

## RESEARCH MONOGRAPH . COMPOUND PROFILE

# Tofisopam

*A 2,3-benzodiazepine without classical GABA-A activity; a non-sedating anxiolytic marketed in Europe.*

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| AUTHOR         | Kodiac bioLabs Research                |
| COMPOUND CLASS | 2,3-benzodiazepine atypical anxiolytic |

## ABSTRACT

Tofisopam (1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine; CAS 22345-47-7; molecular formula C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>; molecular weight 382.46) is a 2,3-benzodiazepine developed at EGIS (Hungary) in the 1960s and approved in Hungary, France, and other European and Asian markets under the trade name Grandaxin. Distinct from the 1,4-benzodiazepine class (diazepam, lorazepam, etc.) by the position of the nitrogens in the diazepine ring: the 2,3 isomer does not bind the classical benzodiazepine site on GABA-A receptors and lacks the GABA-A-mediated sedation, anxiolysis, and dependence of conventional benzodiazepines. The mechanism is incompletely characterized; possibilities include phosphodiesterase IV inhibition and modulation of dopaminergic signaling. Plasma half-life is approximately 6 to 8 hours; metabolism is hepatic. Approved indications in markets where registered include anxiety disorders, autonomic instability, and post-stress recovery; off-label use in fatigue and reactive depression. Not approved in the US. Used as a reference 2,3-benzodiazepine.

# 1. 1. Compound Identification

**Tofisopam** is described as 2,3-benzodiazepine atypical anxiolytic. A 2,3-benzodiazepine without classical GABA-A activity; a non-sedating anxiolytic marketed in Europe.

## 1.1. 1.1 Class summary

2,3-benzodiazepine atypical anxiolytic

## 1.2. 1.2 Subtitle

A 2,3-benzodiazepine without classical GABA-A activity; a non-sedating anxiolytic marketed in Europe.

## 2. 2. Abstract

Tofisopam (1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3-benzodiazepine; CAS 22345-47-7; molecular formula C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>; molecular weight 382.46) is a 2,3-benzodiazepine developed at EGIS (Hungary) in the 1960s and approved in Hungary, France, and other European and Asian markets under the trade name Grandaxin. Distinct from the 1,4-benzodiazepine class (diazepam, lorazepam, etc.) by the position of the nitrogens in the diazepine ring: the 2,3 isomer does not bind the classical benzodiazepine site on GABA-A receptors and lacks the GABA-A-mediated sedation, anxiolysis, and dependence of conventional benzodiazepines. The mechanism is incompletely characterized; possibilities include phosphodiesterase IV inhibition and modulation of dopaminergic signaling. Plasma half-life is approximately 6 to 8 hours; metabolism is hepatic. Approved indications in markets where registered include anxiety disorders, autonomic instability, and post-stress recovery; off-label use in fatigue and reactive depression. Not approved in the US. Used as a reference 2,3-benzodiazepine.

### 3. Mechanism of Action

2,3-benzodiazepine; does not bind the classical GABA-A benzodiazepine site. Mechanism incompletely characterized; possible PDE IV inhibition and dopaminergic modulation.

The mechanistic profile described above represents the consensus position from peer-reviewed literature where available; for compounds with sparse formal characterization, this section reflects vendor-grade reports and structurally-related class pharmacology and should be interpreted with appropriate caution.

## 4. 4. Pharmacokinetics and Routes of Administration

Pharmacokinetic data are summarized within the abstract for compounds with formal Phase 1 records. Compounds without published human pharmacokinetic studies are noted as such; investigators should treat the absence of data as a research limitation.

## 5. 5. Reported Research Dose Ranges

Clinical 50 to 300 mg per oral administration daily, in divided doses. Rodent studies 5 to 50 mg/kg/day.

Doses are scaled from clinical use where the compound is approved as a medicine, from Phase 2/3 trials where development advanced, or from rodent dose-response data scaled by allometric assumptions where the compound has no human clinical record. Investigators should treat dose ranges from research-chemical-grade vendors as starting points for their own pharmacokinetic and tolerability characterization rather than validated dosing recommendations.

## 6. Sourcing and Quality Verification

Investigators should obtain analytical confirmation of identity (mass spectrometry; for peptides, additionally amino acid analysis or N-terminal sequencing) and purity (HPLC area-percent, ideally greater than 95 percent) on every lot. Vendor certificates of analysis vary in quality; third-party analytical confirmation through independent laboratories (e.g., Janoshik Analytical, Anabolic Lab) is the gold standard for research-grade peptides and small molecules.

For compounds with established pharmaceutical-grade marketing in any jurisdiction, sourcing from the marketed product (where legal and accessible) provides the highest quality assurance.

## 7. 7. Reconstitution and Handling

Peptides should be reconstituted in bacteriostatic water or sterile water for injection in the volume appropriate to the desired concentration; lyophilized peptides should be allowed to come to room temperature before reconstitution to minimize precipitation. Reconstituted peptides should be stored refrigerated and used within the timeframe specified by the manufacturer (typically 14 to 30 days for bacteriostatic water reconstitutions, shorter for sterile water).

Small molecules: storage conditions vary by compound; consult the certificate of analysis for the specific product. Most are stable at room temperature in dry, dark conditions; oxidation-sensitive compounds (e.g., catecholamine precursors) require cool storage and protection from light.

## 8. 8. Stack Interaction Considerations

Investigators combining this compound with other research substances should consider receptor-level interactions (additive effects at shared targets), enzyme-level interactions (CYP-mediated drug-drug interactions where applicable), and pharmacodynamic interactions (additive sedation, additive serotonergic activity, additive hemodynamic effects).

The stack interaction section in published monographs of well-characterized compounds is necessarily incomplete for any specific combination; investigators should treat novel combinations with elevated caution and titrate gradually.

## 9. 9. References

1. Petocz L. The pharmacological profile of tofisopam. Pol J Pharmacol Pharm 1993.
2. Rundfeldt C, et al. Tofisopam: a non-sedative benzodiazepine. CNS Drug Rev 2005.
3. Saletu B, et al. EEG mapping in patients with anxiety: tofisopam. Neuropsychobiology 1990.

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