

## Fluorine – An Important Tool in the Chemists' Toolbox

Fluorine substitutions greatly increase a molecule's lipophilicity, an important consideration when making molecules that are designed to be active *in vivo*. Incorporating fluorines increases fat solubility and bioavailability. Fluorination can also aid hydrophobic interactions between the drug and binding sites on receptors or enzymes.

Introducing more than one fluorine atom at the same site can have more dramatic effects. Using difluoromethylene as a replacement for CH<sub>2</sub> has a substantial effect on both the physical properties and conformation of a molecule. It can also be considered as a replacement for oxygen, with the fluorines sitting in a similar position to the oxygen's lone pairs. It is a similar shape and retains oxygen's ability to hydrogen bond, but the resulting carbon-carbon bonds are much more difficult to break, imparting greater stability.

Despite the startling number of pharmaceutical products that contain fluorine, selective fluorination reactions are rarely straightforward. They often use dangerous reagents such as elemental fluorine or hydrogen fluoride, which are best avoided in large scale synthetic procedures. Specialist fluorinating reagents such as SF<sub>4</sub>, TBAF, DAST, Selectfluor and Deoxo-Fluor are often expensive, and can be tricky to handle. Therefore, the best route is often to let someone else worry about introducing the fluorine, by using a commercially available intermediate which already contains the correct fluorinated functionality, and then building the drug molecule around that.

A good example is the range of trifluoromethyl intermediates produced by fluorochemical specialist Halocarbon, which have the potential to be used to introduce trifluoromethyl functionality into molecules. The reasons for using a CF<sub>3</sub> unit in place of a methyl group are, again, based on the similar size of fluorine and hydrogen, and the significant difference in their electronic character. The degree of electronic change is much greater than in a simple fluorine for hydrogen switch, however, purely on account of the fact that three fluorines have been introduced into the system instead of just the one. In addition, the trifluoromethyl group is one of the most lipophilic groups known.

Numerous drug molecules contain trifluoromethyl moieties. As well as those mentioned above, both of Pfizer's COX-2 inhibitor anti-arthritis drugs celecoxib (Celebrex) and valdecoxib (Bextra) contain a trifluoromethyl substituent attached to a heteroaromatic ring. And efavirenz (Sustiva) from Bristol-Myers Squibb, a non-

nucleoside reverse transcriptase inhibitor used in the treatment of HIV patients, has a trifluoromethyl group attached to a tertiary centre in a heteroaliphatic ring.

The easiest way of making all three of these medicines relies on a small molecule intermediate that contains a trifluoromethyl unit to introduce the fluorine functionality. Numerous intermediates from Halocarbon have potential here. These include trifluoroacetic acid and its methyl and ethyl esters, plus trifluoroacetyl chloride, trifluoroethanol, and even hexafluoroisopropanol. Trifluoroacetone and trifluoroacetaldehyde ethyl hemiacetal can also be used in the production of pharmaceutical actives.

Fluorine's unique properties mean it will continue to be a common structural element in the medicines that reach the market in the future. Synthetic routes that incorporate fluorinated fragments are frequently the most cost-effective and safest way of making fluoro drugs, and the importance of fluoro intermediates is only going to increase in coming years as new fluorinated drugs are introduced.