World Health Organization

Critical review report:

Flubromazepam

Expert Committee on Drug Dependence

Forty-sixth Meeting

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Contents

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Executive summary

Flubromazepam (Chemical Abstracts Services registry number: 2647-50-9; IUPAC name: 7-bromo-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) is a 1,4-benzodiazepine that was originally developed as a candidate medication but was never approved for use. The first documented detection of flubromazepam by government authorities was in Sweden in 2013. Since then, the compound has been detected in products or in biological samples in at least 11 countries: Australia, Austria, Belgium, Canada, China, Germany, Italy, Norway, Sweden, the United Kingdom (Wales) and the USA. Flubromazepam is not under international control. It is classified in schedule IV under Canadian law and is controlled under psychoactive drug regulations in Germany, the United Arab Emirates and the United Kingdom.

Online forum posts suggest that the primary route of administration of flubromazepam is oral (tablets, capsules, powder). Informational websites for users list a dosage range according to intoxicating effects: "light" (3–5 mg), "common" (5–8 mg) and "strong" (8–12 mg). The onset of effects after oral use is estimated to be 15–90 min, and the duration of action is 12–18 h, although durations of up to 3 days have been reported. The calculated elimination half-life ranges from 100 to 106 h. The available data indicate that enterohepatic circulation of flubromazepam is probable and may contribute to its long half-life. After ingestion, flubromazepam is extensively metabolized, and only small amounts of unmetabolized compound are detectable in urine. The major phase-I metabolites include monohydroxylated (3-hydroxyflubromazepam, hydroxyflubromazepam), debrominated (debromoflubromazepam) and monohydroxylated debrominated (debrominated 3-hydroxy-flubromazepam) compounds, whereas phase-II metabolites consist of the glucuronides of the hydroxylated metabolites.

Little information is available on the pharmacological effects of flubromazepam. A quantitative model of the structure–activity relation predicts that the binding value of flubromazepam for the GABA-A receptor, expressed as log 1/c, is 8.37, which is comparable to that of midazolam. In vivo, it induced conditioned place preference after intraperitoneal injection to mice but was not self-administered intravenously by this species, although the dose of the infusion may have been too low for adequate evaluation. Peripherally, flubromazepam produced some signs of cardiotoxicity (i.e. impairment of cardiomyocyte viability, inhibition of hERG potassium channels and increased RR intervals), but it did not affect the level of PAK1 protein, a biomarker of cardiotoxicity.

Measurable concentrations of flubromazepam have been found in post-mortem blood samples in several countries, including Australia, Germany, the United Kingdom and the USA. It has also been detected in biological samples from drivers suspected of driving under the influence of drugs and from clinical admissions to emergency departments. The extent to which flubromazepam contributed to the negative health outcomes in these instances is uncertain. In most of the reported deaths, flubromazepam was only one of several substances identified in analysis of biological sample(s). While impaired driving after use of flubromazepam has been reported, co-use with another psychoactive substance is common, and only mild impairment was reported in several cases in which flubromazepam was the sole or major substance detected.

The primary source of information about its psychological effects is self-reports in online forums by people who have used flubromazepam. The reasons given for its use include intentional seeking of psychoactive effects and self-medication (e.g. anxiety, sleep-inducing modulation of a stimulant effect or as an aid to withdrawal from another benzodiazepine). Common effects of flubromazepam included anxiolysis, euphoria, relaxation, increased confidence, muscle relaxation, empathy, confusion and amnesia. Online forum posts of self-reported use of flubromazepam should be considered anecdotal, as there was no analytical confirmation of sole use of flubromazepam.

1 Substance identification

A International Nonproprietary Name

Not assigned

B Chemical Abstract Service (CAS) Registry Number

2647-50-9

C Other chemical names

2*H*-1,4-Benzodiazepin-2-one, 7-bromo-5-(*o*-fluorophenyl)-1,3-dihydro- (7CI, 8CI)

7-Bromo-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (ACI)

7-Bromo-5-(2-fluorophenyl)-1,3-dihydrobenzo[*e*]-1,4-diazepin-2-one

Canonical SMILES

O=C1NC=2C=CC(Br)=CC2C(=NC1)C=3C=CC=CC3F

InChI

InChI=1S/C15H10BrFN2O/c16-9-5-6-13-11(7-9)15(18-8-14(20)19-13)10-3-1-2-4-12(10)17/h1-7H,8H2,(H,19,20)

InChI Key

ZRKDDZBVSZLOFS-UHFFFAOYSA-N

D Trade names

Flubromazepam is sold principally under its own name *(1)*.

E Street names

Flubromazepam is sold principally as tablets, capsules or powders under its own name *(1)*. "Liquid Xanax" is a street name for flubromazepam *(2)*.

F Physical appearance

Synthetic flubromazepam has been described as a white powder *(3,4)* or a crystalline solid *(5)*.

G WHO review history

Flubromazepam has not previously been reviewed by the WHO Expert Committee on Drug Dependence.

2 Chemistry

A Chemical name

IUPAC name:

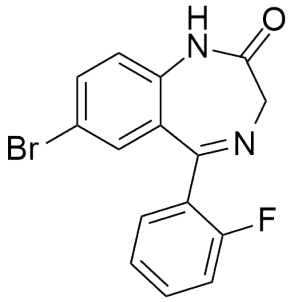
7-Bromo-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one

CA Index Name:

2*H*-1,4-Benzodiazepin-2-one, 7-bromo-5-(2-fluorophenyl)-1,3-dihydro- (9CI, ACI)

B Chemical structure

Free base:



Molecular formula: $C_{15}H_{10}BrFN_2O$

Molecular weight: 333.16 g/mol

C Stereoisomers

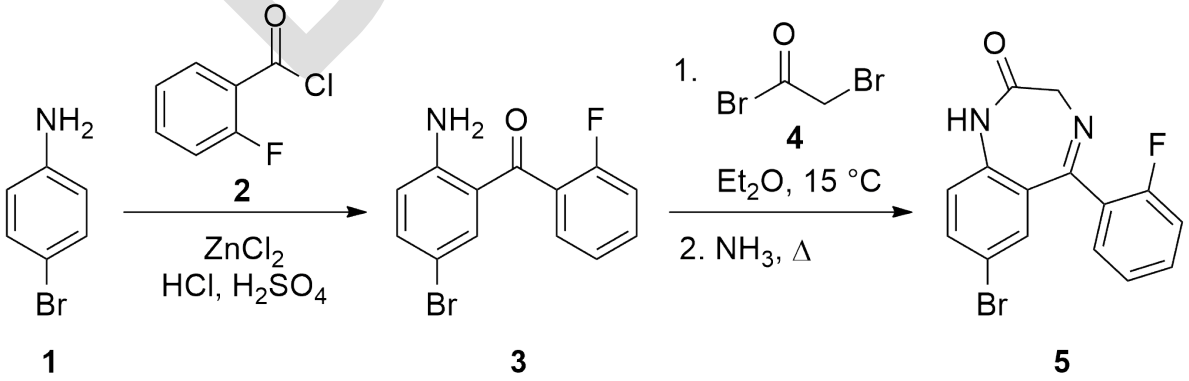
No stereoisomers of flubromazepam have been described.

D Methods and ease of illicit manufacture

Flubromazepam is a 1,4-benzodiazepine that is structurally related to the internationally controlled substance phenazepam, in which the chlorine atom has been replaced by a fluorine atom. Flubromazepam was first prepared and studied by Sternbach and co-workers in the early 1960s *(6–9)*.

Flubromazepam is conveniently prepared by the method depicted in scheme 1 *(10)*, in which *p*-bromoaniline (**1**) undergoes Friedel-Crafts acylation with *o*-fluorobenzoyl chloride (**2**) to form the 2-aminobenzophenone **3**. Then, a two-step annulation sequence involving 2-bromoacetyl bromide (**4**) (step 1) to prepare the 2-bromoacetamidobenzophenone intermediate (not shown) and treatment with ammonia and heat to promote ring closure through imine formation (step 2) afford the final product flubromazepam **5** *(10)*.

No information was available on the routes of synthesis used for the flubromazolam products circulating on the market. The synthesis reported in the literature, although simple, requires a chemical synthetic laboratory and qualified personnel.



Scheme 1. Synthesis of flubromazepam

E Chemical properties

Melting-point

189–190 °C *(3,11)*

Boiling-point

No information was found.

Solubility

Flubromazepam is soluble in dimethylformamide and in dimethyl sulfoxide (DMSO) at a concentration of 25 mg/mL, in ethanol at a concentration of 10 mg/mL, in methanol at a concentration of 1 mg/mL and in a 1:1 mixture of DMSO:phosphate-buffered saline (pH 7.2) at a concentration of 0.5 mg/mL *(5)*.

F Identification and analysis

Flubromazepam and its deuterated derivative are available as reference materials that can be purchased from various commercial suppliers and used in routine analysis associated with forensic and clinical investigations *(5)*.

Analytical methods for the identification of flubromazepam in seized sample matrices include infrared spectroscopy, proton nuclear magnetic resonance and gas chromatography–mass spectrometry (MS) *(4)*.

Flubromazepam was analysed in urine by an immunochemical assay *(12)*. Several analytical methods have been developed for qualitative and quantitative determination of flubromazepam in human blood, urine, vitreous humour, bile, hair, brain and muscle by liquid chromatography (LC) coupled either to high-resolution (MS) or triple-quadrupole MS *(13)*.

3 Ease of conversion into controlled substances

Flubromazepam can be convert to flubromazolam in a single one-pot synthesis that requires the equipment of a chemical synthetic laboratory and qualified personnel *(14)*.

4 General pharmacology

A Routes of administration and dosage

The available data and user reports indicate that oral consumption of flubromazepam is the most common route of administration. Most submitted samples positive for flubromazepam have been formulated as tablets or powder *(15,16)*, and online sales sites advertise flubromazepam in the form of pellets, powder, liquid, capsules and infused blotters *(17,18)*. Further, people who use flubromazepam have reported oral use in the form of tablets or powder solubilized with a solvent such as propylene glycol *(19,20)*.

No studies were found on human dosage; however, one informational website categorized doses according to their intoxicating effects as “light” (3–5 mg), “common” (5–8 mg) and “strong” (8–12 mg) *(21)*. For comparison, the website lists the following doses for diazepam: “light” (2.5–5 mg), “common” (5–15 mg) and “heavy” (15–30 mg) *(22)*. These data agree with the dose range of 4–12 mg reported in published summaries of online surveillance research *(17,23)*. Higher doses may be used; for example, the estimated flubromazepam dose in one fatal case of co-ingestion of flubrobromazepam and an opioid (U-47700) was 40 mg (based on measured blood concentrations of flubromazepam and its metabolites and knowledge of its pharmacokinetics, see section 4B) *(24)*. The basis for the information on typical recreational doses is not clear, and, given its anecdotal nature, caution is suggested in interpreting the data.

B Pharmacokinetics

Analysis of the pharmacokinetics of flubromazepam showed that, like other benzodiazepines, it is lipophilic (log $D_{7.4}$ = 2.87 ± 0.05), highly protein bound (96.4% ± 0.9), and has acid-base dissociation constants of 3.25 ± 0.10 (pK_a1) and 10.74 ± 0.05 (pK_a2) *(25)*. Its metabolism is extensive, with only small amounts of unmetabolized drug detectable in urine *(26)*. The major phase-I metabolites are monohydroxylated (3-hydroxyflubromazepam, hydroxyflubromazepam), debrominated (debromoflubromazepam) and monohydroxylated debrominated (debrominated 3-hydroxy-flubromazepam) compounds *(24,26–28)*, whereas the phase-II metabolites consisted of the glucuronides of the hydroxylated metabolites *(26)*.

Although reports that flubromazepam has a long half-life are consistent, estimates of the duration of the half-life vary. According to one online source, the onset of effects occurs 15–90 min after administration, the duration of action is 12–18 h, and the after-effects last for more than 36 h *(21)*. Other sources suggest that the effects of flubromazepam may last for up to 3 days *(18)*. The basis for the information is not clear. Laboratory studies of pharmacokinetics have reported an elimination half-life of 100–106 h *(18,26)*. A pattern of decreasing serum levels followed by increasing serum levels, with a plateau between 24–57 or 76 h and then a return to decreasing levels suggests enterohepatic circulation of flubromazepam, which may contribute to its long half-life *(23,26)*. It is not known whether its metabolites are psychoactive.

C Pharmacodynamics

Little information is available about the pharmacodynamics of flubromazepam. The results of a quantitative structure–activity relationship model indicate that the predicted binding value of flubromazepam for the GABA-A receptor, expressed as log 1/c, is 8.37 *(29)*. In comparison, the predicted log 1/c values for flubromazepam and midazolam are identical. Log 1/c is defined as the logarithm of the reciprocal of the IC_{50} for displacement of [^{3}H]-diazepam from rat cerebral cortex synaptosomes.

5 Toxicology

Little information was available on the toxicology of flubromazepam. A single published study of the cardiotoxicity of the compound found that flubromazepam impaired the viability of cardiomyocytes and inhibited hERG potassium channels in cell models *(30)*. In vivo, the compound increased the RR interval in rats (e.g., bradycardia) but did not affect QTc intervals. It also did not affect levels of PAK1 protein, a biomarker of cardiotoxicity.

6 Adverse reactions in humans

Measurable concentrations of flubromazepam have been found in post-mortem blood samples in several countries, including Australia *(31)*, Germany *(24)*, Norway *(32)*, the United Kingdom *(17)* and the USA *(33)*; however, other drugs were also detected in many cases, and the extent to which flubromazepam contributed to the deaths was not often specified. In cases in which clinical observation of the patient was possible, the symptoms included agitation, delirium, central nervous system depression, dilated pupils and tachycardia *(34,35)*. Flubromazepam has also been reported in blood samples from impaired drivers in Europe and the USA *(36–38)*. In these studies, the blood concentrations of flubromazepam were from 4.7 to 1200 ng/mL, and other chemicals were often present. While driver impairment was reported in one case (maximum flubromazepam concentration = 161 ng/mL), the driver also tested positive for several stimulants *(39)*. No or mild impairment has been reported in other cases *(34,36,37)*. In two cases, flubromazepam was the sole compound, with blood concentrations ranging from 7 to 600 ng/ml *(36)*.

Several sources have consolidated subjective reports from people who used flubromazepam *(16,17,23)*. At typical recreational doses, the common effects of flubromazepam included anxiolysis, euphoria, relaxation, increased confidence, muscle relaxation, empathy, confusion and amnesia. These self-reported experiences of use of flubromazepam should be considered anecdotal, as no analytical confirmation of sole use was obtained.

7 Dependence potential

A Studies in experimental animals

No information was found.

B Studies in humans

No information was found.

8 Abuse potential

A Studies in experimental animals

Conditioned place preference procedures are sometimes used to assess the rewarding effects of a drug according to the principles of classical conditioning.

Flubromazepam (0.1 mg/kg intraperitoneally) induced conditioned place preference (as compared with the vehicle) in male C57BL/6J mice in a three-compartment procedure *(30)*. At this dose, flubromazepam did not affect motor behaviour. A lower dose (0.01 mg/kg) did not significantly affect place preference. In the same study, flubromazepam (0.01 and 0.1 mg/kg/infusion) was assessed in a separate group of mice trained in an intravenous self-administration assay. Mice did not self-administer flubromazepam; however, the dosage may have been too low for adequate evaluation. For example, the training dose for diazepam self-administration in rodents is typically 0.5–2 mg/kg/infusion *(40)*.

Data on human use suggest that flubromazepam is only slightly less potent than diazepam (see section 4A).

B Studies in humans

No information was found.

9 Therapeutic applications and extent of therapeutic use and epidemiology of medical use

There are no known therapeutic uses for flubromazepam.

10 Listing on the WHO Model List of Essential Medicines

Flubromazepam is not listed on the 22nd WHO Model List of Essential Medicines or on the 8th WHO Model List of Essential Medicines for Children.

11 Marketing authorization (as a medicinal product)

Flubromazepam has no known marketing authorization.

12 Industrial use

Flubromazepam has no known use in industry.

13 Non-medical use, abuse and dependence

Although flubromazepam was first synthesized in the 1960s as part of medication development, it was never submitted for regulatory approval or brought to the legal drug market. In 2013, it appeared on the European recreational drug market, and its use quickly spread throughout Europe and to other areas of the world, including North America *(41,42)*. In addition to intentional use of flubromazepam for its benzodiazepine-like psychoactive effects (see section 6), some people have reported self-medication with flubromazepam for indications such as anxiety, to aid sleep and to offset the effects of stimulant use *(17,35)*. Flubromazepam has been detected only rarely as the sole analyte in

biological samples collected postmortem or pursuant to suspected intoxication while driving or upon clinical contact (e.g., emergency department admission). In some cases, flubromazepam is co-ingested because it is a constituent of a product that contains combinations of benzodiazepines (e.g. tablet, capsule, powder), including preparations falsely labelled as legal prescription drugs (e.g. alprazolam, diazepam) *(16)*. In other cases, the compound has been used in combination with drugs in other classes, including opioids and stimulants *(24,35,39)*.

The prevalence of chronic use and dependence of flubromazepam have not been reported. On online forums, one of the motivations mentioned for using flubromazepam is avoidance of withdrawal from other benzodiazepines *(17)*, perhaps because of its long half-life. These reports should be considered anecdotal, as no analytical confirmation of chronic use of flubromazepam (or its sole use) was reported.

14 Nature and magnitude of public health problems related to misuse, abuse and dependence

Since its emergence as a novel psychotropic substance in 2013, flubromazepam has been analytically confirmed in post-mortem samples as well as in samples collected from impaired drivers and emergency department admissions in several countries, including Australia *(31)*, Belgium *(39)*, Canada *(43)*, Germany *(24)*, Italy *(35)*, Norway *(36,37)*, Sweden *(44)*, the United Kingdom *(17,33)* and the USA *(38,42)*. It has also been detected in over 100 product samples submitted to laboratories in Wales and the USA *(15,16)*.

Between July 2016 and October 2021, 23 cases (four post-mortem) of analytically confirmed flubromazepam were reported to the Early Warning System Tox-Portal *(33)*. Flubromazepam was the only listed substance detected in 20 cases. In five nonfatal cases, flubromazepam was designated as contributory (medium) on the causality scale used in the system. Between March 2014 and June 2023, flubromazepam was the sole (or one of only a few) substance(s) detected in 88 samples analysed by Welsh authorities *(16)* and in 23 samples analysed by a laboratory based in the USA *(15)*. A substantial number of products were falsely labelled as approved prescription benzodiazepine (e.g., diazepam, alprazolam). Flubromazepam has also been detected in has been detected in infused paper/cards in post sent to prison inmates in Scotland *(45)*. Of the 475 samples containing novel benzodiazepines seized between February 2019 and January 2023, flubromazepam alone was identified in 34 samples and flubromazepam in combination with another novel benzodiazepine was found in an additional 63 samples. Samples included tablets and powder in the early part of the sampling period; however, visitation restriction during the Covid-19 pandemic was associated with increased formulation as infused paper/cards that were sent via the mail.

While flubromazepam has been associated with fatalities, intoxication while driving and clinical admissions, the extent to which it contributed to the negative health outcomes in these instances is uncertain. In most of the reported deaths, flubromazepam was only one of several substances identified in analysis of the biological sample(s) *(17,24,31,32)*. While impaired driving after use of flubromazepam has been reported, co-use with another

psychoactive substance is common, and only mild impairment was reported in a couple of cases in which flubromazepam was the sole or major substance detected *(36,37)*.

15 Licit production, consumption and international trade

No information was found.

16 Illicit manufacture and traffic and related information

In Europe, the first appearance of flubromazepam was in Sweden in 2013 *(41)*, while the first reports in the USA appeared in 2014 *(42,46)*. Between 2014 and 2018, flubromazepam use increased, with 99 cumulative detections and a peak of 57 detections in 2017 *(42)*. Between 2017 and 2021, the number of detections of flubromazepam in biological samples decreased, representing less than 1% of the total benzodiazepine detections *(38)*. In the last quarter of 2022, nine samples contained flubromazepam *(47)*.

Samples containing flubromazepam submitted to an anonymous testing site from 2016 to the present were received from Austria (n=1), China and other Asian countries (n=4) and the USA (n=11) *(15)*. As submission of samples was voluntary, the distribution of sites of origin may not represent the distribution or trafficking of flubromazepam in the world. Other countries in which flubromazepam has been detected include Australia *(31,33)*, Belgium *(39)*, Canada *(43)*, Germany *(24)*, Italy *(35)*, Norway *(36,37)*, Sweden *(18,44)* and the United Kingdom *(16,17,33)*.

17 Current international controls and their impact

Flubromazepam is not under current international control.

18 Current and past national controls

Flubromazepam is classified as a schedule IV substance under Canadian law and is regulated under psychoactive drug control regulations in Germany, the Russian Federation, Switzerland, Türkiye, the United Arab Emirates and the United Kingdom. Flubromazepam does not appear to be controlled under national regulations in other countries.

19 Other medical and scientific matters relevant for a recommendation on scheduling of the substance

No other matters were identified.

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