



## Therapeutic Efficacy of Nitrazepam

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### ABSTRACT

Chemically referred to as 1,3-dihydro-1-nitro-2-oxo-5-phenyl-2H-1,4-benzodiazepine-2-one, nitrazepam (NTZ) is a hypnotic agent that is part of the benzodiazepine class and has been used to treat disorders related to stress. According to the British Pharmacopoeia, non-aqueous titrimetry is the accepted method for determining it. The assay of NTZ in pharmaceutical formulations has been reported using a number of additional techniques based on HPLC, complexometry with cadmium-2-methyl-5-nitrobenzenesulphonate, and derivative UV spectrophotometry. Some of these methods involve different manipulation steps and are not straightforward for routine pharmaceutical formulation analysis. Spectrophotometric techniques are still widely used for the estimation of therapeutics in both pure and dosage forms because they are thought to be a very practical and economical method. In the current work, orcinol is used as the coupling agent in the development and optimization of spectrophotometric techniques based on the diazo-coupling reaction. For the purpose of determining nitrazepam in both pure and pharmaceutical formulations, the developed methods are straightforward, sensitive, and accurate.

**Keywords:** Nitrazepam, HPLC, UV, titrimetry, cadmium-2-methyl-5-nitrobenzenesulphonate.

### Introduction

Nitrazepam is a 1,4-benzodiazepinone with nitro and phenyl groups substituted at positions 5 and 7, respectively. It is also known as 1,3-dihydro-2H-1,4-benzodiazepin-2-one. It is used as a hypnotic to treat infants' epileptic spasms (West's syndrome) and to temporarily manage insomnia. It is used to treat severe, incapacitating anxiety and insomnia in the short term. In addition, it contains skeletal muscle relaxant, anticonvulsant, amnesic (caused to forget), and sedative (calming) qualities. One class of benzodiazepine medication is nitrazepam. Both the amount of time needed to fall asleep and the length of sleep are shortened by nitrazepam. Additionally, it helps control myoclonic seizures.



Figure 1: Mogadon tablets

## Structure of Nitrazepam

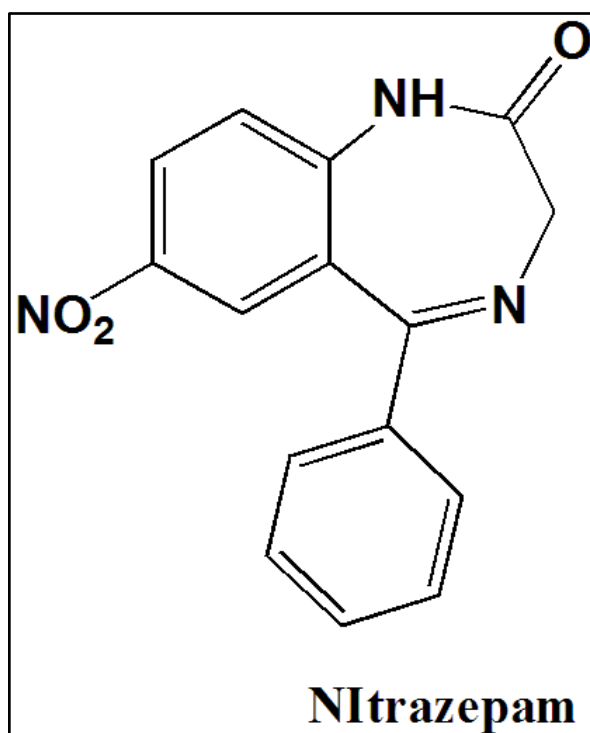


Figure 2: Structure of Nitrazepam

## Physiochemical Properties

S. NO.	PHYSICAL AND CHEMICAL PROPERTIES	
1	Molecular weight	281.27 g/mol
2	Physical appearance	Solid
3	Melting point	225°C
4	Octanol/water partition coefficient	2.25
5	Solubility	>42.2 [ug/mL]
7	Number of chiral centers	Not present

## Structural Active Relationship

1. In order to bind with derivatives of 5-phenyl-1,4-benzodiazepin-2-one, Ring A needs to have an aromatic or heteroaromatic ring.
2. When using heterocycles as ring A, the drug's pharmacological activity is low.
3. Ring B requires a proton-accepting group in order to bind with GABAA.
4. Maximum activity is noted when the proton-accepting group is present on ring B's 2-position and in coplanar spatial orientation with ring A.
5. The selectivity for binding with GABA BZR subpopulations is altered when sulfur is substituted for oxygen in ring B, but the anxiolytic properties remain unaltered.
6. The agonist activity is unaffected, but when the ring B's imine nitrogen or methylene 3-position is substituted, the antagonist activity falls.
7. The 3-hydroxy derivatives are quickly eliminated from the body.
8. The presence of 4-position nitrogen and the 4,5-double bond is not necessary for anxiolytic activity.
9. If a C=N bond is swapped out for a C-N bond, the BZR affinity is reduced.
10. The binding with BZR does not require the presence of 5-phenyl ring C.

11. When substitution occurs at the ortho position, the drug's agonist property remains unchanged.

### Method of Synthesis

i. 2-Amino-5-nitrophenyl(phenyl) methanone is produced by the condensation of nitroaniline, benzoyl chloride, and zinc chloride.

ii. A compound is created when 2-chloroacetyl chloride reacts with ammonia, and then that compound reacts with tosyl hydroxide to produce nitrazepam.

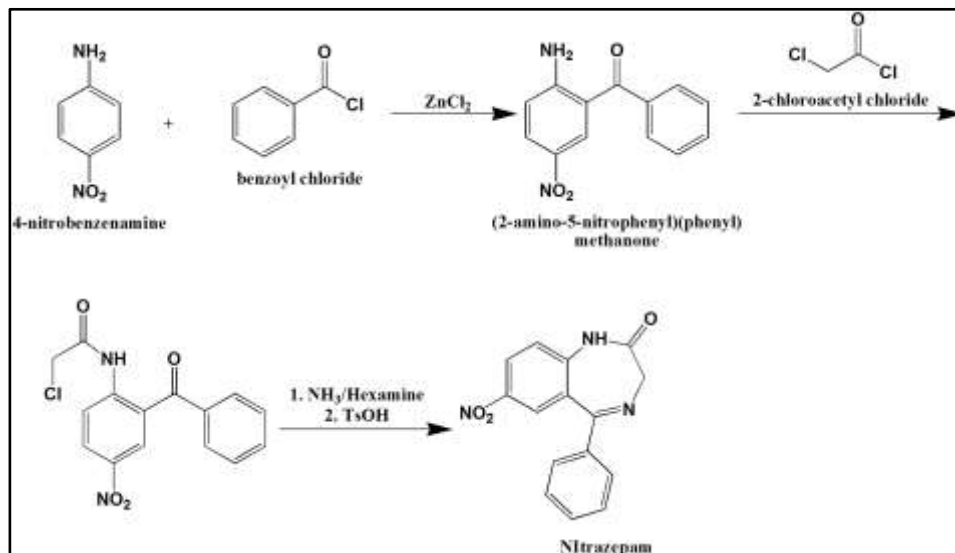


Figure 3: Method of synthesis of Nitrazepam

### Medical Uses

Short-term sleep issues (insomnia) such as trouble falling asleep, frequent awakenings, early awakenings, or a combination of these are treated with nitrazepam.

When other medications are ineffective, nitrazepam is occasionally used to treat epilepsy. In treating West syndrome, an age-dependent epilepsy that affects the very young, it has been found to be more successful than clonazepam.

Nitrazepam is sometimes used as a last resort after other anti-seizure medications have failed because it has demonstrated efficacy in treating infantile spasms in uncontrolled studies. However, long-term treatment usually results in drowsiness, hypotonia, and most importantly, tolerance to anti-seizure effects, which limits the use of nitrazepam.

### Side Effects

#### More common

Central nervous system depression, which can manifest as sleepiness, vertigo, headaches, fatigue, ataxia, depression, impaired memory, impaired motor functions, a "hangover" feeling in the morning, slurred speech, and decreased physical performance are among the more frequent side effects that may occur. There have been reports of inattention, muscle weakness, double vision, diminished alertness, and numbed emotions. There have also been reports of rebound insomnia and unpleasant dreams. With an elimination half-life ranging from 15 to 38 hours (mean elimination half-life of 26 hours), nitrazepam is a long-acting benzodiazepine.[13] After taking nitrazepam at night, users may experience "hangover" effects the next day, including drowsiness and impaired psychomotor and cognitive abilities. These effects can make it difficult for users to drive safely and raise the risk of hip fractures and falls.

#### Less common

Hypotension, palpitations, rash or pruritus, gastrointestinal problems, and changes in libido are less frequent side effects that may occur. There have also been reports of headache, hypothermia, delirium tremens, retrograde amnesia, depression or increased dreaming, disorientation, and severe sedation.

#### Contraindications

Patients with chronic obstructive pulmonary disease (COPD) should not take nitrazepam, especially if they are experiencing an acute exacerbation of the disease, as hypnotics may cause serious respiratory depression. Similar to other hypnotic medications, nitrazepam raises the possibility of getting into a car accident. In a study evaluating the driving abilities of sedative hypnotists, it was discovered that nitrazepam users exhibited significant impairments

in driving skills up to 17 hours after dosing, while temazepam users did not exhibit any significant impairments in driving ability. These outcomes demonstrate how long-acting nitrazepam is.

### Pharmacology

Nitrazepam is lipophilic, has a long half-life, and is metabolized hepatically through oxidative pathways. It increases the binding of GABA to GABA<sub>A</sub> receptors by acting on benzodiazepine receptors in the brain, which are connected to GABA receptors. Major inhibitory neurotransmitter GABA slows down the central nervous system and is responsible for promoting sleep, relaxing muscles, controlling anxiety, and causing seizures. The effects of nitrazepam and zopiclone, two z-drugs used to treat insomnia, are comparable. It's possible that nitrazepam and other benzodiazepines' ability to bind to voltage-dependent sodium channels rather than benzodiazepine receptors is what gives them their anticonvulsant qualities. In mouse spinal cord cell cultures, benzodiazepines appear to limit sustained repetitive firing by slowing sodium channel recovery from inactivation. Inhibiting polysynaptic pathways in the spinal cord of decerebrate cats is how nitrazepam produces its muscle-relaxing effects. It fully agonistically interacts with the benzodiazepine receptor. Some of the pharmacological characteristics of nitrazepam in rats may be influenced by the endogenous opioid system. The mouse brain's cerebral glycine and alanine contents decrease when nitrazepam is administered. Benzodiazepine receptor activation may be the cause of the decline. When nitrazepam is administered at high doses, it reduces the turnover of histamine in the mouse brain by acting on the benzodiazepine-GABA receptor complex. Human cortisol suppression has been observed with nitrazepam. It is an agonist of the peripheral-type benzodiazepine receptors present in rat neuroblastoma cells as well as the central benzodiazepine receptors.

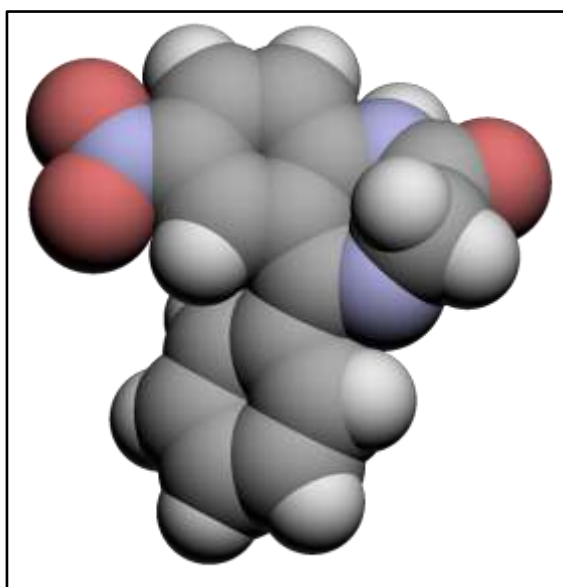


Figure 4: Docking of Nitrazepam

### Pharmacokinetics

Plasma proteins bind nitrazepam primarily. Nitrazepam is one of the lipid-soluble, highly cerebrally absorbed benzodiazepines.<sup>(90)</sup> Nitrazepam takes approximately two hours (0.5 to five hours) to reach peak plasma concentrations after oral administration. Nitrazepam has a half-life of 16.5 to 48.3 hours. Nitrazepam has a half-life of approximately 29 hours in young adults and 40 hours in elderly people. Human growth hormone levels are markedly elevated by nitrazepam at both low and high dosages (5 mg and 10 mg, respectively). The 68-hour half-life of nitrazepam in the cerebrospinal fluid suggests that the drug is removed from the fluid incredibly slowly. The bioavailability and rate of absorption of nitrazepam are unaffected by concurrent food consumption. Nitrazepam can therefore be taken with or without food.

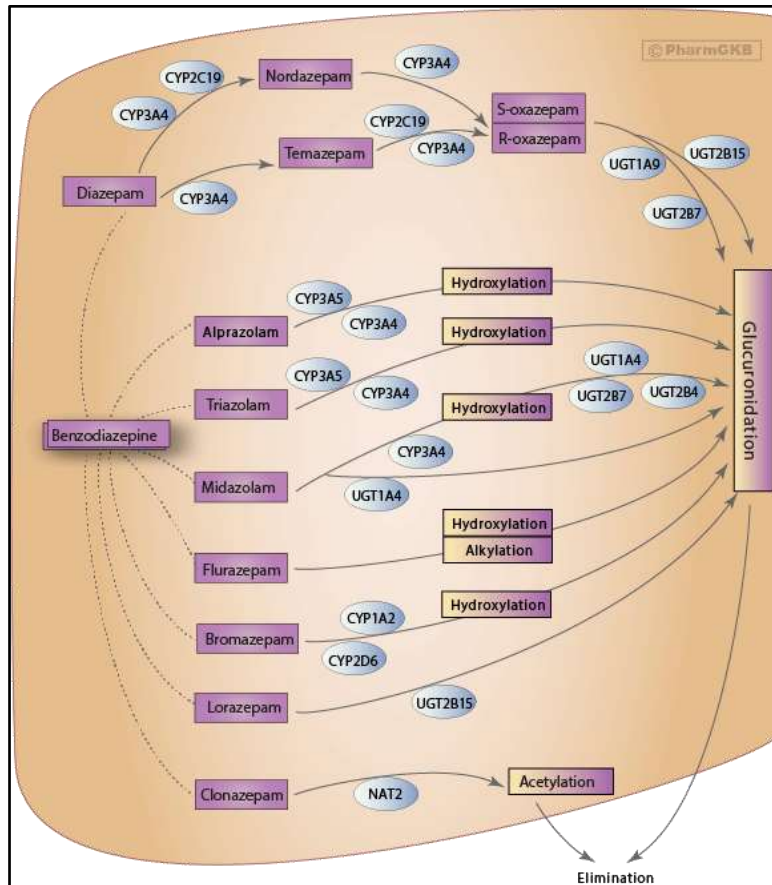


Figure 5: Nitrazepam pathway

**Metabolism**

The metabolites of nitrazepam in man and rat is shown in Figure 6 with the exception of substance IV, which was described by Beyer and Sadee, and substance X, which is still hypothetical, the other compounds listed have been proved by Rieder and Wendt to be biotransformation products of the drug appearing in the urine. They have been isolated by various procedures of extraction, column chromatography, and thin-layer chromatography, and their chemical structure has been elucidated by chemical reactions, comparison with authentic samples, mass spectrometry, nuclear magnetic resonance spectrometry, and in the cases of II and III, also by ultraviolet and infrared spectrometry. The main metabolic pathway in man and rats indicates (V) the reduction of the nitro group to the corresponding amino II and by acetylation of II-two the VII acetamide derivative III, which is the major metabolite. A small proportion of II and III is hydroxylated in position III yielding compounds IV and V.

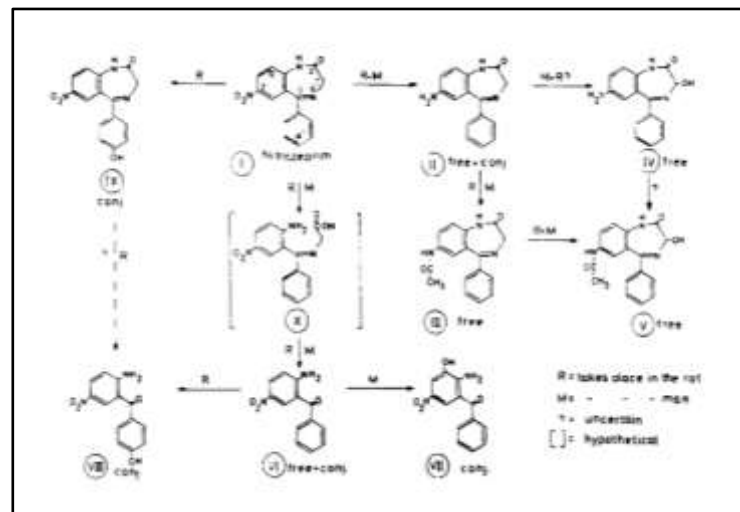


Figure 6: Metabolism of Nitrazepam

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### Precautions

When treating patients who have a history of substance or alcohol abuse, benzodiazepines should be used very cautiously. Elderly patients should be prescribed the lowest effective dose that is feasible. Elderly people who are given excessively strong sedation run the risk of unintentional events like falls. If, despite treatment, the insomnia does not go away after 7–10 days, there may be a primary mental health condition, a physical illness, or a misperception of the sleep state. An undiagnosed mental or physical illness may be the cause of worsening insomnia or the appearance of new abnormalities in thinking or behavior. Moreover, it has been noted that these anomalies are related to the use of medications that block benzodiazepine receptors. Patients who have previously shown paradoxical reactions to alcohol and/or sedative medications should use nitrazepam with caution.

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### Drug abuse and withdrawal

When benzodiazepines are abruptly stopped, withdrawal symptoms have been observed. These symptoms are similar to those associated with alcohol and barbiturates and include convulsions, tremors, abdominal and muscle cramps, vomiting, sweating, dysphoria, perceptual disturbances, insomnia, headache, extreme anxiety, tension, restlessness, confusion, and irritability. Nitrazepam withdrawal symptoms may also occur. Derealization, depersonalization, hyperacusis, numbness and tingling in the extremities, hypersensitivity to light, sound, and physical contact, hallucinations, and epileptic seizures are possible symptoms in severe cases. Higher dosages and prolonged usage are typically linked to more severe symptoms; however, patients receiving therapeutic dosages for as little as one to two weeks may also experience withdrawal symptoms, such as anxiety during the day in between doses. Patients who have experienced seizures in the past should pay special attention to the tapering recommendation. Patients with significant personality disorders, alcoholism, or drug abuse in the past are more likely to develop dependence. If giving nitrazepam to these people is absolutely necessary, care must be taken.

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### Conclusion

Nitrazepam is a highly potent sedative that can be used as an anti-psychotic drug. The synthesis method is much easier and is easily producible.

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