New isotopic labeling process to speed up candidate drug assessment

September 3 2015

A team of CEA researchers, in collaboration with two laboratories associating INSA Toulouse , CNRS and Université Paul Sabatier (Toulouse), has developed a new labeling process that will make it possible to speed up in vivo studies of candidate drugs. This original and pioneering process is based on a reaction mechanism discovered using computer modeling. The results were published in *Angewandte Chemie* on August 13, 2015.

Currently, less than one "candidate drug" in ten that reaches the stage of clinical trials goes on to be made available on the market. This figure is even lower in the case of candidates for certain central nervous system pathologies. This makes the time-to-market increasingly lengthy and, in particular, implies higher development costs. Now, however, this trend could be reversed thanks to the early identification of the most effective and least harmful candidate drugs by assessing their behavior in vivo (in animals and also in humans) right from the initial stages of development. To achieve this, we need to "stick" a label on such molecules, without altering their nature, which will allow them to be accurately detected and traced within the organism. One technique consists in replacing certain atoms (H, C, F, etc.) of the molecule with their (stable or radioactive) isotopes. This gives us a labeled molecule. Hydrogen (H), present in all organic molecules used in human health science, can be replaced with deuterium (stable) or tritium (radioactive).

One of the major challenges in isotope chemistry is to find a way to synthesize labeled molecules quickly, cheaply and using environment-

friendly techniques. Incorporating deuterium or tritium at a defined position on a molecule with pharmacological potential generally requires the use of chemical precursors and there are several stages involved in its construction.

A team from CEA, in collaboration with the Laboratoire de Physique et Chimie de Nano-Objets (CNRS/INSA Toulouse/Université Paul Sabatier) and the Laboratoire de Chimie et Coordination (CNRS) based in Toulouse, has developed a labeling method using "C-H activation." This method, which can be performed under mild conditions, is therefore applicable to complex and fragile molecules and uses ruthenium nanoparticles with a deuterium-impregnated surface. The researchers worked on the isotopic exchange in a C-H bond, in the case where the carbon atom is chiral, i.e. it has four different groups of atoms bonded to it. A chiral carbon atom cannot be superimposed upon its mirror image (as is the case for our two hands). The huge majority of drugs and potential drug molecules contain this type of carbon. The researchers have successfully demonstrated the exceptional potential of ruthenium nanoparticles with a deuterium-impregnated surface in activating an isotopic exchange on chiral carbon without altering the initial three-dimensional structure of the molecule. Associated with these results, the research teams in Toulouse carried out a computational chemistry study which revealed the extremely novel reaction mechanism involved in this process. This opens up new possibilities in chemistry and biology and paves the way toward new developments in labeling that may be find applications in fundamental research and drug chemistry or even materials chemistry.

Provided by CEA