World Health Organization

Critical Review Report:

FLUALPRAZOLAM

Expert Committee on Drug Dependence

Forty-second Meeting

Geneva, 21-25 October 2019

This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization

Contents

Acknowledgements

This document was produced for the WHO Expert Committee on Drug Dependence (ECDD) under the overall direction of the WHO Secretariat led by Dr Gilles Forte (Division of Access to Medicines, Vaccines, and Pharmaceuticals). The document was written by Dr Suzanne Nielsen under the technical direction of Dr Dilkushi Poovendran (Division of Access to Medicines, Vaccines, and Pharmaceuticals). The report was edited by Professor Kim Wolff. The member state questionnaire was produced under the technical direction of Ms Judith Sprunken (Division of Access to Medicines, Vaccines, and Pharmaceuticals).

The WHO Secretariat would also like to thank the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA), International Narcotics Control Board (INCB), United Nations Office of Drugs and Crime (UNODC), and Member States for providing relevant information for the review of substances.

Executive Summary

Flualprazolam (sometimes referred to as 'flualp') is a triazolo-benzodiazepine, similar to triazolam and alprazolam and structurally different from benzodiazepines such as diazepam. It is considered a 'novel' or 'designer' benzodiazepine. It was first patented in the 1970's but was never marketed.

Preclinical studies described in the patent documentation demonstrate that flualprazolam has sedative effects similar to other benzodiazepines. It is a higher potency benzodiazepine with relatively short onset of action, similar to alprazolam.

It is sold by several internet companies for research purposes with discussions on online forums indicating that some people consume flualprazolam for its psychoactive effects, and report similar effects, including adverse effects, to alprazolam. There is very little published literature to describe the pharmacology, toxicology or dependence potential for flualprazolam itself, though what is known suggest that the effects are comparable to the structurally similar alprazolam.

1. Substance identification

A. International Nonproprietary Name (INN)

NA

B. Chemical Abstract Service (CAS) Registry Number

28910-91-0

C. Other Chemical Names

2'-Fluoro Alprazolam
ortho-Fluoro Alprazolam
28910-91-0
SCHEMBL7327360
8-Chloro-6-(2-fluoro-phenyl)-1-methyl-4h-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine
8-chloro-6-(2-fluorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine

D. Trade Names

None

E. Street Names

Flualp

F. Physical Appearance

White powder

G. WHO Review History

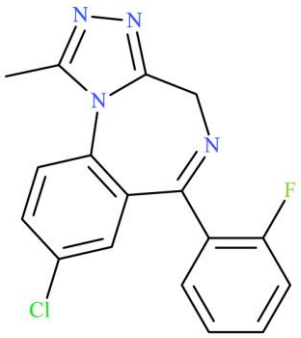
Flualpraozolam has not previously been pre-viewed or critically reviewed.

2. Chemistry

A. Chemical Name

IUPAC Name: 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine
CA Index Name: N/A

B. Chemical Structure



Free base:

Molecular Formula: C17H12ClFN4
Molecular Weight: 326.75

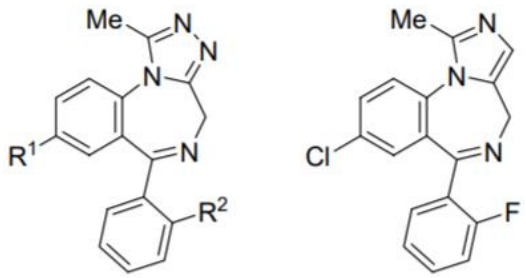
C. Stereoisomers

None

D. *Methods and Ease of Illicit Manufacturing*

Flualprazolam is manufactured by several laboratories for research purposes and is easily available by internet. Preparation of a range of triazolo-benzodiazepines were initially described in the patent application by Hester (1976). Later, alternate methods for synthesizing alprazolam were published which included the formation of flualprazolam as an intermediary in the process of synthesizing other benzodiazepines (Fustero et al., 2006). Fustero et al (2006) provided three schemes indicating the alternative method to produce the triazolobenzodiazepines alprazolam (Figure 1, 1b) or triazolam (Figure 1, 1c) or midazolam (Figure 1, 2) (Fustero et al 2006[1]). Alprazolam and triazolam are structurally similar to flualprazolam, with the R1 in figure 1b or 1c replaced with a F (fluorine).

Figure 1

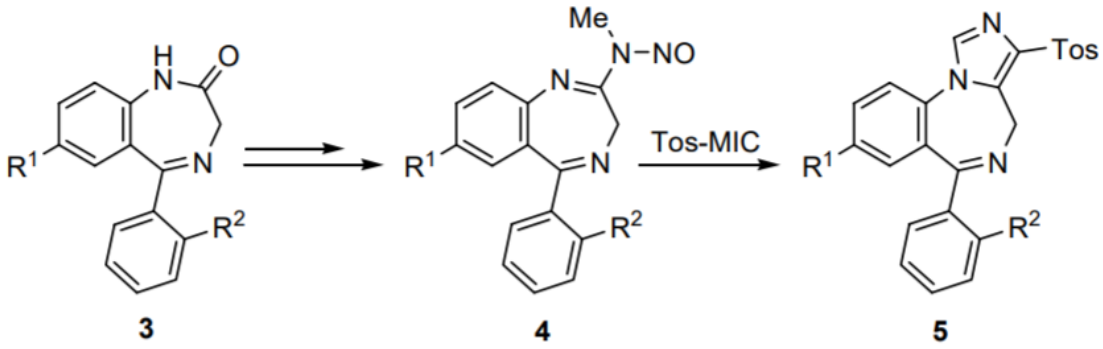


1b (R^1=Cl, R^2=H) **2**
1c (R^1=Cl, R^2=Cl)

[1] Figures and schemes reproduced from Fustero et al 2006. Original publication notes reproduction is permitted for noncommercial purposes

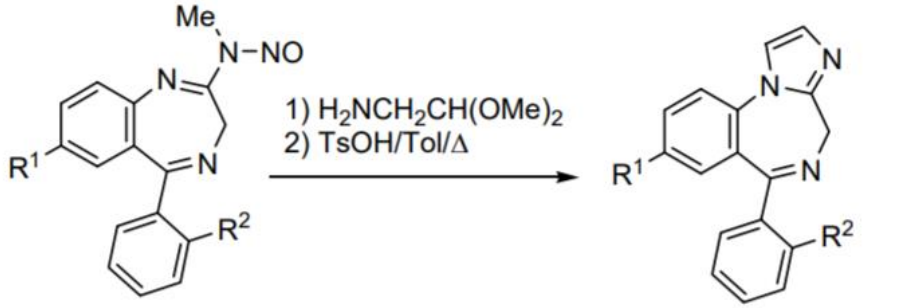
Fustero et al (2006) had previously described the use of these 1,4-benzodiazepine-derived N-nitrosoamidines 4 as synthetic equivalents of imidoylchlorides in their reaction with Tos-MIC to form 3-(4-tosyl)imidazo[1,5-a][1,4]benzodiazepines (5, in Scheme 1 below).

Scheme 1



Treatment of N-nitrosoamidines 4 (see 6, Scheme 2, below) with aminoacetaldehyde dimethylacetal resulted in the corresponding amidines in an addition-elimination sequence. Fustero et al (2006), described that these amidine derivatives were heated in toluene at 80º C in the presence of two equivalents of p-toluenesulfonic acid (TsOH) to provide imidazo[1,2-a][1,4]benzodiazepines 6 in "very good yields" (Scheme 2).

Scheme 2

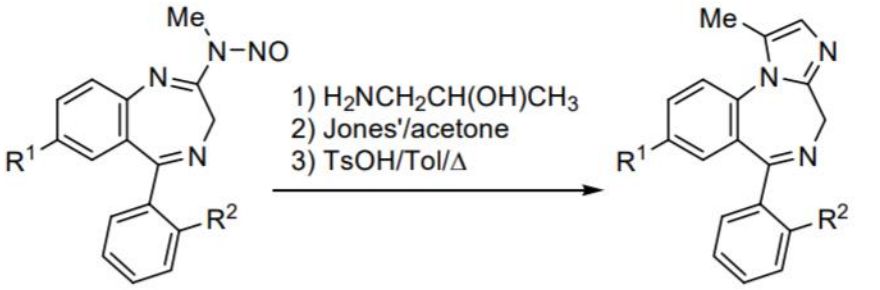


4a (R^1=Cl, R^2=F)
4b (R^1=Cl, R^2=H)

6a (R^1=Cl, R^2=F, 79%)
6b (R^1=Cl, R^2=H, 80%)

Fustero et al (2006) further describes "The N-nitrosoamidine functionality in compounds 4 can also be replaced through reaction with 1-amino-2-propanol. The hydroxyl functionality present in this newly created amidine was subsequently oxidized to the corresponding methyl ketone through treatment with Jones' reagent. p-Toluenesulfonic acid-mediated cyclization under the conditions described above afforded tricyclic benzodiazepines 7 in moderate yields (Scheme 3)"

Scheme 3



4a (R^1=Cl, R^2=F)
4b (R^1=Cl, R^2=H)
4c (R^1=Cl, R^2=Cl)

7a (R^1=Cl, R^2=F, 50%)
7b (R^1=Cl, R^2=H, 48%)
7c (R^1=Cl, R^2=Cl, 52%)

Fustero et al (2006) lastly described treating N-nitrosoamidines (4) with acetylhydrazine produce the corresponding amidines. Next these were cyclized by heating in dimethylformamide (DMF) in the presence of TsOH to create "very good yields" of triazole-fused 1,4-benzodiazepines 1 (Scheme 1)." Flualpraozlam is represented as in Scheme 3, Figure 7a.

E. Chemical Properties

Melting point: No data

Boiling point: No data

Solubility: Partially soluble (National Forensic Laboratory (NFL) Slovenia, 2018)

F. Identification and Analysis

Flualprazolam was identified from three blood samples in The Centre for Forensic Science Research and Education Laboratories through data mining of data files acquired in 2018 (March) and 2019 (June), a process that the laboratory developed for real-time discovery and detection of novel psychoactive substances (Krotulski and Logan, 2019). Flualprazolam was added to their library database in March 2019. Samples were identified from Pennsylvania (n = 2) and Indiana (n = 1). Samples were identified using Gas Chromatography Mass Spectrometry (GC-MS) using a sample diluted in methanol, against a reference purchased from Caymen Chemicals. Testing was also performed using liquid chromatography quadrupole time of flight mass spectrometry (LC-QTOF), resulting in positive identification against a reference material.

A report from the National Forensic Laboratory in Slovenia also reports successful characterisation and identification using nuclear magnetic resonance, High Performance Liquid Chromatography – Time of flight (HPCL-TOF), GCMS and Fourier transform infrared

spectroscopy (FTIR) Attenuated Total Reflection (ATR)(National Forensic Laboratory (NFL) Slovenia, 2018).

Newer methods of detection of 13 designer benzodiazepines including flualprazolam have been described which enable detection from post-mortem blood using liquid chromatography-tandem mass spectrometry (Mei et al., 2019). The method involves treating analytes with solid phase extraction, before undergoing separation on a C18 column and analysing using a mass spectrometer in electrospray positive mode using multiple reaction monitoring (Mei et al., 2019). This method of post-mortem blood testing was described as valid, reliable and robust, and was able to identify flualprazolam in one of 13 post-mortem blood samples collected between 2016-2018 that were reanalysed using this method.

3. Ease of Convertibility Into Controlled Substances

There were no published data specifically regarding the ease of convertibility of flualprazolam to other controlled substance, though the process is described for the formation of flualprazolam as an intermediary in the process of synthesizing other benzodiazepines including alprazolam (Fustero et al., 2006). It seems from this that flualprazolam could be converted into a controlled substance such as alprazolam, a Schedule IV substance as per the convention on Psychotropic Substances, 1971.

4. General Pharmacology

A. Routes of administration and dosage

Oral doses of 0.125mg – 2 mg are described in the published literature (Zawilska and Wojcieszak, 2019, Moosmann and Auwarter, 2018). A report from an online forum described doses in this range (0.25 mg – 0.5mg) (Reddit, 2019).

B. Pharmacokinetics

Flualprazolam is a triazolo-benzodiazepine, which differ structurally from benzodiazepines such as diazepam, and offer distinct differences in pharmacological activity and in time-course of effect (Garzone and Kroboth, 1989). Specific information about flualprazolam pharmacokinetics is scarce however information is available for the structurally similar 1,4-triazolobenzodiazepines, alprazolam and triazolam. The published literature demonstrates that both alprazolam and triazolam have high affinities for the benzodiazepine receptor (Garzone and Kroboth, 1989). Peak alprazolam and triazolam concentrations occur within an hour, reflecting rapid absorption. The volume of distribution of alprazolam and triazolam is approximately 1L and both are highly bound to plasma proteins; alprazolam (70%) and triazolam (~ 85%). The mean elimination half-life for alprazolam in healthy adults ranges from 9.5 to 12 hours (Garzone and Kroboth, 1989). For alprazolam elimination, liver disease prolongs elimination, but kidney disease does not. Onset of action for flualprazolam is reported to be 10-30 min with a duration 6-14h (Zawilska and Wojcieszak, 2019). An individual report from an online forum suggest an onset of action in approximately 30-40minutes (Reddit, 2019).

The 1,4-triazolo ring prevents the oxidative metabolism of the classical benzodiazepines which results in formation of active metabolites with long elimination half-lives.

C. Pharmacodynamics

Limited descriptions of the effects of flualpraozlam are available. One online report described sedition and impairment from this dose reported (Reddit, 2019). It would be expected that these effects are produced in a similar way to other benzodiazepines, which is via allosteric modulation of the GABA reception, potentiating the action of GABA, leading to sedative effects and impairment.

The only studies describing acute and pre-clinical effects of alprazolam were reported in the patent application (Hester, 1976). Preclinical studies described in the patient application indicate that flualprazolam demonstrated sedative effects on the Chimney Test with intraperitoneal (IP) doses of 0.09 mg/kg; and a sedative dose in the Dish test of 0.15 ng/kg with IP administration, and 0.045mg/kg when administered orally.

Sedative/tranquilizer effects were also seen on the Pedestal Test at doses IP of 0.20 mg/kg or oral doses of 0.9mg/kg. Flualprazolam was shown to be protective against nicotine induced convulsions and tonic extensor fits and death at doses of 0.04mg/kg (oral), and had muscle relaxant or antispasmodic activity against the effects of strychnine administration at 1mg/kg.

5. Toxicology

No preclinical studies were identified that had examined the acute toxicity or chronic health effects of flualprazolam or its metabolites in animals.

The United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory on NPS Toxicology Portal (Tox-Portal), an online tool established in 2017 that collects data on toxicology and harm related to the use of NPS, included 42 reports that involved flualprazolam. These reports predominantly represented people aged 15-24 years old (26 of 42 cases), and predominantly male (37 of 42 cases). Forty of the 42 cases were reported in the USA with two cases from Finland. In five cases the samples were documented to have been collected post mortem and 21 were noted to be ante-mortem samples. The remaining cases had no additional information on context. Most cases provided an indication of the contribution or impact of a substance on the case. In five cases flualprazolam was determined to be causal to the event (that is, a high probability of causality). In 22 cases flualprazolam was documented to have a medium probability of causality, in one case the contribution of flualprazolam was assessed to have a low probability of causality. There were 12 further cases the contribution of the flualprazolam was documented to be undetermined.

6. Adverse Reactions in Humans

There are limited reports that document adverse reactions with flualprazolam, which is likely to be due to the lack of availability of registered therapeutic product. No published literature covering adverse reactions was able to be identified. It is likely that adverse reactions would be similar to alprazolam due to its similar potency, onset and action and half-life. Given its structural similarity, flualprazolam is thought to have similar sedative effects. A report on an online forum describes an instance nonmedical where loss of memory, disinhibition and criminal activity occurred (Reddit, 2019). This report is consistent with previous reports with alprazolam (Jones et al., 2011). A separate online report on a blog describes a user reporting sedation similar to alprazolam (RCEShare, 2019).

7. Dependence Potential

A. Animal Studies

No animal studies could be identified on Pubmed or Google Scholar.

B. Human Studies

No human studies could be identified on Pubmed or Google Scholar that specifically cover flualprazolam. The dependence liability of benzodiazepines in general is well documented. Given the fast onset of action and similarities to alprazolam it would be expected to have a relatively high dependence liability, similar to alprazolam.

8. Abuse Potential

A. Animal Studies

No animal studies could be identified on Pubmed or Google Scholar. The patent application for flualprazolam described preclinical studies on mice where sedative/tranquilising effects and muscle relaxant effects were observed, consistent with other benzodiazepines that are used nonmedically for these effects (Hester, 1976). See Section 4 for additional detail on pharmacological effects from pre-clinical studies.

B. Human Studies

No human studies could be identified on Pubmed or Google Scholar that describe abuse liability. Information on online forums such as Reddit and Bluelight indicate that flualprazolam is used for its benzodiazepine effects, reported to be similar to alprazolam, with information about dosage with nonmedical use, and reports of effects including sedation, reduced anxiety and loss of consciousness (Bluelight.org, 2019b, Reddit, 2019). The nonmedical use of flualprazolam is likely to be similar to other benzodiazepines.

Limited abuse liability studies are available to inform the potential for nonmedical use with alprazolam, though study studies have demonstrated that alprazolam (another triazolo-benzodiazepine) has been shown in some studies to have a demonstrably greater abuse

liability compared with diazepam, especially for those with a personal or family substance use disorder history (Ait-Daoud et al., 2018).

9. Therapeutic Applications and Extent of Therapeutic Use and Epidemiology of Medical Use

Flualprazolam is not currently used clinically with no registered products or data pertaining to its therapeutic use.

10. Listing on the WHO Model List of Essential Medicines

Flualprazolam is not listed on the 20th WHO Essential Medicines List (EML) or on the 6th WHO Essential Medicines List for Children (EMLc)

11. Marketing Authorizations (as a Medicinal Product)

Synthesized and patented in 1976 but no subsequent marketing as a medicinal product. Marketed as a research chemical since 2017.

12. Industrial Use

No known industrial use.

13. Non-Medical Use, Abuse and Dependence

Reports on online forums from those that have used flualprazolam nonmedically (with pellets purchased online) describe it to be similar to clonazepam and alprazolam (Reddit, 2019). These are consistent with preclinical studies described in the patent application demonstrating sedative/tranquilizer and muscle relaxant effects (Hester, 1976).

14. Nature and Magnitude of Public Health Problems Related to Misuse, Abuse and Dependence

Limited information is available about the effects of flualprazolam, though public health concerns are likely to be similar to alprazolam and other similar benzodiazepines which are higher potency with a relatively fast time of onset. Flualprazolam is likely to cause disinhibition and sedation that would impair driving, and when combined with substances such as opioids, would contribute to increased overdose through benzodiazepine-potentiated of opioid-induced respiratory depression. Flualprazolam does not yet appear to be listed on Erowid.org, a member-supported organization providing access information about psychoactive plants, chemicals, and related issues.

There appears to be emerging (n = 34, 2 mentions in 2015, and the remainder since 2017) numbers of posts where flualprazolam is mentioned on bluelight.org, an international, online, harm-reduction community, with threads describing use for euphoric and anxiolytic effects, noting its low cost and ability to purchase it as a research chemical (Bluelight.org, 2019a).

15. Licit Production, Consumption and International Trade

Produced by numerous laboratories for research use and is readily available on the internet. Information on preparation of flualprazolam is contained in the patent application (Hester, 1976), and is also published by Fustero et al. (2006).

16. Illicit Manufacture and Traffic and Related Information

Online forums discuss that of illicit manufacture of pills containing flualprazolam has occurred. "For example, an alert about counterfeit alprazolam containing flualprazolam was reported on a harm reduction website in the United States (DrugsData, 2019) with the alert also shared on other harm reduction websites (Dance Safe, 2019)"

Project ION Incident Communication System (IONICS) is a secure online communication platform run by the International Narcotic Control Board (INCB) dedicated to real-time communication of incidents involving suspicious shipment of, trafficking in, or manufacture or production of NPS. No incident involving the flualprazolam have been communicated through IONICS.

17. Current International Controls and Their Impact

Flualprazolam is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and Past National Controls

NA

19. Other Medical and Scientific Matters Relevant for a Recommendation on the Scheduling of the Substance

None

References

1. AIT-DAOUD, N., HAMBY, A. S., SHARMA, S. & BLEVINS, D. 2018. A Review of Alprazolam Use, Misuse, and Withdrawal. *Journal of addiction medicine,* 12**,** 4-10.
2. BLUELIGHT.ORG. 2019a. Available: https://www.bluelight.org/xf/search/187893/?q=flualprazolam&t=post&o=date [Accessed 20/08/19].
3. BLUELIGHT.ORG. 2019b. *What drugs have do you really want to try but have never had the chance?* [Online]. Available: https://www.bluelight.org/xf/threads/what-drugs-have-do-you-really-want-to-try-but-have-never-had-the-chance.878528/ [Accessed 20/08/19].
4. DrugsData. 2019. "S903 Counterfeit Alprazolam: SampleID 7343". https://drugsdata.org/7343 [accessed Sep 26 2019]
5. DANCE SAFE. 2019. *#TestIt Alert: Capsule Of White Powder Sold As Alprazolam (Xanax) In North Carolina Found To Contain Exclusively Flualprazolam* [Online]. Available: https://dancesafe.org/testit-alert-capsule-of-white-powder-sold-as-alprazolam-xanax-in-north-carolina-found-to-contain-exclusively-flualprazolam/ [Accessed 07/08/19].
6. FUSTERO, S., GONZÁLEZ, J. & DEL POZO, C. 2006. 1,4-Benzodiazepine N-Nitrosoamidines: Useful Intermediates in the Synthesis of Tricyclic Benzodiazepines. *Molecules,* 11**,** 583-588.
7. GARZONE, P. D. & KROBOTH, P. D. 1989. Pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet,* 16**,** 337-64.
8. HESTER, J. 1976. *6-Phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepines. Patent US 3987052*.
9. JONES, K., NIELSEN, S., BRUNO, R., FREI, M. & LUBMAN, D. 2011. Benzodiazepine prescribing and violence: implications for general practitioners *Australian Family Physician,* 40**,** 862-865.
10. KROTULSKI, A. & LOGAN, B. 2019. Flualprazolam. *In:* UNIVERSITY, C. A. T. (ed.).
11. MEI, V., CONCHEIRO, M., PARDI, J. & COOPER, G. 2019. Validation of an LC-MS/MS Method for the Quantification of 13 Designer Benzodiazepines in Blood. *J Anal Toxicol*.
12. MOOSMANN, B. & AUWARTER, V. 2018. Designer Benzodiazepines: Another Class of New Psychoactive Substances. *Handb Exp Pharmacol,* 252**,** 383-410.
13. NATIONAL FORENSIC LABORATORY (NFL) SLOVENIA 2018. Analytical Report - Flualprazolam (C17H12ClFN4). Ljubliana, Slovenia: National Forensic Laboratory.
14. RCESHARE. 2019. *First time experience with flualprazolam* [Online]. Available: https://rceshare.blogspot.com/2019/01/first-time-with-flualprazolam-experience.html [Accessed 29/07/19].
15. REDDIT. 2019. *My Most Recent Experience With Flualprazolam* [Online]. Available: https://www.reddit.com/r/BartardStories/comments/ajixd4/my_most_recent_experience_with_flualprazolam/ [Accessed 05/08/19].
16. ZAWILSKA, J. B. & WOJCIESZAK, J. 2019. An expanding world of new psychoactive substances—designer benzodiazepines. *NeuroToxicology,* 73**,** 8-16.

Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances

Refer to separate Annex 1: Report on WHO questionnaire for review of psychoactive substances