K24 *In Silico* Simulation of Fentalog Raman Spectra

Madison R. Schackmuth, BS, Huntsville, TX 77340; Patrick Buzzini, PhD, Sam Houston State University, Huntsville, TX 77340; Darren L. Williams, PhD, Sam Houston State University, Huntsville, TX 77341*

Learning Overview: After attending this presentation, attendees will be familiar with the use of Gaussian modeling for the simulation of fentalog Raman spectra.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by encouraging preemptive characterization of novel fentalog structures with Gaussian modeling of Raman spectra.

Fentanyl and its analogs (fentalogs) are mu (μ) receptor agonists capable of causing severe respiratory depression in conjunction with the typical opioid toxidrome.[1] The number of deaths associated with fentanyl and its analogs has increased, particularly in North America, and cases involving seized fentalogs more than doubled from 2015 to 2016.[2,3] Potential hazards to law enforcement, emergency responders, and forensic scientists have also drawn concern. Screening methods that can keep pace with the fentalog development are in high demand. Raman spectroscopy is non-destructive and capable of elucidating chemical structures of substances through packaging in solution, in all states of matter.[4] Due to safety concerns and licensure requirements for obtaining powdered forms of Schedule I controlled substances, modeling of fentalog structures was performed *in silico*. Predictive modeling of Raman spectra can be used to explore the properties of novel synthetic structures and create libraries prior to their appearance on the illicit drug market.

Gaussian 09 software package and density functional theory calculations were used to simulate Raman spectra for the fentalogs. The fentanyl structure was modeled in GaussView 5.0 software. The geometry of the structure was optimized, and the vibrational frequencies determined through simulation with the Gaussian 09W software. Four levels of theory were used to optimize the geometry including molecular mechanics, semi-empirical, Hartree-Fock (HF), and Density Functional Theory (DFT). The simulation excluded solvation as a parameter and was optimized at room temperature. Fentanyl was optimized at a vibration theory/geometry optimization of B3LYP/6-311G(d)/B3LYP/6311G(d). The structures of seven fentalogs ((+)-Cis-3-methylfentanyl, 4-ANPP, acetylfentanyl, butyrylfentanyl, furanylfentanyl, isobutyrylfentanyl, and norfentanyl) were modified in GaussView 5.0 from the optimized fentanyl structure. The analogs were simulated through three levels of theory and basis sets: HF STO-3G, DFT B3LYP 6-31G(d), and DFT B3LYP 6-311G(d). The total energies (Hartree) of the simulated structures were compared to assist in selecting the lowest energy structure. The transition wavenumbers and intensities calculated by Gaussian were plotted in a spreadsheet. A normal distribution was plotted around each transition wavenumber (spectral line) considering the spectral resolution (transition width) as the standard deviation. The normal distribution was multiplied by the transition intensity. The area under the normal distribution curve at each increment wavenumber value along the x-axis was summed to graph the simulated intensity. Elevated baseline and baseline slope parameters were simulated by adding a user-defined value to the spectral intensities. Spectral resolution was administratively set at 8 cm^{-1}. The fentalog spectra are consistent across modification groups with the presence or absence of bands corresponding to specific vibrations that can be utilized for differentiation.

Reference(s):

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2. UNODC (2016) United Nations Office on Drugs and Crime Global Smart Update Volume 17.
3. EMCDDA (2017) *European Drug Report 2017: Trends and Developments.* Publications Office of the European Union, Luxembourg.
4. Izake EL (2010) Forensic and Homeland Security Applications of Modern Portable Raman Spectroscopy. *Forensic Science International* 202: 1-8.

Raman Spectroscopy, Fentalogs, Gaussian