug market. As the opioid dependent population has increased, the parallel transition to more potent opioids, such as fentanyl analogues, has also increased. Since 2015, the Drug Enforcement Administration (DEA) has responded with six temporary scheduling actions to control nine fentanyl analogues in Schedule I of the Controlled Substances Act. Responding to the introduction of new fentanyl analogues in the illicit drug market remains a priority for the DEA.

Background

Fentanyl was first synthesized in Belgium in the late 1950s. Structurally, fentanyl belongs to the 4-anilidopiperidine structural class, a group of substances that have been well studied for their analgesic effects. Fentanyl analogues have chemical structures that are similar to that of fentanyl, but with small chemical structural modifications. A large number of fentanyl analogues have been synthesized and evaluated to establish structure-activity relationships. Structure-activity relationships that detail the various modifications possible to fentanyl's chemical structure have been described in the scientific literature. [2, 3, 4, 5, 6, 7, 8, 9, 10, 11] These structure-activity relationships

[1] United Nations Office on Drugs and Crime, *Fentanyl and Its Analogues – 50 Years On*, 17 Global Smart Update, (March 2017).

[2] W.F.M. Van Bever, C.J.E. Niemegeers, K.H.L. Schellekens & P.A.J. Janssen, *N-4-Substituted 1-(2-Arylethyl)-4-piperidinyl-N-phenylpropanamides, a Novel Series of Extremely Potent Analgesics with Unusually High Safety Margin*,26 Arzneimittelforschung, 1548-1551 (1976).

[3] J.R. Bagley, R.L. Wynn, F.G. Rudo, B.M. Doorley & H.K. Spencer, *New 4-(Heteroanilido)piperidines, Structurally Related to the Pure Opioid Agonist Fentanyl, with Agonist and/or Antagonist Properties*, 32 Journal of Medicinal Chemistry, 663-671 (1989).

[4] J.R. Bagley, L.V. Kudzma, N.L. Lalinde, J.A. Colapret, B.S. Huang, B.S. Lin, T.P. Jerussi, M.J. Bengenga, B.M. Doorley, M.H. Ossipov, T.C. Spaulding & H.K. Spencer, *Evolution of the 4-Anilidopiperidine Class of Opioid Analgesics*, 11 Medicinal Research Reviews, 403-436 (1991).

[5] P. Maguire, N. Tsai, J. Kamal, C. Cometta-Morini, C. Upton & G. Loew, *Pharmacological Profiles of Fentanyl Analogs at Mu, Delta, and Kappa Opiate Receptors*, 213 European Journal of Pharmacology, 219-225 (1992).

[6] G.A. Brine, P.A. Stark, Y. Liu & F.I. Carroll, *Enantiomers of Diastereomeric cis-N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]N-phenylpropanamides: Synthesis, X-ray Analysis, and Biological Activities*, 38 Journal of Medicinal Chemistry, 1547-1557 (1995).

[7] Lj. Dosen-Micovic, M. Ivanovic & V. Micovic, *Steric Interactions and the Activity of Fentanyl Analogs at the Mu-Opioid Receptor*, 14 Bioorganic and Medicinal Chemistry, 2887-2895 (2006).

highlight the relative ease of modifying chemical structures in this structural class. Some fentanyl analogues that have emerged on the illicit market were previously described in the scientific and patent literature, often accompanied by pharmacological data and detailed instructions for their synthesis.

Chemistry of fentanyl and its analogues

The synthesis of fentanyl and fentanyl analogues requires familiarity with synthetic organic chemistry. The design of new fentanyl analogues, however, is a straightforward endeavor. New analogues can be synthesized using the same chemical steps that are used to make fentanyl. With substitution of one or more of the chemicals used in these synthetic steps, a new substance can be produced. For example, a group of fentanyl analogues (e.g., acetyl fentanyl, acryl fentanyl, butyryl fentanyl, furanyl fentanyl, and others) can all by synthesized in a single step starting from 4-anilino-*N*-phenethylpiperidine (4-ANPP), a Schedule II immediate precursor to fentanyl. Figure 1 shows one of several known synthetic routes to fentanyl. In this pathway, a different chemical can be substituted at any stage in the synthesis to create structural modifications to fentanyl and ultimately produce a new final chemical structure. The ease of creating new fentanyl analogues is attractive to medicinal chemists researching this structural class. Unfortunately, this structural class is attractive to clandestine chemists for the same reason.

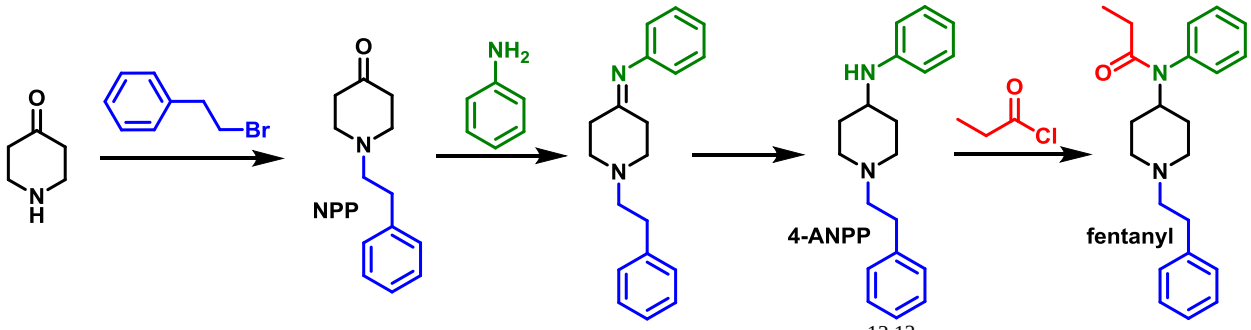

Figure 1: A synthetic route to fentanyl.[12,13]

Since 2015, many new fentanyl analogues on the illicit drug market differ from fentanyl by modification of the acyl group, the aniline ring, or both (see Table 1). Historically, fentanyl

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[8] S. Vuckovic, M. Prostran, M. Ivanovic, Lj. Dosen-Micovic, Z. Todorovic, Z. Nesic, R. Stojanovic, N. Divac & Z. Mikovic, Fentanyl Analogs: Structure-Activity-Relationship Study, 16 Current Medicinal Chemistry, 2468-2474 (2009).

[9] G. Weltrowska, N.N. Chung, C. Lemieux, J. Guo, Y. Lu, B.C. Wilkes & P.W. Schiller, "*Carba"-Analogues of Fentanyl are Opioid Receptor Agonists*, 53 Journal of Medicinal Chemistry, 2875-2881 (2010).

[10] Y. Higashikawa & S. Suzuki, *Studies on 1-(2-phenethyl-4-(N-propionylanilino)piperidine (Fentanyl) and Its Related Compounds. VI. Structure-analgesic Activity Relationship for Fentanyl, Methyl-substituted Fentanyls and Other Analogues*, 26 Forensic Toxicology, 1-5 (2008).

[11] R.S. Vardanyan & V.J. Hruby, *Fentanyl-related Compounds and Derivatives: Current Status and Future Prospects for Pharmaceutical Applications*, 6 Future Medicinal Chemistry, 385-412 (2014).

[12] A. Jonczyk, J. Jawdosiuk & M. Makosza, *Poszukiwanie Nowej Metody Syntezu Srodka Analgetycznego "Fentanyl*," 57 Przemysl Chemiczny, 131-134 (1978).

[13] S.H. Zee & W.K. Wang, *A New Process for the Synthesis of Fentanyl*, 27 Journal of the Chinese Chemical Society, 147-149 (1980).

analogues have included structural modifications to every part of fentanyl's chemical structure: the phenethyl group, the piperidine ring, the aniline ring, and the acyl group (Figure 2).

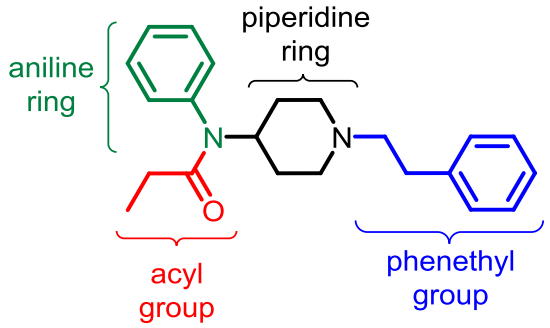
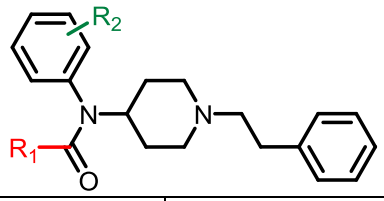


Figure 2. Fentanyl sites of substitution.

Table 1. Examples of recent structural modifications to fentanyl observed on the illicit market.



Substance	R_1	R_2
fentanyl[14]	$-CH_2CH_3$	H
acetyl fentanyl	$-CH_3$	H
butyryl fentanyl	$-CH_2CH_2CH_3$	H
furanyl fentanyl	-furan-2-yl	H
4-fluoroisobutyryl fentanyl	$-CH(CH_3)_2$	*para*-F
acryl fentanyl	$-CH=CH_2$	H
ortho-fluorofentanyl	$-CH_2CH_3$	*ortho*-F
tetrahydrofuranyl fentanyl	-tetrahydrofuran-2-yl	H
methoxyacetyl fentanyl	$-CH_2OCH_3$	H
cyclopropyl fentanyl	-cyclopropyl	H
valeryl fentanyl	$-CH_2CH_2CH_2CH_3$	H
isobutyryl fentanyl	$-CH(CH_3)_2$	H
para-chloroisobutyryl fentanyl	$-CH(CH_3)_2$	*para*-Cl
para-methoxybutyryl fentanyl	$-CH_2CH_2CH_3$	*para*-OCH_3
cyclopentyl fentanyl	-cyclopentyl	H
ocfentanil	$-CH_2OCH_3$	*ortho*-F
para-fluorobutyryl fentanyl	$-CH_2CH_2CH_3$	*para*-F

Figures 3 and 4 include fentanyl analogues controlled in the United States in the 1980s, and in the past three years, respectively. Though these figures do not provide a comprehensive list of fentanyl analogues encountered on the illicit drug market, they do illustrate structural modifications to each part of the fentanyl structure. Many additional structural modifications remain possible, and based on historical trends, it is anticipated new fentanyl analogues will be

[14] Fentanyl is included for reference.

encountered on the illicit market. Currently, there are 18 fentanyl analogues listed in Schedule I and 5 fentanyl analogues, in addition to fentanyl, listed in Schedule II.

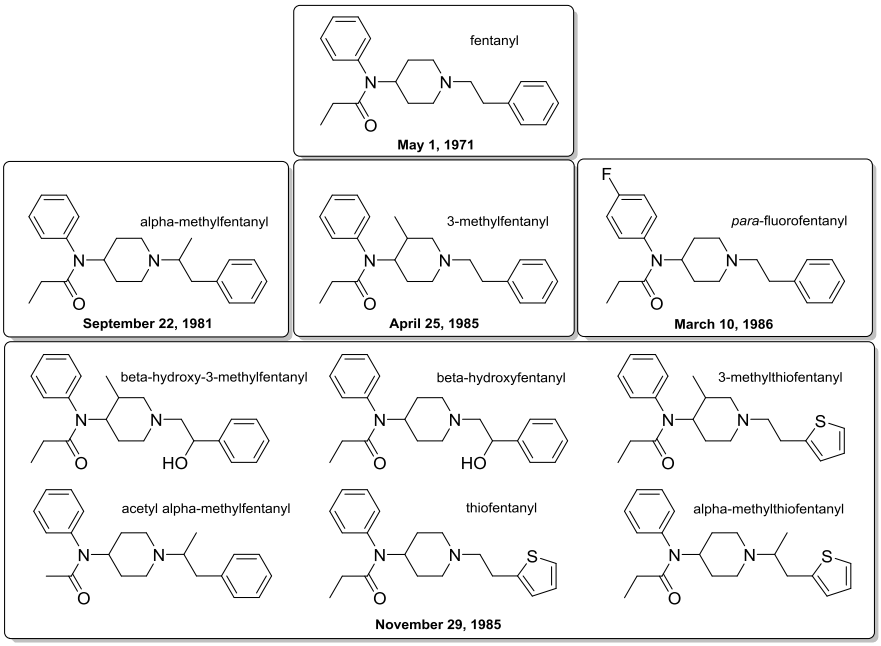


Figure 3. Fentanyl analogues controlled in Schedule I in the 1980s.[15,16]

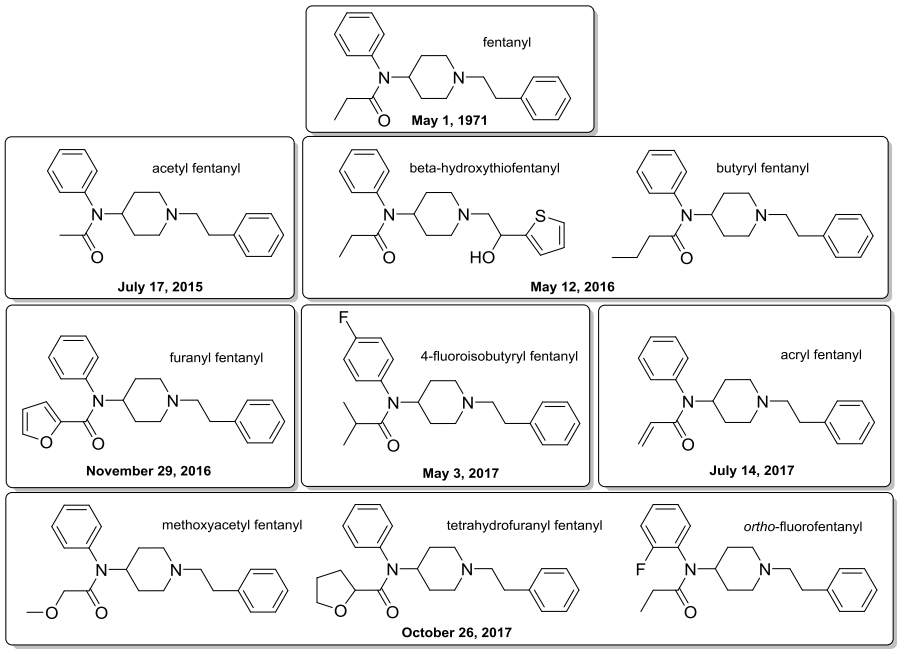


Figure 4. Fentanyl analogues controlled in Schedule I since 2015.[17,18]

[15] The chemical structure of fentanyl is shown for reference.

[16] May 1, 1971, Pub. L. No. 91-513; September 22, 1981, 46 Fed. Reg. 46799; April 25, 1985, 50 Fed. Reg. 11690; November 29, 1985, 50 Fed. Reg. 43698; March 10, 1986, 51 Fed. Reg. 4722.

[17] The chemical structure of fentanyl is shown for reference.

Forensic laboratory data showed that law enforcement encounters of fentanyl and fentanyl analogues markedly increased since 2012. For example, according to DEA's National Forensic Laboratory Information System (NFLIS), a national forensic drug laboratory reporting system that systematically collects results from drug chemistry analyses conducted by federal, state and local forensic laboratories across the country, law enforcement encounters of fentanyl increased by more than 50-fold from 694 reports in 2012 to 36,134 reports in 2016.[19] NFLIS reports for fentanyl analogues increased from 3 in 2012 to 6,926 in 2016. As of October 30, 2017, NFLIS reports for January - June 2017 for fentanyl and fentanyl analogues were 21,872 and 6,808, respectively.

Conclusion

In summary, the fentanyl analogues that have been encountered on the illicit market have been related to fentanyl in chemical structure, many additional structural modifications remain possible, and, based on historical trends, it is anticipated that new fentanyl analogues will be encountered on the illicit market. We believe a class approach based on structure would capture fentanyl-related substances. Thank you for the opportunity to discuss the chemical structures of fentanyl and fentanyl analogues. I welcome the chance to answer any questions the Commission may have during the upcoming hearing.

[18] July 17, 2015, 80 Fed. Reg. 42381; May 12, 2016, 81 Fed. Reg. 29492; November 29, 2016, 81 Fed. Reg. 85873; May 3, 2017, 82 Fed. Reg. 20544; July 14, 2017, 82 Fed. Reg. 32453; October 26, 2017, 82 Fed. Reg. 49504.
[19] Database queried on October 30, 2017.