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## PROJECT TITLE:

Development of Green Synthetic Methodologies for Stable Isotope-labelled Anticancer Drugs

## Project description (max 300 words)

The incorporation of stable isotopes, such as deuterium, carbon-13, and nitrogen-15 into bioactive compounds is of critical importance in Drug Research and Discovery (R&D) processes. Isotope-labelled drugs are indeed considered key tools in pharmacokinetic and metabolic studies, facilitating the assessment of ADMET profiles with accuracy, and in diagnosis and treatment monitoring, acting as non-radioactive tracers for imaging techniques like Positron Emission Tomography (PET).<sup>1</sup> Additionally, deuterated drugs, where one or more hydrogen atoms are replaced by bioisosteric deuterium atoms, proved to have increased stability and longer half-life thanks to the kinetic isotope effect such as in Deutetrabenazine (Austedo®), the first deuterated drug approved by FDA in 2017.<sup>2</sup> Isotope labelling represents nowadays a hot topic in medicinal chemistry research and the development of new synthetic methods enabling precise incorporation into complex molecular architectures, with efficiency and selectivity, is of utmost importance to reduce times, costs, and environmental impact in the obtainment of safer and more effective therapeutic agents.<sup>3</sup>

Therefore, the research topic of the current PhD proposal concerns:

- 1) Development of new synthetic methodologies to access isotope-labelled compounds with potential anticancer activity via advanced green approaches involving multicomponent reactions, photochemistry, flow-, and mechano-chemistry.<sup>4</sup>
- 2) Evaluation of the biological, pharmacodynamic and pharmacokinetic properties of the newly synthesized compounds exploiting preclinical experimental models of human tumors.<sup>5-7</sup>

The expertise of the tutors in medicinal chemistry and chemical synthesis, as well as in the field of biomedical research and in preclinical drug development, will ensure the PhD student a broad and high-level training path. The tutors' access to research funds, contracts and research agreements on behalf of third parties will guarantee adequate financial support for carrying out research and training activities.

## REFERENCES

- 1) C. S. Elmore, R. A. Bragg. Isotope chemistry; a useful tool in the drug discovery arsenal. *Bioorg. Med. Chem. Lett.* **2015**, 25, 167-171 (DOI: 10.1016/j.bmcl.2014.11.051).
- 2) C. Schmidt. First deuterated drug approved. *Nat. Biotechnol.* **2017**, 35, 493-494 (DOI: 10.1038/nbt0617-493).

- 3) K. R. Campos, P. J. Coleman, J. C. Alvarez, S. D. Dreher, R. M. Garbaccio, N. K. Terret, R. D. Tillyer, M. D. Truppo, E. R. Parmee. The importance of synthetic chemistry in the pharmaceutical industry. *Science* **2019**, 363, eaat0805 (DOI: 10.1126/science.aat0805).
- 4) C. Russo, F. Brunelli, G. C. Tron, M. Gustiniano. Isocyanide-Based Multicomponent Reactions Promoted by Visible Light Photoredox Catalysis. *Chem.-Eur. J.* **2023**, 29, e202203150 (DOI: 10.1002/chem.202203150).
- 5) C. Irace, G. Misso, A. Capuozzo, M. Piccolo, C. Riccardi, A. Luchini, M. Caraglia, L. Paduano, D. Montesarchio, R. Santamaria. Antiproliferative effects of ruthenium-based nucleolipidic nanoaggregates in human models of breast cancer in vitro: insights into their mode of action. *Sci Rep.* **2017**, 7, 45236 (DOI: 10.1038/srep45236).
- 6) M. Piccolo, M. G. Ferraro, F. Raucci, C. Riccardi, A. Saviano, I. Russo Krauss, M. Trifuoggi, M. Caraglia, L. Paduano, D. Montesarchio, F. Maione, G. Misso, R. Santamaria, C. Irace. Safety and Efficacy Evaluation In Vivo of a Cationic Nucleolipid Nanosystem for the Nanodelivery of a Ruthenium(III) Complex with Superior Anticancer Bioactivity. *Cancers* **2021**, 13, 5164. (DOI: 10.3390/cancers13205164).
- 7) M. G. Ferraro, M. Bocchetti, C. Riccardi, M. Trifuoggi, L. Paduano, D. Montesarchio, G. Misso, R. Santamaria, M. Piccolo, C. Irace. Triple Negative Breast Cancer Preclinical Therapeutic Management by a Cationic Ruthenium-Based Nucleolipid Nanosystem. *Int. J. Mol. Sci.* **2023**, 24, 6473 (DOI: 10.3390/ijms24076473).

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