



**World Health
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Critical review report: Adinazolam

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Executive summary

Adinazolam [Chemical Abstracts Service registry No: 37115-32-5 (free base); 8-chloro-*N,N*-dimethyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-1-methanamine (ACI)] is a triazolobenzodiazepine that was originally developed as a candidate medication for anxiety and mood disorders but was never approved for use. The first documented detections of adinazolam on the recreational market were made in 2015 in Germany, Slovenia and Sweden. Since then, the compound has been detected in products or in biological samples in several other countries (Austria, Canada, China, Wales and the USA). Adinazolam is not under international control. It is classified as schedule IV under Canadian law and is controlled under psychoactive drug regulations in Germany and the United Kingdom.

When adinazolam was being considered for as a candidate medication, several studies were published on its pharmacokinetics in humans and its pharmacodynamics in humans and rodent models. Adinazolam is typically administered orally. After administration, it is almost completely metabolized to its primary hepatic metabolite, *N*-desmethylinazinolam (NDMAD). NDMAD has also been tested in humans and in animal models and found to have potent psychoactivity, suggesting that adinazolam is a prodrug. Clearance occurs via the kidneys. In vivo, adinazolam binds to the benzodiazepine receptor with moderate affinity but has negligible affinity for several other major receptors (e.g., histamine, serotonin, adrenergic norepinephrine, cholinergic or dopamine). It had anticonvulsant, anxiolytic and antidepressant properties in animal models, but studies in humans of its effectiveness as an antidepressant had mixed results. During a 6-week dosing regimen, adinazolam did not affect blood pressure, pulse or respiration, nor did it alter routine clinical laboratory values. Clinical studies revealed that adinazolam (and its metabolite *N*-desmethylinazinolam) induced dose-dependent decreases in psychomotor performance and increases in sedation and amnesia. An early study of recreational drug users revealed that adinazolam caused significant increases in items on the Addiction Research Center Inventory related to “mental high,” “physical high” and “street value” as compared with placebo. Virtually no information is available on user forums on its psychological effects.

Little information was available on fatal and non-fatal poisonings after analytically confirmed use of adinazolam. The presence of adinazolam in post-mortem blood samples has been confirmed analytically in three cases in the USA since April 2022; however, adinazolam was only one of several benzodiazepines present in the samples. An additional fatality was reported in Poland, but, again, the presence of other substances complicated determination of the extent to which adinazolam contributed to the death.

1. Substance identification

A. International Nonproprietary Name (INN)

Adinazolam

B. Chemical Abstracts Service registry number

37115-32-5 (free base)
57938-82-6 (methanesulfonate (1:1))
57561-75-8 (lithium salt)
867019-46-3 (carbonic acid, dilithium salt)

C. Other chemical names

Free base:

8-Chloro-*N,N*-dimethyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine-1-methanamine (ACI)
8-Chloro-1-[(dimethylamino)methyl]-6-phenyl-4*H*-s-triazolo[4,3-*a*][1,4]benzodiazepine
Adinazolam
U 41123

Methanesulfonate:

4*H*-[1,2,4]Triazolo[4,3-*a*][1,4]benzodiazepine-1-methanamine, 8-chloro-*N,N*-dimethyl-6-phenyl-, monomethanesulfonate (9CI)
Adinazolam mesylate
Adinazolam methanesulfonate
Adinazolam monomethanesulfonate
Deracyn
U 41123F

D. Trade names

The trade name Deracyn has been registered for adinazolam methanesulfonate, but the product has never been marketed.

E. Street names

Adinazolam is sold as tablets or powders under the chemical name Adinazolam.

Novel psychoactive substances (NPS) belonging to the benzodiazepines class can be purchased mainly on the online drug market under various street names, such as “legal benzodiazepines”, “designer benzodiazepines” and “research chemicals” (1).

F. Physical appearance

White or yellowish powder (2)

Adinazolam was identified in seized sample of white powder and in white tablets marked “D/CD” (1).

G. WHO review history

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

2. Chemistry

A. Chemical name

IUPAC name:

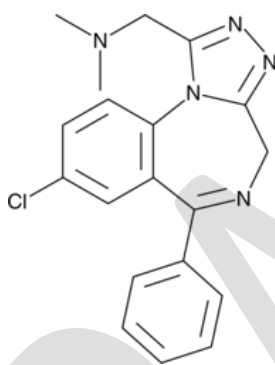
1-(8-Chloro-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin-1-yl)-*N,N*-dimethylmethanamine

Chemical Abstracts Index name:

4*H*-[1,2,4]Triazolo[4,3-*a*][1,4]benzodiazepine-1-methanamine, 8-chloro-*N,N*-dimethyl-6-phenyl- (9CI, ACI)

B. Chemical structure

Free base:



Molecular formula: C₁₉H₁₈ClN₅

Molecular weight: 351.83 g/mol

C. Stereoisomers

No stereoisomers of adinazolam have been described.

D. Methods and ease of illicit manufacture

Several synthetic procedures for the preparation of adinazolam have been reported in the literature since the early 1970s (e.g., 3–8).

A convenient synthesis would include introduction of a triazole ring into 1,4-benzodiazepine precursors, such as nordazepam, which are readily available as pure substances because of their pharmaceutical use. Alternatively, adinazolam can be prepared by cyclization of 2-amino-5-chlorobenzophenone with methyl 2-aminoacetate (9). Treatment of nordazepam with phosphorous pentasulfide gives 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-thione, and subsequent cycloaddition of *N,N*-dimethyl-acetyl hydrazine gives adinazolam free base (6).

A high-yielding one-step synthesis route for adinazolam involves the reaction of estazolam (a readily available marketed pharmaceutical substance) with dimethyl(methylene)ammonium chloride (a cheap, readily available marketed reagent) (10).

No information was available on the routes of synthesis used for the adinazolam products circulating on the market. All the syntheses reported in the literature, although simple, require the equipment of a chemical synthetic laboratory and qualified personnel.

E. Chemical properties

Melting-point

171–172.5 °C (7)

Boiling-point

No information was found.

Solubility

Soluble in dichloromethane and methanol (2).

The free base of adinazolam is insoluble in water, while the salt (mesylate) is soluble in water (> 100 mg/mL) (11).

F. Identification and analysis

Synthetic adinazolam was characterized by proton and carbon nuclear magnetic resonance (¹H NMR and ¹³C NMR), mass spectrometry (MS) and infra-red spectroscopy (IR) (10).

Adinazolam and two of its metabolites, α-hydroxy alprazolam and estazolam, are available as reference materials from commercial suppliers for routine analysis in forensic and clinical investigations (12).

Analytical methods for identification of adinazolam in seized sample matrices include gas chromatography (GC)-MS; GC-IR; liquid chromatography (LC)-MS, ionic chromatography, ¹H-NMR and ¹³C-NMR (2). Biological fluids have also been analysed by radioimmunoassay, fluorescence polarization immunoassay and enzyme immunoassay; however, presumptive detection by immunoassay must be confirmed with chromatographic techniques (13, 14). GC-MS and high-performance LC coupled with ultraviolet detection have been used for identification and quantification of adinazolam and its major metabolites in human liver microsomes and human urine and blood (13, 15, 16). Urine, serum and plasma samples were also analysed by LC coupled with either high-resolution MS or triple-quadrupole MS for quantification of adinazolam (17, 18). These platforms were also used to quantify adinazolam in post-mortem femoral blood and urine (19) and to assess adinazolam metabolism in human liver microsomes (20).

Two metabolites of adinazolam, estazolam and α-hydroxyalprazolam, are licensed benzodiazepines. In order to detect adinazolam use, both the parent drug and any metabolites should be assessed (13, 20, 21).

3. Ease of conversion into controlled substances

No information was found.

4. General pharmacology

A. Routes of administration and dosage

Adinazolam is usually administered orally, often in tablet or capsule form but sometimes as a powder (9, 22). Recreational dosages range from 5 to > 50 mg, the most common being 15–30 mg (9, 23). The onset of effects occurs within 10–25 min, while acute effects last 2–5 h and after-effects for up to 16 h (23). Adinazolam was tested at doses up to 90 mg/day (average, 50

mg/day) in controlled clinical trials when it was under consideration as a candidate antidepressant medication (24, 25).

B. Pharmacokinetics

Because adinazolam was originally investigated as a possible antidepressant with a novel site of action, studies were conducted to determine its pharmacokinetics. In humans, the bioavailability of adinazolam is estimated to be 40%, intestinal metabolism playing a significant role before hepatic metabolism (26, 27). After oral administration and absorption, adinazolam is quickly and almost completely metabolized to a primary metabolite, *N*-desmethyadinazolam (NDMAD) (26, 27), the isoenzyme CYP 3A4 playing a major role in its biotransformation (28). Psychoactivity was found to be more closely associated with plasma levels of NDMAD rather than of adinazolam, and the investigators suggested that adinazolam is actually a prodrug (27). Subsequent studies in which NDMAD was evaluated directly in humans support the earlier hypothesis that NDMAD is more potent than its parent compound (26, 29). NDMAD is subsequently metabolized to didesmethyladinazolam (DDMAD) (28); however, this metabolite is considered not to be clinically significant in mediating the behavioural effects of adinazolam. Consistent with identification of these metabolites after administration *in vivo*, NDMAD and DDMAD were also identified as primary metabolites of adinazolam in incubated pooled human liver microsomes (20). NDMAD is eliminated mainly via the renal route (28). The pharmacokinetics of adinazolam were as follows: volume of distribution (L), 106; elimination half-life (h), 2.9; and clearance (mL/min), 444 (27).

C. Pharmacodynamics

Adinazolam and NDMAD bind to benzodiazepine receptors, as measured by displacement of [³H]flunitrazepam ($k_i = 208$ and 6.96 nM, respectively) (30). Further, modelling predicted moderate binding affinity of adinazolam at the GABA_A receptor ($\log 1/c = 7.18$) (9). In contrast, adinazolam has negligible binding affinity for histamine H₁, muscarinic, α_1 - and α_2 -adrenergic, 5-HT_{1A}, 5-HT₂ or dopamine D₂ receptors (31, 32). *In vivo*, adinazolam was an effective, potent anticonvulsant in rodent models (30, 31) and suppressed increases in stress-induced plasma corticosteroid concentrations in rats, which was deemed indicative of anxiolytic activity (31). It was also effective in several rodent models of depression (31). The results of a voltammetry study in anaesthetized rats showed that adinazolam (10 mg/kg) significantly decreased hippocampal norepinephrine and serotonin release via a pre-synaptic mechanism, an effect that the author hypothesized is related to its putative antidepressant effects (33).

Adinazolam has been studied clinically for its potential therapeutic effects in the treatment of depression, anxiety and panic disorder (24, 25, 34, 35). While one study found that adinazolam was moderately effective as an antidepressant (24), another indicated that the antidepressant effect was transient and had dissipated by day 7 of a 6-week study (25). The US Food and Drug Administration has not issued regulatory approval for use of adinazolam in any therapeutic indication.

5. Toxicology

Although there have been no systematic studies of the toxicology of adinazolam, some of the clinical trials in which adinazolam pharmacokinetics was evaluated in healthy volunteers included measurement of physiological parameters. Acute oral doses of up to 50 mg adinazolam and its major metabolite NDMAD did not alter blood pressure, pulse or respiration, and neither substance substantially affected values in undefined "safety laboratory tests" (26). Furthermore, no abnormal

laboratory values were found in a clinical trial of individuals with depression given adinazolam for 6 weeks (average daily dose, 50 mg orally) (25). Oral and intravenous administration of either adinazolam or NDMAD was associated with decreased serum concentrations of uric acid, suggesting increased clearance of this substance (26, 36). Adinazolam given at 2.5 or 5 mg/kg to rats did not affect blood pressure or heart rate (37).

6. Adverse reactions in humans

Few user reports of recreational use of adinazolam are available, and most of the information on adverse reactions in humans is derived from controlled clinical trials of the drug and its major metabolite, NDMAD. The incidence of adverse effects after acute administration of adinazolam at doses up to 50 mg orally or 20 mg intravenously was consistently higher than in the placebo group (26, 36, 38), although the effects were usually mild or moderate. Sedation and drowsiness were the untoward effects most often mentioned.

One case report described a shift to mania in three individuals with bipolar disorder who were receiving adinazolam in a clinical trial (39); however, another study did not support this finding (24).

Several clinical trials included measurement of psychomotor and/or cognitive parameters, which indicated that adinazolam and NDMAD each induced dose-dependent decrements in psychomotor performance in card-sorting tasks and increased amnesia and sedation (26, 29, 38, 40).

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. Adinazolam (at 2 and 4 mg/kg) induced conditioned place preference (as compared with the vehicle) in male hooded Lister rats in a two-compartment procedure (41). No studies have been conducted of self-administration.

B. Studies in humans

Bird et al. (42) evaluated dependence on adinazolam (30 and 50 mg) in a double-blind placebo-controlled study with recreational drug users. Dependence was measured from items in the Addiction Research Center Inventory. Both doses of adinazolam induced significant increases in items related to “mental high” and “physical high”. The 50-mg dose also induced significant increases in “street value” over that with placebo. Adinazolam at 50 mg induced more physical and mental sedation than lorazepam (2–4 mg) or diazepam (20 mg), but it also induced greater “mental unpleasantness” than placebo up to 4 h after ingestion.

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

Although adinazolam was investigated as a putative antidepressant or anti-anxiety agent in early studies (24, 25), investigation of the compound was discontinued for unspecified reasons. There is no approved therapeutic use of adinazolam.

10. Listing on the WHO Model Lists of Essential Medicines

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

11. Marketing authorizations (as a medicinal product)

Adinazolam has no known marketing authorization.

12. Industrial use

Adinazolam has no known industrial use.

13. Non-medical use, abuse and dependence

Adinazolam appeared on the European recreational drug market in 2015 in Germany, Slovenia and Sweden (1, 9). Adinazolam has been detected in formulations containing combinations of benzodiazepines (e.g., tablets, capsules, powders), including falsified pharmaceutical preparations labelled as a legal prescription drugs (e.g., "Xanax") (22). Little information on its non-medical use is available, and it is rarely mentioned in online forums on substance use.

No information was available on the prevalence of chronic use or dependence on adinazolam.

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

Little information is available on fatal and non-fatal poisonings with analytically confirmed use of adinazolam. Investigators in Poland described a fatality in which a woman ingested adinazolam in combination with opioids and a selective serotonin reuptake inhibitor (13). The concentrations of adinazolam in post-mortem blood and urine samples were 18.0 and 82.1 ng/mL, respectively. The role of adinazolam in her death is unknown, although the authors speculated that the combination of adinazolam (a benzodiazepine) and U-47700 (an opioid) may have contributed. In the USA, three fatal cases have been reported since April 2022 in which adinazolam was detected in post-mortem blood samples; however, as adinazolam was only one of several benzodiazepines present in the samples, its contribution to the deaths cannot be determined (43).

15. Licit production, consumption and international trade

No information was available.

16. Illicit manufacture and traffic and related information

The first documented seizure of adinazolam in Europe was in Germany in 2015, which was followed shortly thereafter by detection in samples collected in Slovenia and Sweden (1, 9). Samples containing adinazolam that were submitted to an anonymous testing site (since 2019) were received from Austria (n=1), China (n=1) and the USA (n=4) (22). As submission of samples was voluntary, the distribution of sites is not expected to be representative of the distribution or trafficking of adinazolam in the world. Between January 2021 and March 2022, adinazolam was also detected in 19 samples submitted to the Welsh Emerging Drugs and Identification of Novel Substances Project (44). In Canada, adinazolam was detected in seized samples (tablets) that “appeared to be Xanax” (45).

17. Current international controls and their impact

There is no current international control of adinazolam.

18. Current and past national controls

Adinazolam is classified as a schedule IV substance under Canadian law and is regulated under psychoactive drug control regulations in Germany and the United Kingdom. It does not appear to be controlled under national regulations in other countries.

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

No information was available.

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