

Comparative hepatotoxicity of next-gen kinase inhibitors in 3D liver microtissues

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Abstract

We compare hepatotoxicity profiles of several next-generation kinase inhibitors using 3D liver microtissues. Using viability assays, functional readouts and high-content imaging, we identify compound-dependent effects and propose a tiered approach for early screening.

Keywords: toxicology; hepatotoxicity; PFAS; high-content imaging; open pipelines

Introduction

Drug-induced liver injury remains a major contributor to drug attrition. 3D microtissues better replicate liver microarchitecture and metabolic competency than 2D cultures. Here we evaluate multiple kinase inhibitors with a standardized 3D platform.

Methods

3D spheroid cultures were prepared from primary human hepatocytes and non-parenchymal support cells. Compounds were dosed at multiple concentrations for 72 hours. Endpoints included ATP viability, albumin secretion, CYP activity and high-content image features. Data were analyzed using standard statistical tests and dose–response modeling.

Sample	N	Mean	SD
Control	10	0.12	0.03
Low Dose	10	0.18	0.04
High Dose	10	0.45	0.10

Results

Across tested compounds, we observed diverging toxicity signatures: Compound A showed early loss of ATP with mitochondrial phenotypes, while Compound B displayed delayed reductions in albumin secretion. Dose–response modeling yielded IC50 estimates and a rank order of hepatotoxic potency.

Discussion

These results showcase the utility of 3D microtissues for early hepatotoxicity profiling and support integration of multi-endpoint data to reduce false negatives/positives in lead selection.

Conclusion

This illustrative study demonstrates representative reporting structure, sample results and open methods for reproducibility. The content is synthetic and intended for demo/testing purposes only.

References

1. Smith J. et al. 3D hepatic models for preclinical safety. Toxicol Sci. 2022.
2. Johnson K. & Lee M. High-content imaging in hepatotoxicity screening. ALTox. 2020.

