SENSORS AND PROBES

Organic chemistry expands imaging options

A new fluorination approach enables the synthesis of diverse PET probes.

The unnatural isotope fluorine-18 generates a clear signal in positron emission tomography (PET). Oncologists routinely rely on the radiotracer [^{18}F]fluorodeoxyglucose to diagnose cancer and track how a tumor responds to treatment. However, applications of PET imaging are limited by the kinds of fluorinated molecules that researchers can make.

The barrier lies with incorporating fluorine into molecules more complex than glucose. Doing so requires attaching a fluorine atom to a carbon atom in the presence of interfering functional groups, a difficult task. Synthesis is made even more difficult because the half life of ^{18}F is less than two hours, leaving little time to produce, purify and administer a labeled probe. Not only that, but the chemistry must work with procedures that are practical in a hospital setting and, because only nanomoles of ^{18}F are typically available, the synthesis must work on very small scales. Recently, researchers led by Jacob Hooker at Massachusetts General Hospital and Tobias Ritter at Harvard University described a new approach that meets these stringent requirements.

In traditional PET probe synthesis, ^{18}F is produced as nucleophilic fluoride, which works well for synthesizing many simple molecules, such as labeled glucose, but is not useful for creating other types of labeled molecules, including many drugs and molecular probes. It is possible to create ^{18}F that acts as an electrophile, but this has historically been done by first making [^{18}F]F_2 gas, which often is highly contaminated with the PET-inactive natural isotope (^{19}F) and also is very toxic and reactive. To get around this problem, the researchers found a new way to capture ^{18}F in an electrophilic form. They used an intermediate called a palladium aryl complex in which a palladium atom is attached to several molecular groups, including an aromatic ring, a functional group found in many biologically interesting molecules. In the subsequent steps, the palladium complex transfers the fluorine to the aromatic ring, creating an aryl fluoride that can be used in the synthesis of PET tracers.

The researchers are planning to use the new chemistry to investigate how a labeled molecule binds serotonin receptors in the brain. "We can make molecules that were hard to make before, so now we can ask questions that were difficult to ask before," says Ritter.

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RESEARCH PAPERS

Lee, E. *et al.* A fluoride-derived electrophilic late-stage fluorination reagent for PET imaging. *Science* **334**, 639–642 (2011).