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Abstract

Metabolism of Cathinones in Functional Hepatocyte-like Cells Derived from Human Neonatal Mesenchymal Stem Cells: An Enantioselectivity Approach †

Barbara Silva [1,2,*], Joana Saraiva Rodrigues [3], Joana Paiva Miranda [3], Ana Sofia Almeida [1,2,4], Carla Fernandes [2,4], Paula Guedes de Pinho [1] and Fernando Remião [1]

1 UCIBIO-REQUIMTE, Laboratório Associado i4HB—Instituto de Saúde e Bioeconomia, Laboratório de Toxicologia, Departamento de Ciências Biológicas, Faculdade de Farmácia, Universidade do Porto, Rua Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal
2 Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, Rua de Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal
3 Instituto de Investigação do Medicamento (iMed.ULisboa), Faculdade de Farmácia, Universidade de Lisboa, Avenida Professor Gama Pinto, 1649-003 Lisboa, Portugal
4 Centro Interdisciplinar de Investigação Marinha e Ambiental (CIIMAR), Universidade do Porto, Avenida General Norton de Matos, 4450-208 Matosinhos, Portugal
* Correspondence: barbarapolerisilva@gmail.com
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Abstract: Liver damage is a common issue associated with synthetic cathinones abuse. Indeed, human stem cell-derived hepatocyte-like cells (HLCs) have been used as alternative *in vitro* models for hepatotoxicity studies, due to their ability to maintain a stable hepatic-specific phenotype. Furthermore, all cathinone derivatives are chiral, and their biological effects can differ for each enantiomer. Thus, the aim of this work was to evaluate the cytotoxicity and metabolism of pentedrone and methylone enantiomers using HLC models. Human neonatal mesenchymal stem cells were differentiated into HLCs by a three-step differentiation protocol and maintained under 2D and 3D culture conditions. Subsequently, pentedrone and methylone enantiomers were isolated by HPLC using a chiral stationary phase. Cell viability was evaluated through the CellTiter-Glo assay and the formation of methylone and pentedrone metabolites was analyzed by GS-MS. The racemates of pentedrone and methylone exhibited potential hepatotoxicity in a concentration-dependent manner in both models. Different cytotoxic profiles for pentedrone enantiomers were observed in HLC 3D, with *R*-(-)-pentedrone being the most cytotoxic. Concerning HLC 2D metabolic assays, *S*-(-)-methylone was preferentially metabolized via *N*-demethylation, whereas *R*-(+)-methylone was metabolized by *O*-demethylation and *N*-hydroxylation. However, in HLC 3D assays, *R*-(+)-methylone was preferentially metabolized by all metabolic pathways, except for *O*-demethylation. Regarding pentedrone enantiomers, the metabolic pathways studied were more pronounced for *R*-(-)-pentedrone, namely *N*-demethylation and β-keto reduction in both models. Overall, this study revealed stereoselectivity in cytotoxicity and metabolism pathways for pentedrone and methylone.

Keywords: pentedrone; methylone; cytotoxic; metabolism; enantiomers; HLCs

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