

PrimeView

Contemporary synthetic strategies in organofluorine chemistry

Synthetic manifolds that enable the functionalization of organic molecules with fluorine have greatly expanded the repertoire of fluorinated molecules. Current fluorination and fluoroalkylation reactions have built on traditional industrial methods using anhydrous hydrogen fluoride, fluorine gas, freons and halons.

Experimentation

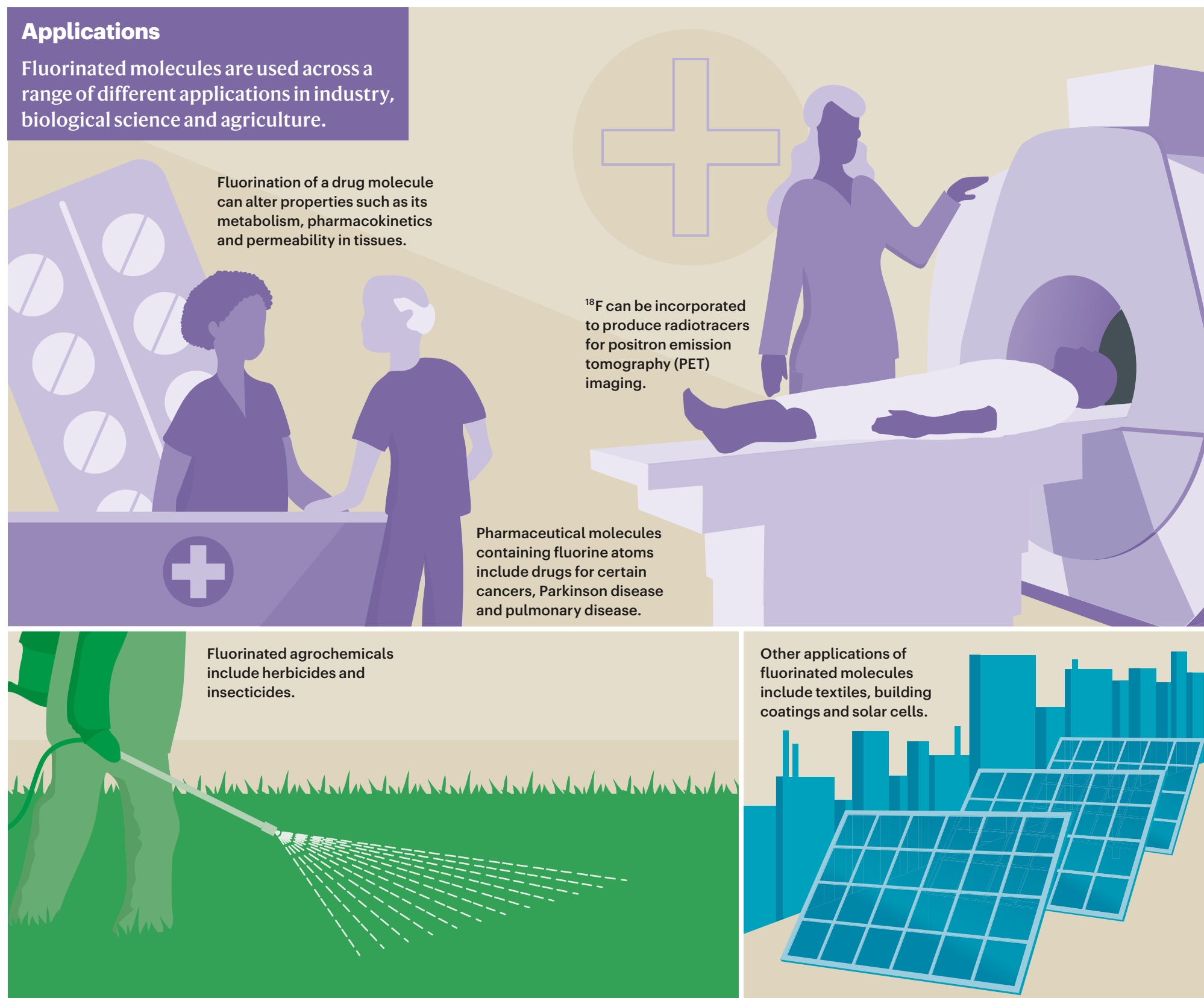
Many novel nucleophilic and electrophilic fluorination reagents and transition metal-based catalytic manifolds now exist for fluorinating molecules at sp^2 and sp^3 carbons. C–H fluorination methods using transition metal catalysis commonly use a Pd^{II}/Pd^{IV} catalytic cycle, which mediates C–F bond formation through reductive elimination, and a variety of directing groups can be used to aid regioselectivity. The main alternative to transition metal-catalysed reactions are photocatalytic and non-photocatalytic radical-based protocols. Early approaches required a radical initiator, although protocols without the need for an initiator now exist.

● **Radical-based fluorination strategies** require reagents with low N–F bond dissociation energies, such as Selectfluor.

A range of trifluoromethylation reagents have been developed, including Ruppert–Prakash ($TMSCF_3$) and Umemoto reagents. Among transition metal-catalysed reactions, copper is the most commonly used metal, and catalysis occurs via the generation of a $CuCF_3$ complex followed by a reductive elimination from $RCu^{III}CF_3$. Generation of CF_3 radicals can functionalize alkenes or alkynes with CF_3 ; functionalization of alkyl radicals is also possible, but less developed. Difluoromethylation of sp^3 carbons can be achieved by nucleophilic addition or substitution reactions of substrates with reagents such as $PhSO_2CF_2H$, and copper-catalysed difluorination of alkyl radicals has been recently developed. Difluorination of heteroaromatic compounds and heteroatoms are other convenient methods for functionalizing molecules with CF_2H groups. Monofluoromethyl groups can act as bioisosteres for pharmaceutically relevant functional groups such as CH_3 and CH_2OH and several nucleophilic, electrophilic and radical monofluoromethylating reagents now exist.

Applications

Fluorinated molecules are used across a range of different applications in industry, biological science and agriculture.



Reproducibility and data deposition

All small molecules synthesized using these methods should be characterized using 1H NMR spectroscopy, ^{13}C NMR spectroscopy and high-resolution mass spectrometry. PET tracers must be manufactured using automated synthesis to GMP standards with a radiochemical yield of 5–40% and ideally prepared on or close to the site of use, owing to the short half-life of ^{18}F (~110 min).

Limitations and optimizations

The similar steric properties of fluorinated products and their precursors can cause purification issues. Furthermore, their similar reactivity profiles can cause overfluorination, although monofluorination can be favoured over polyfluorination by modifying the reaction conditions. Many fluorination reagents, such as Selectfluor, *N*-fluorobenzenesulfonimide (NFSI) and silver fluorides suffer from low atom economy and high costs. Metal catalysts can also be expensive and could be impractical for industrial application. Indeed, most novel methods have only been demonstrated on the mmol scale so far and further studies are needed to evaluate the viability of methods following scale-up. More traditional fluorination reactions using anhydrous or freons are still favoured in industry owing to their low cost at a large scale (kg).

Outlook

New fluorination and fluoroalkylation methods and manufacturing technologies must be developed in an environmentally responsible way. Future methods are likely to include light-promoted radical reactions, and electrochemistry may facilitate late-stage fluorination reactions. Finally, synthetic biology techniques could allow for enzymatic fluorination and fluoroalkylation in the near future.