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Development of the metabolic pathway scheme of a novel anticonvulsant based on the results of metabolic study in human liver microsomes

Anastasiia Demko[1]*, Hanna Severina[1], Tiina Sikanen[2], Päivi Järvinen[2], Victoriya Georgiyants[1]

[1]*National University of Pharmacy, 53 Hryhoriia Skovoroda St., 61002 Kharkiv, Ukraine*
[2] *University of Helsinki, Yliopistonkatu 4, 00100 Helsinki, Finland*
**Corresponding author e-mail: demkoanastasiia@gmail.com*

Introduction. The examination of metabolic pathways for novel pharmacologically active compounds is an essential phase in their preclinical safety and efficacy assessment. This study aimed to identify the primary metabolic transformation routes of the promising anticonvulsant 2-(2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-N-[(2,4-dichlorophenyl)methyl]acetamide (MaIO 168) within the human liver microsomal (HLM) system.

Materials and methods. Incubation studies of MaIO 168 were conducted in HLM, both with and without the cofactors NADPH and UDPGA, and under benzil-mediated inhibition to evaluate the contribution of individual metabolic pathways. The experimental data were integrated and the metabolic pathway scheme was constructed using KingDrawHD software.

Results and discussion. With both cofactors present, MaIO 168 exhibited a gradual and stable decrease in concentration, indicative of a moderate metabolic conversion rate. In the absence of cofactors, the compound remained stable, confirming no nonspecific binding to microsomal proteins. Incubations with benzil demonstrated significantly more intensive metabolism with NADPH alone compared to UDPGA alone, suggesting a predominant oxidative pathway mediated by cytochrome P450 (CYP) isoenzymes, with glucuronidation playing a minor role.

Based on the acquired data, a generalized metabolic pathway for MaIO 168 was proposed (Fig. 1), identifying oxidative hydroxylation as the primary biotransformation route, followed by hydrolysis and O-glucuronidation. Dehalogenation of halogen-substituted fragments, typical for similar CYP-mediated transformations, may also occur as a secondary pathway.

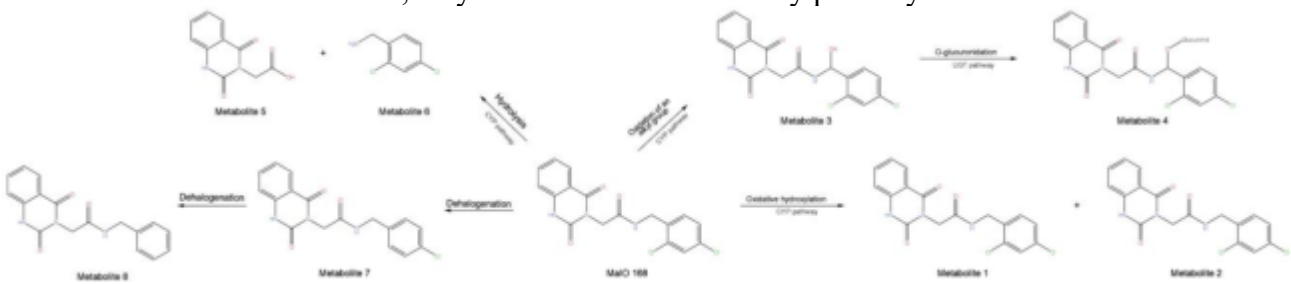

Figure 1

Conclusions. MaIO 168 demonstrates moderate metabolic stability, with biotransformation occurring predominantly via oxidative pathways facilitated by CYP450 enzymes. This proposed metabolic scheme enhances our comprehension of the compound's metabolic destiny in humans and establishes a foundation for subsequent pharmacokinetic and toxicological studies.

References

1. El Kayal WM, Shtrygol SY, Zalevskyi SV, Shark AA, Tsyvunin VV, Kovalenko SM, et al. Synthesis, in vivo and in silico anticonvulsant activity studies of new derivatives of 2-(2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)acetamide. Eur J Med Chem. 2019;180:134-42.