# PHOTOCHEMICAL STRATEGY FOR CARBON ISOTOPE EXCHANGE WITH $CO_2$

**Victor Babin,[1] Alex Talbot,[1] Alexandre Labiche,[1] Gianluca Destro,[1] Antonio Del Vecchio,[1] Charles S. Elmore,[2] Frédéric Taran,[1] Antoine Sallustrau,[1] Davide Audisio[1]***

*Service de Chimie Bio-organique et Marquage, CEA/DRF/JOLIOT/SCBM, Université Paris Saclay, France ;[2] Isotope Chemistry, Pharmaceutical Science, R&D, AstraZeneca, Gothenburg, Sweden.*
*alexandre.labiche@cea.fr*

Carbon radioisotope labeling has a remarkable impact on public health. Long lived $\beta^-$ isotope carbon-14 ($^{14}C$, $t_{1/2}$ 5730 years) is important for the collection of biological data in Absorption, Distribution, Metabolism and Excretion (ADME) studies.[1] The use of carbon-14 is attractive to study the pharmacokinetic parameters of new drugs or to evaluate the fate of drug candidates.

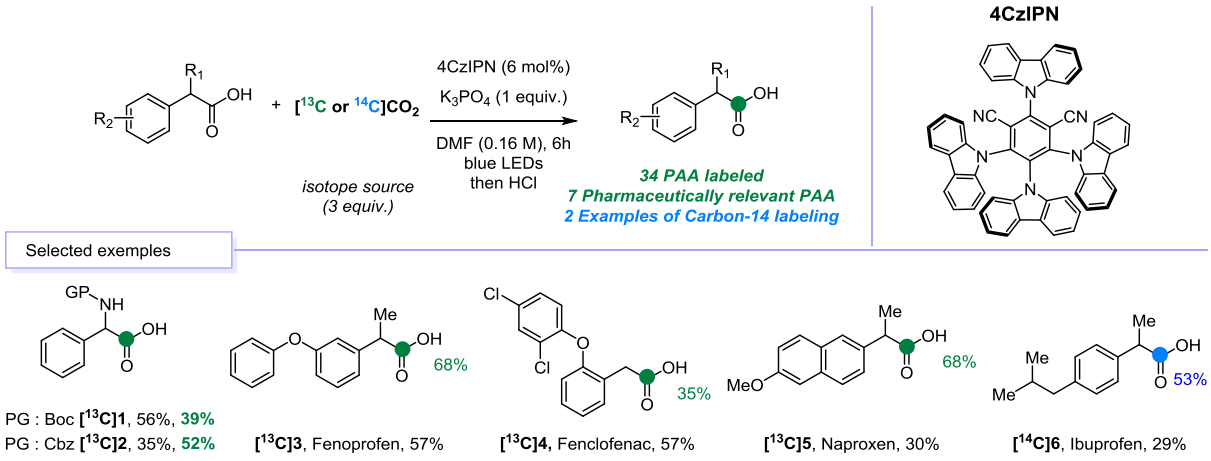
Unfortunately, traditional multi-step synthesis of [$^{14}C$]-labeled compounds generates high amounts of radioactive waste and are demanding in terms of resources and sustainability. Recently, new strategies based on the concept of Carbon Isotope Exchange (CIE) have been developed as a response to this issue.[2] CIE aims to selectively break a stable $^{12}C$-$^{12}C$ bond and replace it with a new $^{12}C$-$^{14}C$ bond in a single operation, directly from the end-use molecules without the need of structural modification or pre-functionalization.

Carboxylic acids are an important functional group in pharmaceuticals, especially the Phenyl Acetic Acid (PAA) moieties that are found in Non-Steroidal Anti-Inflammatory (NSAI) drugs such as Naproxen or Ibuprofen[3].

Last year, our group and the group of Prof. Lundgren independently developed a transition-metal-free CIE procedure on PAA. Thought effective, the use of drastic thermal conditions (up to 190 °C) remains a significant limitation.

In order to develop milder conditions, we investigated a photocatalytic approach, utilizing [$^{13}C$]$CO_2$ and [$^{14}C$]$CO_2$ as a primary C1 source. We found that the reaction occurs without the need of structural modification in one single step and in presence of an organic photocatalyst: 4CzIPN. This procedure, enabled the labeling of 34 PAA, including non-natural amino acids, which could not be labeled using thermal conditions and 7 pharmaceutically relevant compounds with carbon-13.[4,5]

As a proof of concept, we successfully labeled with carbon-14 the most known NSAI drugs: Ibuprofen in 29% yield with a 53% insertion of [$^{14}C$]$CO_2$.




[1] E. M. Isin, C. S. Elmore, G. N. Nilsson, R. A. Thompson, L. Weidolf, *Chem. Res. Toxicol.* **2012**, 25, 532-542.
[2] K. Hinsinger, G. Pieters, *Angew. Chem. Int. Ed.* **2019**, 58, 9678-9680.
[3] (a) G. Destro, K. Horkka, O. Loreau, D.-A. Buisson, L. Kingston, A. Del Vecchio, M. Schou, C. S. Elmore, F. Taran, T. Cantat, D. Audisio, *Angew. Chem. Int. Ed.* **2020**, 59, 13490-13495. (b) D. Kong, P. J. Moon, E. K. J. Lui, O. Bsharat, R. J. Lundgren, *Science* **2020**, 369, 557-561.
[4] V. Babin, A. Talbot, A. Labiche, G. Destro, A. Del Vecchio, C. S. Elmore, F. Taran, A. Sallustrau, D. Audisio, *ACS Catalysis* **2021**, 11, 2968-2976.
[5] This publication appeared concomitant to our report, see: D. Kong, M. Munch, Q. Qiqige, C. J. C. Cooze, B. H. Rotstein, R. J. Lundgren, *J. Am. Chem. Soc.* **2021**, 143, 2200-2206.