E27 Flubromazepam: Synthesis and Characterization of Positional Isomers for Forensic Analysis

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Learning Overview: The goal of this presentation is to demonstrate a complementary application of organic and analytical chemistry for the forensic analysis of Novel Psychoactive Substances (NPS).

Impact on the Forensic Science Community: This presentation will impact the forensic science community by providing: (1) useful reference data for flubromazepam, a designer benzodiazepine of interest, and its 11 positional isomers; (2) a synthetic scheme to prepare pure standards of additional benzodiazepine positional isomers; and (3) a baseline analytical protocol to facilitate future forensic analysis, whether through new reference spectra or through predictions derived from spectral pattern recognition.

Benzodiazepines constitute a class of sedative, depressant, and relaxant compounds, many of which are controlled under Schedule IV of the United States Code Controlled Substances Act. Positional isomers of benzodiazepines are nearly identical structurally and are expected to exhibit similar bioactivity as a result. But due to the technically legal status of various benzodiazepine isomers, as the definition of "analog" in the Code of Federal Regulations does not apply to Schedule IV benzodiazepines, they represent potentially attractive substitutes for drug abuse. Few of these positional isomers are represented in scientific literature and, consequently, the reference analytical data or commercial reference standards necessary for accurate identification are not available to forensic chemists. Therefore, if a positional isomer of a scheduled benzodiazepine were ever presented as a legal alternative by a distributor, positive identification would prove challenging due to the lack of characteristic reference data.

In this study, flubromazepam, a recognized designer benzodiazepine since 2012, was targeted for synthesis and characterization due to its potential for federal scheduling. Currently, flubromazepam is not federally scheduled within the United States, but the strict laws imposed on military personnel to ensure operational readiness still make this a compound of active interest to the United States Department of Defense. Additionally, flubromazepam has appeared as evidence submitted in forensic casework with regard to investigations concerning drug-related civilian crimes and military operational readiness violations.

This project was divided into two phases: synthesis and characterization. First, a uniform synthetic method was developed to prepare purified reference materials of each positional isomer of flubromazepam for which the positions of aromatically bound bromine and fluorine were varied. Traditional methods are not optimal for these positional isomers, as they are low-yielding and non-regioselective, leading either to amounts of precursor so small as to prevent completion of the synthesis or to mixtures of isomers that are difficult to separate. Though the chemistry employed in this study would likely not be used by typical drug distributors, sufficient pure quantities of each isomer were successfully obtained for analysis.

Second, the corresponding analytical reference spectra for each positional isomer of flubromazepam were collected. The structural identification of synthesized flubromazepam isomers were validated primarily using High Resolution Accurate Mass Spectrometry (HRAMS) and both Proton and Carbon Nuclear Magnetic Resonance (^{1}H-/^{13}C-NMR). Isomers were then characterized using traditional forensic analytical techniques such as Gas Chromatography/Mass Spectrometry (GC/MS), Liquid Chromatography/Mass Spectrometry (LC/MS), and Gas Chromatography/solid phase Infrared Spectroscopy (GC/IR). From this data, an analytical scheme was developed to accurately identify and differentiate each positional isomer of flubromazepam. Additionally, pattern recognition by NMR and IR was established to enable predictive analysis of unknown positional isomers that may appear in future forensic cases.

Flubromazepam, Positional Isomer, Novel Psychoactive Substance (NPS)