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In vitro and *in silico* evaluation of 5-MeO-DMT, LSD, and mescaline's interaction with CYP450 enzymes

Andreia Machado Brito-da-Costa [1,2,3,*], Mariana Carvalho [1,2], Ricardo Jorge Dinis-Oliveira [1,2,4,5], Áurea Madureira-Carvalho [1,6], Sérgio F. Sousa [7,*] and Diana Dias da Silva [1,3,6,8,*]

[1] Associate Laboratory i4HB - Institute for Health and Bioeconomy, 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] UCIBIO – Applied Molecular Biosciences Unit, Laboratory of Toxicology, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal
[4] FOREN-Forensic Science Experts, Dr. Mário Moutinho Avenue, n.° 33-A, Lisbon, Portugal
[5] Department of Public Health and Forensic Sciences, and Medical Education, Faculty of Medicine, University of Porto, Porto, Portugal
[6] UCIBIO - Applied Molecular Biosciences Unit, Forensics and Biomedical Sciences Research Laboratory, University Institute of Health Sciences (1H-TOXRUN, IUCS-CESPU), 4585-116 Gandra, Portugal
[7] LAQV/REQUIMTE, BioSIM – Biomedicine Department, Faculty of Medicine, University of Porto, Porto, Portugal
[8] LAQV/REQUIMTE, ESS, Polytechnic of Porto, Rua Dr. António Bernardino de Almeida, 400 4200-072, Porto

* Correspondence: andreia.costa@iucs.cespu.pt (AMBC); sergiofsousa@med.up.pt (SFS); dds@ess.ipp.pt (DDS)

Abstract

Background: 5-Methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), lysergic acid diethylamide (LSD), and mescaline are classic hallucinogens known for their recreational use, which increased in the last decades. Despite some available data on the metabolism of these drugs [1-3], a scientific gap exists regarding their possible interactions with CYP450 enzymes. Nevertheless, this information is of crucial relevance to predict drug-drug interactions and understand toxicological phenomena, in particular interindividual variability. **Objective**: This study aimed to evaluate *in vitro* and *in silico* the interaction of 5-MeO-DMT, LSD, and mescaline with the enzymes CYP2A6/2B6/2D6/2E1/3A4. **Methods:** The *in vitro* assessment of CYP450 inhibition was performed using the Vivid®CYP450 screening kits. IC_{50} was calculated using GraphPad Prism 9.3.0. For *in silico* assessment, molecular dynamics were performed using the PMEMD.cuda module in AMBER16. Calculations were made on the last 100 ns of the trajectory (stable zone) to assess the interaction mode/strength between enzyme and ligand, namely MMGBSA, per-residue decomposition energy, and hydrogen bonds. **Results:** Based on the IC_{50} (μM), LSD (0.35) and 5-MeO-DMT (3.47) present the capacity to be inhibitors of CYP2D6. Based on the MMGBSA (kcal/mol), LSD showed the highest binding affinities for all enzymes, while mescaline showed the lowest. The strong interaction of LSD with CYP2A6 is mediated by a hydrogen bond established with the protein residue Asn297. For interaction with CYP2B6, the residues Thr302 and Lys479 were important in mediating the interaction with 5-MeO-DMT and LSD. Key residues mediating the interaction of 5-MeO-DMT and LSD with CYP2D6 included Phe120, Leu213, and Phe483. For interaction with CYP2E1, residues Phe207, Phe298, and Thr303 are important; and for CYP3A4, an important hydrogen bond between LSD and Ala370 was identified. **Conclusions:** Both LSD and 5-MeO-DMT are predicted to have strong potential to be CYP2D6 inhibitors. A strong interaction was also identified *in silico* between LSD and CYP2A6.

Keywords: drug-drug interaction; hallucinogens; metabolism; pharmacokinetics; toxicology

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