OPEN ACCESS **Scientific** Letters

IV 1H-TOXRUN INTERNATIONAL CONGRESS 2025 | 08-09 MAY, 2025 Porto, Portugal

*Poster 49*

# Cebranopadol, a first-in-class investigational opioid: Insights from preliminary cytotoxicity assays

**Margarida Almeida [1,ǂ], Beatriz Diogo [1,ǂ], Joana Rocha [1,ǂ], Ricardo Jorge Dinis-Oliveira [1,2,3,4,5], Andrea Cunha [1,6], Juliana Faria [1,2,3,*] and Joana Barbosa [1,2,3]**

[1] University Institute of Health Sciences (1H-TOXRUN, IUCS-CESPU), 4585-116 Gandra, Portugal.
[2] UCIBIO - Applied Molecular Biosciences Unit, Translational Toxicology Research Laboratory, University Institute of Health Sciences (1H-TOXRUN, IUCS-CESPU), 4585-116 Gandra, Portugal.
[3] Associate Laboratory i4HB - Institute for Health and Bioeconomy, University Institute of Health Sciences - CESPU, 4585-116 Gandra, Portugal.
[4] Department of Public Health and Forensic Sciences, and Medical Education, Faculty of Medicine, University of Porto, 4200-319 Porto, Portugal.
[5] FOREN – Forensic Science Experts, 1400-136 Lisboa, Portugal.
[6] UNIPRO, Oral Pathology and Rehabilitation Research Unit, University Institute of Health Sciences-CESPU (IUCS-CESPU), 4585-116 Gandra, Portugal.
[ǂ] these authors contributed equally to this work

* Correspondence: juliana.faria@iucs.cespu.pt

## Abstract

**Background:** Cebranopadol, a promising opioid analgesic undergoing phase III trials, was developed for the treatment of acute and chronic moderate-to-severe pain. Because it is a non-selective ligand acting at more than one member of the opioid receptor family, combining a dual agonist action on mu-, delta-, and kappa-opioid receptors (MOR, DOR, and KOR) and nociceptin/orphanin FQ peptide (NOP) receptors, it has improved efficacy and tolerability over currently available prescription opioids [1,2]. The combined NOP and opioid receptor agonism make cebranopadol a potent analgesic for neuropathic and nociceptive pain, with an optimized safety profile, no significant side effects, and low tolerance and abuse potential [1,3]. Due to the novelty of this molecule, there are very few studies on its toxicological and cytotoxic potential. In this context, this study evaluated cebranopadol cytotoxicity in different cell lines representative of its metabolizing and target tissues. **Objective:** The present study aimed to assess the cytotoxicity profile of cebranopadol in three different cell lines: BV-2 (murine microglia), HepG2 (human hepatocellular carcinoma), and SH-SY5Y (human neuroblastoma). **Methods:** BV-2, HepG2, and SH-SY5Y cells were exposed to increasing cebranopadol concentrations (up to 2.64 μM) for 48 hours and assayed for cytotoxicity through the sulforhodamine B (SRB) assay, whereby the $IC_{50}$ value was determined for each cell line. **Results:** Cebranopadol was found to inhibit HepG2 and SH-SY5Y cell growth with $IC_{50}$ values of 1.81 ± 0.08 μM and 2.28 ± 0.07 μM, respectively; as for BV-2 cells, there was no growth inhibition within the concentration range tested ($IC_{50}$ > 2.64 μM). These values are above the therapeutic concentration range reported for humans [2], supporting cebranopadol safety when used as prescribed. Cytotoxicity may arise in overdose situations. **Conclusions:** The results add information on cebranopadol effects on hepatic and central nervous system cells, demonstrating cell line-dependent sensitivity and low cytotoxicity potential, and corroborating its safety as an alternative therapeutic option for pain control. Metabolic and molecular studies are needed to fully clarify its effects at therapeutic and supratherapeutic concentrations.

**Keywords:** cebranopadol; cytotoxicity; prescription opioids

### Acknowledgments/Funding

This research was funded by Cooperativa de Ensino Superior Politécnico e Universitário (CESPU), project/grant NToxAtOpi_GI2-CESPU-2023.

### References

1. Ziemichod, W. et al. Cebranopadol as a novel promising agent for the treatment of pain. *Molecules* **2022**, *27*, 3987, doi:10.3390/molecules27133987.
2. Kleideiter, E. et al. Clinical pharmacokinetic characteristics of cebranopadol, a novel first-in-class analgesic. *Clin Pharmacokinet* **2018**, *57*, 31-50, doi:10.1007/s40262-017-0545-1.

3. Cannella, N. et al. Cebranopadol, a novel long-acting opioid agonist with low abuse liability, to treat opioid use disorder: Preclinical evidence of efficacy. *Neuropharmacology* **2024**, *257*, 110048, doi:10.1016/j.neuropharm.2024.110048.