

## **Fluorine's Ever-Increasing Impact in Developing Pharmaceuticals**

*In the development of global pharmaceuticals, fluorine is becoming more recognised – and used – as an important drug designer's tool.*

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 fluorine 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.<sup>1</sup> 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. The simplest, least expensive, fluorinating reagents – fluorine and hydrogen fluoride – are both extremely toxic and, because they are volatile, far from trivial work with. They are also an extremely unappealing prospect on a commercial manufacturing scale, as they pose significant containment challenges. More recently introduced fluorinating agents are designed to be easier to handle, but are much more expensive, and can still be difficult to use. Thus, although many of these reagents are less toxic and easier to handle than fluorine or hydrogen fluoride, 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

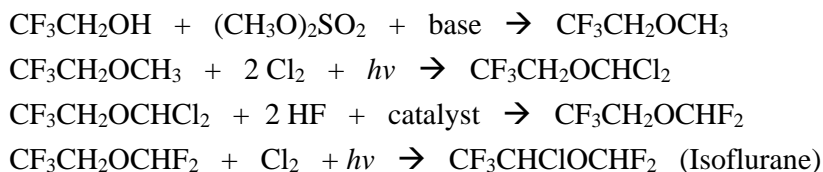
is also one of the most lipophilic groups known, so it provides an extremely useful way of making a molecule more easily delivered to the active site in the body.

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.

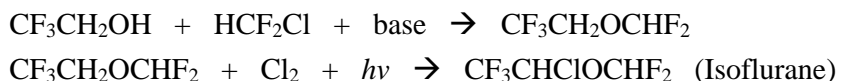
A number of inhaled anaesthetics contain trifluoromethyl functionality, too. These simple molecules include the older fluoroxene (Fluoromar) and halothane (Fluothane), plus the modern anaesthetics desflurane (Suprane, Baxter), and sevoflurane (Ultane, Abbott). Fluoroxene and halothane were introduced 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, trifluoroethanol (TFE) can be used to make isoflurane via several routes. An early synthetic approach called for the methylation of TFE with dimethyl sulphate (Scheme 1). The methyl ether product then was carefully chlorinated with Cl<sub>2</sub> and light. Halide exchange with HF and a catalyst then produced isoflurane. More recently, isoflurane has been produced by reacting TFE with HF<sub>2</sub>CCl and base, then chlorinating the resultant pentafluoroether (Scheme 2).

#### Scheme 1 – ORIGINAL SYNTHESIS OF ISOFLURANE

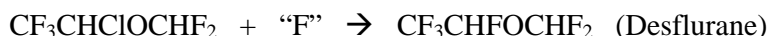


### Scheme 2 – ALTERNATE SYNTHESIS OF ISOFLURANE



It should be noted that there are several published syntheses for the conversion of isoflurane to desflurane (Scheme 3), most of which involve the exchange of a fluorine atom for a chlorine atom. These processes require the use of highly toxic and/or expensive fluorinating agents and often require several difficult separation steps. Recently, Halocarbon has applied for patents that accomplish this conversion through the use of more efficient and environmentally friendly production methods.

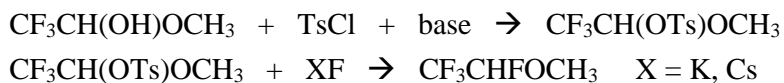
### Scheme 3 – GENERAL SYNTHESIS OF DESFLURANE



Trifluoroacetaldehyde methyl hemiacetal also can be used in the synthesis of 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.

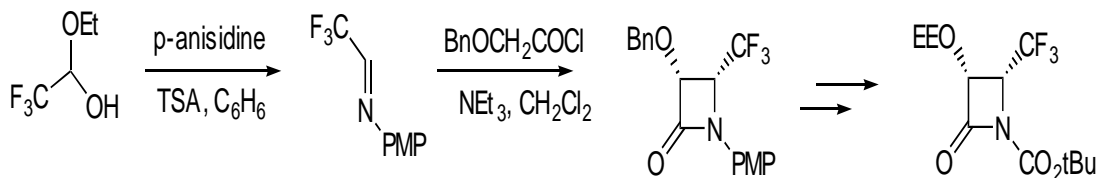
In this desflurane synthesis, trifluoroacetaldehyde methyl hemiacetal is first reacted with tosyl chloride, converting the hydroxyl group to its tosyl derivative. This then behaves as a leaving group, and can be substituted with a further fluoride provided by potassium or caesium fluoride, giving a precursor to desflurane (Scheme 4).

### Scheme 4 – ALTERNATE SYNTHESIS OF DESFLURANE PRECURSOR



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 5).<sup>2</sup>

### Scheme 5 – SYNTHESIS OF A BETA-LACTAM

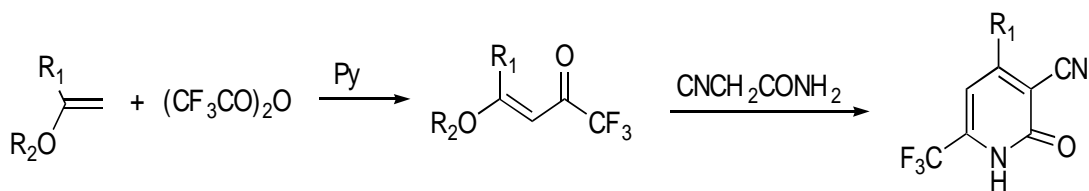


Trifluoroacetaldehyde is a very useful building block, as it can be reacted with numerous different reagents including olefins, dienes, ketene silyl acetals, metal enolates and a variety of aromatic compounds. However, it is often much easier to use it in a hemiacetal form, as illustrated previously, instead.

This is precisely the strategy employed by a group at Gifu University in Japan, who found that trifluoroacetaldehyde required high temperatures or an excess of concentrated sulfuric acid to make their reactions work.<sup>3</sup> They started with the ethyl hemiacetal, and generated the free aldehyde from it *in situ* under very mild conditions. When this was mixed with an enamine at room temperature, the result was a [beta]-hydroxy-[beta]-trifluoromethyl ketone, with no need for any additives in the reaction mixture. The reaction could be carried out in either toluene or hexane as solvent.

Another 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 6).<sup>4</sup>

### Scheme 6 – SYNTHESIS OF A BENZOPYRAN PRECURSOR



Hexafluoroacetone (HFA) – a highly toxic 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. This relatively new addition to Halocarbon's product line has received a great deal of attention in the last few years. HFA has been used to introduce a large amount of fluorination into biologically active molecules such as leucine<sup>5</sup>, vitamin D analogues<sup>6</sup>, and phosphodiesterase inhibitors<sup>7</sup>.

Recently, there has been a great deal of interest in the use of HFA as a protecting group for biologically oriented carboxylates.  $\alpha$ -Hydroxy acids are readily available starting materials that may be used in the synthesis of unusual amino acids. HFA has been shown to react preferentially with these acids in the presence of other carboxylic acids, which can then be converted to other functionality before the HFA protecting group is removed under relatively mild conditions. Work has been done to demonstrate HFA's utility as a protecting/activating group for amino acids that are used in solid phase peptide synthesis. Upon reaction with HFA the carboxyl group of an amino acid is activated for nucleophilic attack, while the amino group is protected. This process allows the incorporation of the amino acid into the growing peptide chain with fewer steps and reagents.

Several groups also have demonstrated the utility of HFA as a co reactant in the regio- and/or stereo-selective epoxidation of olefins by hydrogen peroxide. As a result of its strongly electron-withdrawing nature, HFA forms a complex with hydrogen peroxide that reacts preferentially with olefins that contain electron-donating groups. This selective reactivity has been used in the controlled epoxidation of molecules such as steroids that contain multiple double bonds. HFA also has been used in the oxidation of various heteroatoms and functional groups, as well as in the Baeyer-Villiger rearrangement.

Several other Halocarbon intermediates have great potential in pharma active synthesis, too. Trifluoroethylamine can be used to introduce a  $\text{CF}_3$  group separated from the rest of the molecule by a methylene unit. 3,3,3-trifluoropropene has been used in the synthesis of unnatural amino acids such as 4,4,4-trifluorovaline and 5,5,5-trifluoronorvaline<sup>8</sup>. Hexafluoroisopropanol can add a subunit with two trifluoromethyl groups attached to the same carbon centre, and is also a key building block for the synthesis of the inhalation anaesthetic sevoflurane via several different published routes.

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.

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#### About the author

Joel Swinson

Halocarbon Products Corp.

Joel Swinson is a senior research chemist for Halocarbon Products Corporation (Phone 803-278-3500 ext. 224; Email: [jswinson@halocarbon.com](mailto:jswinson@halocarbon.com)). In this capacity, he is responsible for developing the chemistry for new products and following their scaleup through the pilot, semiworks and production stages. Swinson, who has authored numerous articles, was educated at the Massachusetts Institute of Technology (Cambridge) and earned his Ph.D. at Vanderbilt University (Nashville, Tenn.), followed by postdoctoral research at the University of Florida (Gainesville). Prior to joining Halocarbon, Swinson was the director of technology and services for Chattem Chemicals (Chattanooga, Tenn.).