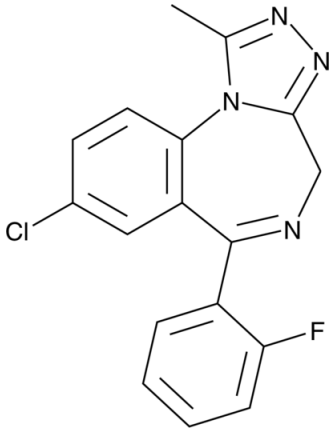
Short Communication for the Analysis of Flualprazolam

Date: May 2020

Synonyms: 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine
2'-Fluoro Alprazolam
ortho-Fluoro Alprazolam

Structure:



Formula: $C_{17}H_{12}ClFN_4$

Molecular Weight (nominal mass): 326.75

Theoretical M+H accurate mass: 327.0807

Pharmacological Drug Class: Central Nervous System Depressant

Suggested LOD: 2 ng/mL

Suggested LOQ: 5 ng/mL

Flualprazolam is a triazolo-benzodiazepine, similar to alprazolam and triazolam, and was first patented in the 1970s. It is not currently marketed or approved for medicinal use in any country. The Drug Enforcement Administration first identified flualprazolam in 2018 (https://ndews.umd.edu/sites/ndews.umd.edu/files/Emerging-Threat-Report-2018-Annual.pdf). In 2019, the 42nd meeting of the World Health Organization Expert Committee on Drug Dependence critically reviewed flualprazolam (https://www.who.int/medicines/access/controlled-substances/Final_Flualprazolam.pdf?ua=1). At its meeting in March 2020, the Commission for Narcotic Drugs voted to place flualprazolam under international control as a Schedule IV substance in the 1971 Convention on Psychotropic Substances.

From the United Nations Office on Drugs and Crime (UNODC) ToxPortal, flualprazolam has been reported over 150 times with the vast majority of reports from North America and Europe. Where blood concentrations were available, post-mortem blood concentrations between 0.8 and 100 ng/mL and blood concentrations of between 5.5 and 57 ng/mL in drug driving, were reported.

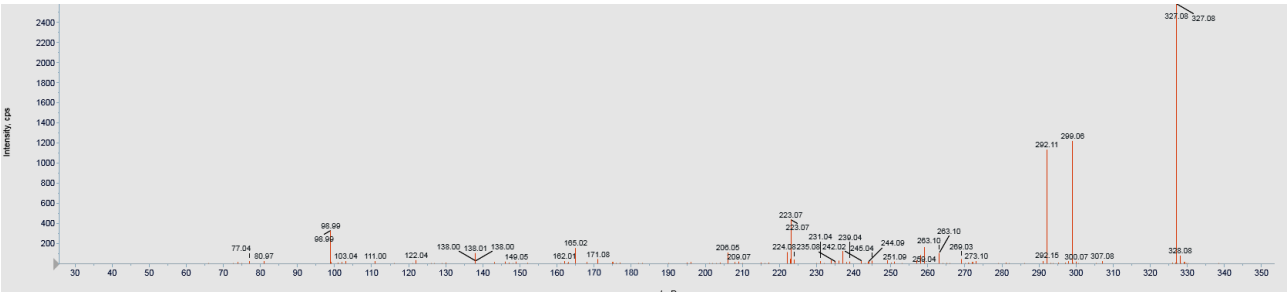
From October 2018 until November 2019, the Toxicology Section of the Orange County Crime Lab (OCCL) in California, USA has had 130 cases of flualprazolam, with 10% from post-mortem cases, and the rest from DUID with one case form a sexual assault. Flualprazolam was detected on an LC-QTOF with no quantitation.

Sacramento County District Attorney's Forensic Laboratory in California has had over 150 cases with concentrations ranging from 5 ng/mL (LOQ) to 150 ng/mL. The average concentration was 25 ng/ml with a median concentration of 18 ng/mL. Their data and data from NMS Labs can be seen in TOXTalk, (2019) Volume 43, Issue 4, along with a GCMS spectrum of flualprazolam.

For both Orange County and Sacramento, the most common co-administered drug is THC, followed by other benzodiazepines with alprazolam being the most common. The majority of cases have submission into the drug section of fake "Xanax" tablets. The Controlled Substance Section of the OCCL had 40 cases of flualprazolam within this same time frame; 20% had another NPS benzodiazepine present.

There are no current reports of flualprazolam concentrations in hair, serum or urine. Initial studies regarding metabolism have indicated alpha-hydroxyflualprazolam, 4-hydroxyflualprazolam glucuronide, flualprazolam-glucuronide and alpha-hydroxyflualprazolam glucuronide. These metabolites were also detected in blood and urine samples from the Orange County Crime Lab.

Flualprazolam LC-MS Spectrum:



[source: Sciex X500R, Orange County Crime Laboratory, California, USA]

Additional References:

Heide G, Høiseth G, Middelkoop G, Øiestad ÅML. Blood concentrations of designer benzodiazepines: Relation to impairment and findings in forensic cases. J Anal Toxicol. (2020) May 5:bkaa043. doi: 10.1093/jat/bkaa043. [Epub ahead of print]

Kriikku P, Rasanen I, Ojanperä I, Thelander G, Kronstrand R, Vikingsson S. Femoral blood concentrations of flualprazolam in 33 postmortem cases. Forensic Sci Int. (2020) Feb;307:110101. doi: 10.1016/j.forsciint.2019.110101. Epub 2019 Dec 19

Wagmann L, Manier SK, Bambauer TP, Felske C, Eckstein N, Flockerzi V, Meyer MR. Toxicokinetics and analytical toxicology of flualprazolam: metabolic fate, isozyme mapping, human plasma concentration, and main urinary excretion products. J Anal Toxicol. (2020) Feb 27. pii: bkaa019. doi: 10.1093/jat/bkaa019. [Epub ahead of print]