The Important Impact of Fluorine in Pharmaceuticals

Fluorine has become an essential tool in drug discovery. Including fluorine atoms in potential medicines can have a variety of dramatic effects on the molecules' properties, perhaps making them more selective, increasing their efficacy, or making them easier to administer. So it is no great surprise that around a fifth of all drugs on the market today contain at least one fluorine substituent.

Indeed, three of the current top ten best sellers contain fluorine atoms, including the biggest blockbuster medicine, Pfizer's lipid lowering agent Lipitor (atorvastatin), which has an aromatic fluorine substituent. TAP's proton pump inhibitor Prevacid (lansoprazole) includes a difluoromethylene unit. And the fluticasone component of GlaxoSmithKline's antiasthma combination product Seretide has no less than three separate fluorine substituents.

There are very few naturally occurring organic compounds that contain fluorine, so it may seem a little odd that the element has become such a key component in the drug design process. Free fluoride ions are much, much less abundant in nature than chloride ions, and as a result bacteria tend to incorporate other halogens, particularly chloride, instead. But when one considers its chemical properties, the reason for the drug designer's enduring love of fluorine becomes much clearer.

Drug designers frequently use naturally occurring molecules as starting points in their studies, altering substitution patterns to change its properties to make it more effective, more selective, or both. And fluorine can make some very big differences. Its high electronegativity means it has a large electronic effect at neighbouring carbon centres, as well as having a substantial effect on the molecule's dipole moment, the acidity or basicity of other groups nearby, not to mention the molecule's overall reactivity and stability. It also means the fluorine centre can act as a hydrogen bond acceptor, and its three non-bonded pairs of electrons even enable it to act as a ligand for alkali metals.

Despite the fact that the fluoride atom is larger than hydrogen, the additional steric demand caused by replacing an H with an F at receptor sites on cells or enzymes is low.[1] The carbon-fluorine bond length is not that much greater than carbon-hydrogen, either, so the switch causes little change to the steric bulk of the molecule.

Although a carbon-fluorine bond is somewhat stronger than other carbon-halogen bonds, fluorine is still a better leaving group than hydrogen, so there is some potential for covalent bonds to be formed between the fluorinated molecule – by loss of fluoride – and an enzyme, for example, either at or near its active site, leading to an inhibition of the enzyme's activity.

One of the most important factors in drug design is that fluorine is much more lipophilic than hydrogen, so incorporating fluorine atoms in a molecule will make it more

fat soluble. This means it partitions into membranes much more readily, and hence the fluorinated molecule has a higher bioavailability.

However, one drawback of introducing fluorine substituents into drug products is that it poses increased challenges in the manufacturing process. Nature rarely makes molecules with fluorine substituents for good reasons. Some of the properties that make fluorine so attractive in drug target molecules also make its chemistry more difficult – not least the high redox potential.

While many different fluorinating agents have been invented over the past decades, the selective introduction of fluorine centres into molecules remains far from straightforward, particularly at the large scales needed for active pharmaceutical ingredient production. Although many are less toxic and easier to handle than either fluorine or hydrogen fluoride, both of which are extremely dangerous chemicals, significant challenges remain.

The simplest solution is often to use a fluorine-containing intermediate instead, such as one of those supplied by Halocarbon. These include molecules with single fluorines, difluoromethylene units and trifluoromethyl groups, as well as fluorinated aromatics. And it means that the difficult fluorination chemistry itself is carried out by experts who are well versed in the art.

One of the most popular fluorine-containing functional groups in drug molecules is the trifluoromethyl moiety. Because it contains three fluorine atoms, it exerts significant changes on neighbouring groups, such as increasing the acidity of other centres nearby. It is also one of the most lipophilic groups known, so it provides an extremely useful way of making a molecule more easily delivered to the active site in the body.

Many familiar drugs contain trifluoromethyl groups. These include the two big selling antidepressants Prozac (fluoxetine) from Pfizer, and Luvox (fluvoxamine), made by Lilly. Both of these drugs contain a para-phenyl trifluoromethyl group. Bristol-Myers Squibb's non-nucleotide reverse transcriptase inhibitor Sustiva (efavirenz) has trifluoromethyl substitution at a tertiary chiral centre. The antiprotozoal drug Lariam (mefloquine) from Roche, used to treat malaria, has two trifluoromethyl groups, one on each of the aromatic rings of a quinoline nucleus. And Pfizer's Celebrex (celecoxib), one of the under-fire category COX-2 inhibitors for treating arthritis, also has a trifluoromethyl group, this time attached to an aromatic pyrazole ring.

A number of inhaled anaesthetics contain trifluoromethyl functionality, too. These simple molecules include the older fluoroxene (Fluoromar) and halothane (Fluothane), plus the modern anaesthetics desflurane (Suprane, Baxter), and sevoflurane (Ultane, Abbott). Fluoroxene and halothane were introduced back in the 1950s, and while the former causes nausea and is flammable at high concentrations, the latter is non-flammable, and has much reduced side-effects. The next generation of fluorine containing inhaled anaesthetics included isoflurane (Abbott's Forane). Desflurane and sevoflurane have been developed

more recently, and sevoflurane in particular has a rapid onset of action, and is eliminated from the body quickly as well.

Many of Halocarbon's fluorinated intermediates contain trifluoromethyl groups, and are ideal building blocks for making these kinds of drug molecules. For example, trifluoroacetaldehyde methyl hemiacetal can be used in a route to the anaesthetic desflurane. The hemiacetal is a more useful alternative to trifluoroacetaldehyde, which is both unstable and a gas, and so is very difficult to use in practice, particularly at a manufacturing scale. As a liquid, with a boiling point of 95–96°C, the hemiacetal is much simpler to use as a synthetic building block.

In the desflurane synthesis, trifluoroacetaldehyde methyl hemiacetal is first reacted with tosyl chloride, converting the hydroxyl group to its tosyl derivative. This then behaves as a leaving group, and can be substituted with a further fluoride provided by potassium or caesium fluoride, giving a precursor to desflurane (Scheme 1).

The ethyl hemiacetal is also a useful building block in the synthesis of trifluoromethyl containing medicines. An example is a trifluoromethylated derivative of the anticancer drug Taxol. Trifluoroacetaldehyde ethyl hemiacetal was reacted with p-anisidine, and the resulting imine was then elaborated to give a beta-lactam. This could then be coupled with a baccatin derivative, with the result being a taxoid containing a trifluoromethyl group (Scheme 2). [2]

A third of Halocarbon's intermediates that has found applications in pharmaceutical molecule synthesis is trifluoroacetic anhydride. The acylating agent will react with a compound containing an active hydrogen, giving trifluoroacetic acid as a by-product. For example, it was used in the construction of a vasodilating benzopyran derivative by scientists at Ciba-Geigy (now Novartis). It was used to trifluoroacetylate a vinyl ether, and the resulting addition product was then reacted with an activated acetamide, giving the desired cyclic precursor with trifluoromethyl substitution (Scheme 3).[3]

Several other Halocarbon intermediates have great potential in pharma active synthesis, too. Trifluoroethylamine can be used to introduce a CF_3 group separated from the rest of the molecule by a methylene unit. Hexafluoroisopropanol can add a subunit with two trifluoromethyl groups attached to the same carbon centre, and is also a potential building block for the synthesis of the inhalation anaesthetic sevoflurane. And hexafluoroacetone – a gas when pure, but a solid that melts at around 20°C in its trihydrated form – can be used to introduce subunits with two trifluoromethyl groups and a hydroxyl function at the same carbon.

The distinctive effects that fluorine substituents have on the properties of active pharmaceutical ingredients mean they will remain popular with the drug discovery chemist. The number of simple, easy to use fluorinated intermediates that are readily available is growing, too, so fluorine containing drugs will surely be causing fewer headaches in production chemists in the future.

1. D. O'Hagan and H.S. Rzepa, Chem. Commun. 1997, 645
2. R.A. Holton and R.J. Biediger, US Patent 1993, 5,243,045
3. R.W. Lang and P.F. Wenk, Helv. Chim. Acta, 1988, 71, 596

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