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## Photo(geno)toxicity induced by reactive drug metabolites

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Metabolites may be more toxic and reactive than the parent drug. Upon irradiation, they can generate reactive intermediates capable of binding to key macromolecules such as DNA. Consequently, identification of metabolites with phototoxic or adduct forming capability still remains a major challenge. Therefore, the goal of the present work is to assess the photo(geno)toxic potential of chlorpromazine (CPZ), diclofenac (DCF) and their metabolites in order to investigate whether the metabolism is key in photosensitized DNA damage. Both CPZ (an anti-psychotic drug) and DCF (nonsteroidal anti-inflammatory drug) are widely prescribed drugs. We have proven that demethylation of chlorpromazine (CPZ) as a consequence of Phase I biotransformation, does not result in a detoxification but leads to metabolites maintaining identical chromophore to the parent drug and exhibiting an even enhanced photo(geno)toxicity. Unlike the case of CPZ demethylation, the DCF hydroxylated metabolites are associated with a change in the chromophore, displaying a bathochromic shift of the absorption band towards the UVA region, thus extending the active fraction of solar light able to produce photosensitivity disorders. The multidisciplinary approach to perform this work encompasses from photochemical (steady-state and laser flash photolysis) to spectroscopic (Electron Paramagnetic Resonance, EPR) and biological studies (neutral red uptake viability test, gel electrophoresis, comet assay) in order to obtain mechanistic insight into the involved process.



Figure 1. Graphical overview of the phototoxicity and photogenotoxicity assays of CPZ, DCF and their metabolites.

## **Recent Publications:**

- 1. G Garcia Lainez et al. (2018) Photo(geno)toxicity changes associated with hydroxylation of the aromatic chromophores during diclofenac metabolism. Toxicol. Appl. Pharmacol. 341:51-55.
- 2. Aparici Espert et al. (2018) Oxidatively generated lesions as internal photosensitizers for pyrimidine dimerization in DNA. ACS Chem. Biol. 13(3):542-547.
- 3. Molins Molina et al. (2017) Singlet oxygen production and in vitro phototoxicity studies on fenofibrate, mycophenolate mofetil, trifusal, and their active metabolites. J. Phys. Org. Chem. 30(9):e3722.
- 4. F Palumbo et al. (2016) Enhanced photo(geno)toxicity of demethylated chlorpromazine metabolites. Toxicol. Appl. Pharmacol. 313:131-137.
- 5. I Vaya (2016) Mechanistic studies on the photoallergy mediated by fenofibric acid: photoreactivity with serum albumins. Chem. Res. Toxicol. 29(1):40-46.

## Biography

Inmaculada Andreu is currently working at the Health Research Institute La Fe de Valencia, Spain as holder of a tenure track grant from the Carlos III Institute of Health and her main research is focused on photo(geno)toxicity of xenobiotics and their metabolites. She is mainly interested in drug toxicology.

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