Fluorine – A vital element in the medicine chest

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A huge number of the drugs that we rely on today were provided by nature – either directly or by giving a starting point for medicinal chemists to work with. Whether made by bacteria, fungi or plants, the range of structurally diverse and biologically active molecules that are made by natural organisms is enormous.

Penicillin? From the mould *Penicillium notatum*. Taxol? From the Pacific yew tree *Taxus brevifolia*. Erythromycin? Made by the bacterium *Streptomyces erythreus*. These are just three examples of hugely important medicines that nature invented – and which provided the inspiration for further medicines to be created by chemists.

Medicinal chemists frequently take a molecule from nature which has some activity, and tinker with its chemical structure to adapt its properties, perhaps to increase the activity or binding strength, or maybe to reduce any side effects the original molecule might have had.

One of the most popular strategies for altering the activity of natural products is to introduce one or more fluorine atoms into the structure. Indeed, around a fifth of all the drugs that are currently on the market contain at least one fluorine substituent – including three of the current top ten selling medicines, Pfizer's cholesterol lowering medicine atorvastatin (Lipitor), TAP's proton pump inhibitor lansoprazole (Prevacid), and the fluticasone component in GlaxoSmithKline's combination asthma treatment Seretide.

But why has fluorine become such a popular element in drug design? After all, there are very, very few naturally occurring molecules that contain fluorine – and all known fluorinated natural products are toxic. The recently discovered bacterium *Streptomyces cattleya* aside, bacteria have evolved that incorporate chlorine rather than fluorine because it is much more abundant in free ion form. And the main route bacteria use to biosynthesise molecules containing halogen atoms – redox chemistry – does not really work with fluorine because its redox potential is so high.

However, this high redox potential is just one of the properties that makes fluorine an interesting substituent in pharmaceutical molecules. Despite its greater size than hydrogen – fluorine's van der Waals radius is 1.35 Å and hydrogen's is 1.1 Å – it is a good hydrogen mimic, and the additional steric demand a monofluorinated analogue exerts at receptor sites on enzymes or cells is minimal (1).

The electronic properties of the two are very different, however. Fluorine is the most electronegative of all the elements, so swapping a fluorine for a hydrogen will have a large electronic effect on neighbouring atoms. The high electronegativity of fluorine pulls electrons towards it, reducing the electron density at the carbon centre in a carbon-fluorine bond. Some of carbon's strongest bonds are formed with fluorine atoms, so the oxidative and thermal stability of the molecule are both increased.

Fluorine's electron withdrawing nature also means that the acidity of organic acids is increased when fluorine substituents are introduced nearby. Examples of the pKa of organic

Table I – Acidity of acetic acid, and its chloro and fluoro analogues

Acid	pKa at 25°C
CH_3CO_2H	4.8
CH_2FCO_2H	2.6
CHF_2CO_2H	1.2
CF_3CO_2H	0.2
CH_2ClCO_2H	2.9
$CHCl_2CO_2H$	1.3
CCl_3CO_2H	0.6

Figure 1

R = H: nitrazepam
R = F: flunitrazepam

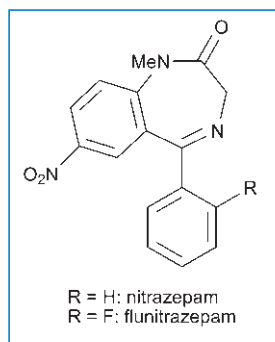acids and their fluorinated analogues are given in Table I. It also gives values for the comparable chlorinated derivatives, which show a much less pronounced effect because of the lower electronegativity of chlorine.

The electron withdrawing nature of fluoride ions and fluorine containing functional groups such as trifluoromethyl, trifluoromethoxy and CF_3SO_2 are very useful in altering the electronic properties of molecules if they are used as substituents.

Incorporating a fluorine centre into a molecule also enhances the acidity of a carbon-hydrogen bond nearby. On the whole, a hydrogen attached to a carbon that is also bonded to a fluorine will become more acidic, though the effect is not as dramatic as it is for other halogen atoms, because the fluorine destabilises the carbanion.

Fluorine substitution also tends to shorten hydrogen bonds, and strengthen them. Each additional fluorine can be expected to shrink a neighbouring hydrogen bond by around 0.1 Å, and increase the interaction energy by around 1 kcal/mol (2).

Perhaps the most important difference between fluorine and hydrogen from a drug design point of view, however, is the difference in lipophilicity between the two. Incorporating fluorine atoms into a molecule increases its fat solubility, which improves its partitioning into membranes, and thus increases its bioavailability. Fluorination can also help to create hydrophobic interactions between the drug and its binding sites on receptors or enzymes.

In addition, fluorine can make a good replacement for oxygen. The van der Waals radii of fluorine, at 1.35 Å and oxygen at 1.40 Å are not that different, and their electronegativities are similar too, at 4.0 for fluorine and 3.5 for oxygen. Additionally, the fluorine in fluoroalkanes and fluoroalkenes is isoelectronic to the oxygen in alkanols and alkenols, and this isosteric effect has been extremely useful in the design of novel drug molecules,

such as in a number of protease inhibitors.

Many of these effects are enhanced by introducing more than one fluorine atom into a molecule. Difluoromethylene groups impart significant physical and conformational changes in a molecule when they are substituted for a methylene group. A difluoromethylene unit is also an excellent replacement for an oxygen, both sterically and electronically, as the fluorines sit in a similar position to the lone pairs of an oxygen atom, so it is a similar shape and retains the ability to form hydrogen bonds, but it is more stable as the carbon-carbon bonds are much more resistant to being broken than carbon-oxygen ones.

FLUORINE CONTAINING DRUGS

One of the earliest synthetic fluorinated drugs to reach the market was the antineoplastic agent 5-fluorouracil. This was first synthesised in the 1950s as part of a systematic study of the activities of a range of fluorine derivatives of naturally occurring purine and pyrimidines (3). It exhibits excellent antitumour activity, inhibiting the enzyme thimidylate synthetase and thus preventing the cellular synthesis of thymidine. It is interesting to note that the corresponding bromo derivative does not have this anticancer activity, presumably because it is too large to be incorporated into the biosynthetic pathway in place of uracil, unlike the fluoro compound. Nearly 50 years on, 5-fluorouracil remains an essential weapon in the arsenal of anticancer drugs.

The popularity of fluorine as a component of drug molecules has spiralled since then, with very many familiar medicines containing fluorine substituents. Many of the drugs that act on the central nervous system, such as antidepressants and tranquillisers, contain fluorine, because the higher lipophilicity it imparts increases the rate at which it is transported across the blood-brain barrier.

Figure 2 – Fluoxetine

Figure 3 – Ciprofloxacin

Figure 4 – Fluconazole

Figure 5 – Mefloquine

An excellent example is Roche's tranquilliser flunitrazepam (Rohypnol), which is the ortho-fluoro derivative of an earlier Roche drug, nitrazepam (Mogadon) (Figure 1). This fluorine substitution serves to increase the activity of the molecule.

Two of the current biggest selling antidepressants also contain fluorine. Pfizer's selective serotonin reuptake inhibitor fluoxetine (Prozac) revolutionised the antidepressant market when it was introduced in 1986, and it contains a trifluoromethyl group (Figure 2). GlaxoSmithKline's rival drug, paroxetine (Seroxat/Paxil), has a shorter duration of action, and contains a para-fluoro phenyl substituent.

Fluorine substitution is widespread in antibacterial drug molecules; indeed, an entire class – the fluoroquinolones – relies on the activity of the fluorine atom. Indeed, this class contains some of the most familiar modern antibiotics – including Bayer's ciprofloxacin (Cipro) (Figure 3), levofloxacin (Levoquin from Ortho-McNeil) – the single isomer of the racemic drug ofloxacin – and norfloxacin, better known as Dainippon's Noroxin. All of these drugs contain a fluorine atom at C-6; a further analogue, sparfloxacin, Zagam from Dainippon, contains a second fluorine at C-8.

Antifungals often contain fluorine substitution, too. One of the most commonly prescribed antifungal agents, fluconazole (Diflucan from Pfizer), contains two aromatic fluorine atoms, at the ortho and para positions of a phenyl group (Figure 4). The newer antifungal flutrimazole (Uriach's Micetal) also has two aromatic fluorines, only this time with an ortho fluorine on one phenyl group and a para fluorine on a second.

An important antiprotozoal medicine also contains fluorine. Mefloquine, Roche's Lariam, is one of the most widely prescribed treatments for malaria, used
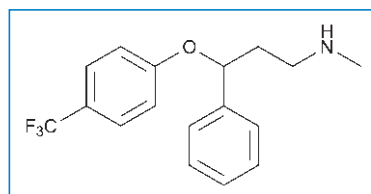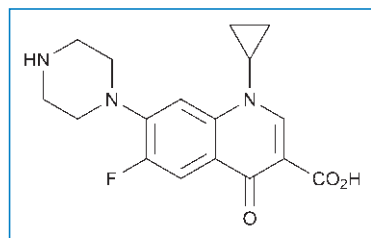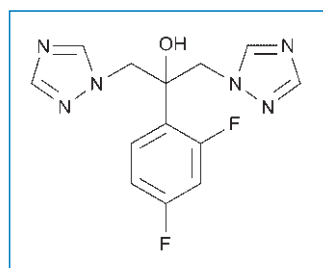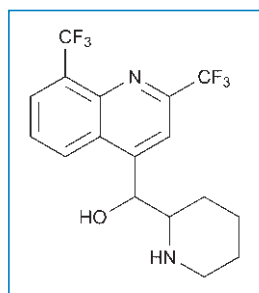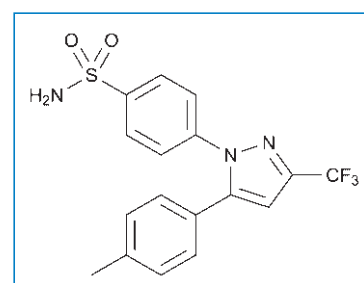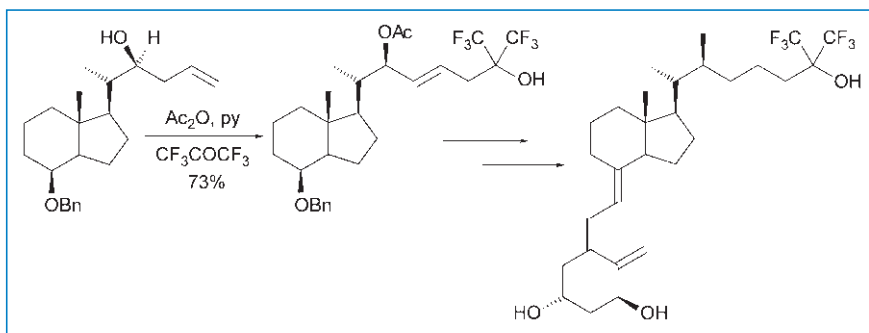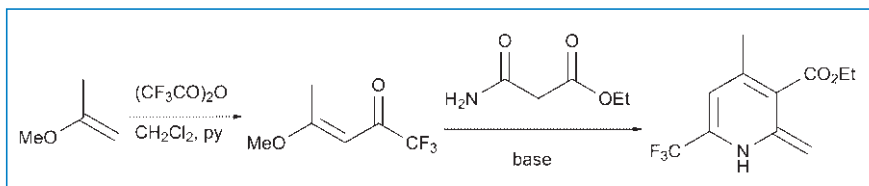

Figure 6 – Celecoxib
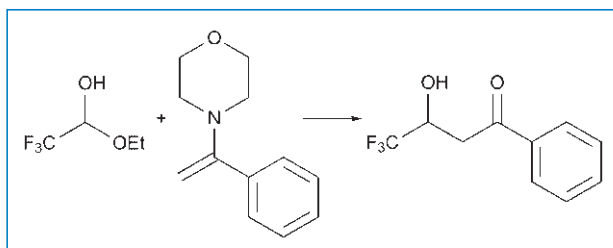
Scheme 1

Scheme 2

Scheme 3

either alone or in combination with the older medicine chloroquine. It has two trifluoromethyl groups, one on each ring of its quinoline core (Figure 5).

Another therapeutic category where fluorine substitution is commonplace is the cholesterol lowering agents, the statins. Atorvastatin – Lipitor – has a para fluoro phenyl substituent. And the newer medicine rosuvastatin (Crestor from AstraZeneca), similarly has a para-fluorophenyl group. These are currently two of the world's biggest selling medicines.

Two of the under fire COX-2 inhibitor class of antiinflammatory drugs for use in arthritis are fluorine containing. Both of Pfizer's COX-2 inhibitors, celecoxib (Celebrex) and valdecoxib (Bextra), have trifluoromethyl groups attached to heteroaromatic rings (Figure 6). Trifluoromethyl groups make excellent replacement for methyl units in drug design because – as with single fluorine for hydrogen replacements – the fluorine and hydrogen atoms have similar sizes but substantially different electronic natures. As three substitutions are being made at the same time and in the same place, however, the electronic change is much greater. An added bonus is the fact that the trifluoromethyl moiety is one of the most lipophilic groups known, which has big advantages for the drug's bioavailability.

FLUORINATING REAGENTS

Over the years, a variety of reagents have been developed that can be used to introduce fluorine into organic molecules. Fluorine itself is

extremely reactive – and extremely toxic. Similarly, anhydrous hydrogen fluoride, while it is very cheap, is corrosive and toxic, and these factors, along with its low boiling point of 19°C, mean that it is far from ideal for use as a reagent, particularly at the large scale required for industrial processes.

As a result, there was a great need for safer, more selective reagents. Over the
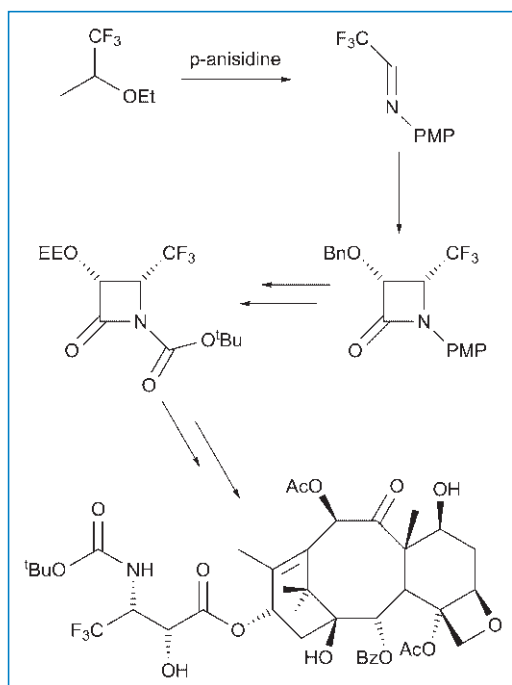
Scheme 4

past few decades, many have been developed, and their availability has had a dramatic impact on the number of fluorinated molecules that have become available and that have been created by the pharmaceutical industry.

Some of the most common fluorinating reagents are, in effect, sources of nucleophilic fluoride ions. This poses a challenge in itself, as the ion's small size and low polarisability mean that it is more inclined to behave as a base than as a nucleophile. However, some of the more familiar fluorinating agents behave in this way, including hydrogen fluoride itself.

DAST – (diethylamido)sulfur trifluoride – is one of the most popular. It was developed at Du Pont in the 1970s (4). DAST was a result of a programme designed to create analogues of sulfur tetrafluoride which, while it is a good fluorinating reagent, requires high temperatures and/or pressures for the reactions to occur, and it is toxic. By replacing one of the fluorines with a diethylamine group, the Du Pont team obtained a nucleophilic fluorinating reagent that will replace both hydroxyl and carbonyl oxygens with fluorine. Primary, secondary and tertiary alcohols will all react, often in good yield.

The tetraalkylammonium fluorides such as the butyl version, TBAF, are stable solid compounds and hence much easier to work with. TBAF is highly nucleophilic, and soluble in organic solvents. It reacts with compounds such as bromides and tosylates via nucleophilic substitution to give the corresponding fluoride derivatives

If the carbon centre to be fluorinated has a high electron density, then a nucleophilic reagent such as DAST or TBAF are of no use. Elemental fluorine can behave as an electrophile, but clearly is impractical because of its gaseous nature and toxicity. Less toxic reagents that are easier to handle have also been made. These include fluoroxytrifluoromethane, a gaseous reagent with a boiling point of -97°C. However, this is as reactive as fluorine gas, and so enormous care is still needed. Acetyl hypofluorite, CF_3CO_2F, is milder than either fluorine gas or CF_3OF, and can be used to fluorinate enolisable beta-diketoesters and beta-diketones, giving monofluorinated compounds.

A number of electrophilic fluorinating reagents that contain nitrogen-fluorine bonds have also been developed. These include a variety of pyridine derivatives, where electron withdrawing subsitutents on the pyridine ring serve to increase the reagent's reactivity.
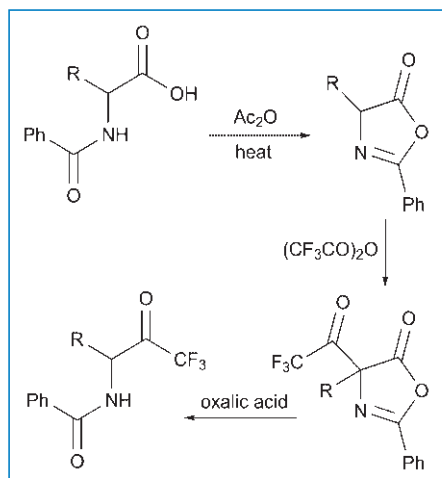
Scheme 5

USING FLUORINATED INTERMEDIATES

However, despite the invention of these fluorinating reagents, direct fluorination is rarely simple, and the reagents remain often toxic and difficult – or even dangerous – to handle. And introducing the fluorine in a regiospecific and stereoselective manner can be a challenge, particularly in complex molecules like most drugs are. As a result, the simplest way to introduce fluorine substitution into a chemical synthesis is by using a fluorinated building block, such as one of the intermediates that are produced by Halocarbon.

The building blocks are particularly useful for introducing trifluoromethyl groups; there are few reagents that can introduce them directly. The commonly used Ruppert's reagent – CF_3-TMS – is now difficult to make thanks to its normal starting material, methyl iodide, being frowned upon by the Montreal Protocol. So alternative strategies are certainly required here.

Hexafluoroacetone was used as a building block in the synthesis of a fluorinated vitamin D analogue by chemists at Japanese company Daikin (5). The team were looking for fluorinated analogues of vitamin D_3, because the basic vitamin had been shown to have suppress proliferation and induce differentiation in human cancer cells, in addition to its role in the regulation of calcium metabolism. They thought that by creating fluorinated analogues, they might be able to separate the calcium regulation functions from its activity in cell differentiation. They believed that this separation could be necessary if these properties were to be exploited in pharmaceutical products to treat diseases such as cancer and psoriasis. They began with commercially available vitamin D_2, and the key step

to construct the side chain was an ene reaction with hexafluoroacetone. As shown in Scheme 1, an alcoholic derivative of vitamin D_2 was first acetylated using acetic anhydride in pyridine, and then reacted with hexafluoroacetone to create the side-chain they required in their derivative. Although the reaction conditions were forcing, it shows the principle that such intermediates can be used to create fluorinated drugs.

An example of the use of trifluoroacetic anhydride came out of the labs of Ciba-Geigy, now Novartis, in Switzerland (6). The company's scientists had identified a benzopyran derivative, BRL 34915, as a potent vasodilator that had potential in the management of essential hypertension, which acted by hyperpolarising vascular smooth muscle cell membranes and opens potassium channels. Following a series of structure-activity relationship studies, they thought that if they used a pyridine ring instead, and introduced electron withdrawing substituents into it, would increase its biological activity.

To incorporate these electron withdrawing trifluoromethyl units, they carried out a trifluoroacetylation reaction on a simple vinyl ether. A range of activated acetamides were added, all of which led to the trifluoromethyl group being found exclusively in the 6 position on the pyridine ring, as shown in Scheme 2. These intermediates could then be elaborated into the desired targets for activity studies.

Another example of the use of a fluorinated intermediate comes from the laboratories of the department of chemistry at Gifu University in Japan (7). Trifluoroacetaldehyde is of particular interest in the construction of molecules with a trifluoromethyl group, as it can be reacted with a variety of reagents such as metal enolates, ketene silyl acetals, olefins, dienes and aromatic compounds. However, noting the disadvantages of previous procedures, such as the high temperatures needed to make the reactions go or the need for an excess of concentrated sulphuric acid, they started with trifluoroacetaldehyde in its

ethyl hemiacetal form instead.

The team found they could generate the free aldehyde in situ under extremely mild conditions, as when it was mixed with an enamine at room temperature in the absence of additives, the corresponding beta-hydroxy-beta-trifluoromethyl ketones were formed. The example given in Scheme 3 gave an 88% yield of the ketone in either toluene or hexane as solvent.

Since the anticancer effects of Taxol were discovered, numerous derivatives have been made in an attempt to improve and refine its activity. Fluorine substitution is an obvious strategy, and a trifluoromethylated derivative was created, using trifluoroacetaldehyde ethyl hemiacetal as a starting point, as shown in Scheme 4 (8).

The hemiacetal was first reacted with p-anisidine which, following a ketene–imine [2+2] cycloaddition and N-acylation, gave a single isomer of the desired trifluoromethyl beta-lactam. This was then coupled with a protected baccatin derivative to give the desired fluorinated taxoid.

Trimethyl ketones are very electrophilic when attached to an enzyme via a hydrate form. The tetrahedral structure mimics the transition state of enzyme hydrolysis. An example is an inhibitor of human leukocyte elastase. The serine protease inhibitor is involved in diseases such as rheumatoid arthritis and cystic fibrosis, and trifluoromethyl groups have been used in an inhibitor of human leukocyte elastase, which contains a trifluoromethyl ketone unit on a tripeptide backbone.

This can be made starting from trifluoroacetic anhydride, as shown in Scheme 5. An oxazolidinone is treated with trifluoroacetic anhydride, and the resulting adduct hydrolysed to give the required fluorinated intermediate.

Amino acids are common building blocks in pharma molecules, so fluorinated analogues are similarly of great potential use. 3,3,3-Trifluoropropene can be used as a starting point for making 4,4,4-trifluorovaline and
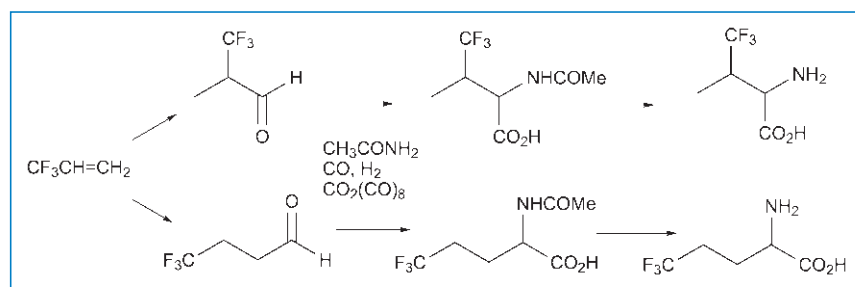
Scheme 6

5,5,5-trifluoronorvaline (9). The alkene is converted into an aldehyde, with the CF_3 unit at either the 2 or 3 position by a cobalt-catalysed regioselective hydroformylation (Scheme 6). These can then be reacted with acetamide, carbon monoxide and hydrogen and then deprotected to give the desired amino acid, which can then be incorporated into peptides and other potential drug molecules.

These are just a handful of examples to show how fluorinated intermediates can be used as building blocks to make pharmaceutically useful molecules. Fluorine's exceptional properties mean its importance in drugs is only likely to increase in the future, and by careful use of the right fluorine containing intermediate, their synthesis can be made simpler – and safer.

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