Fluorinated pharmaceuticals

Fluorinated compounds are of increasing interest as pharmaceuticals, and an extensive range of techniques for making them is now available.

Dr Basil Wakefield, Ultrafine

… the introduction of fluorine into a biologically active compound improves its pharmacological properties …

Although many pharmaceutical actives now bear little or no relationship to natural products, it is surprising how many are still related to natural predecessors. However, fluoro-organic compounds are very rare in nature - and the few that do occur are highly toxic. Moreover, elemental fluorine and hydrogen fluoride both have such a bad reputation as hazardous materials that many chemists were - and still are - averse to using them. How is it, then, that many fluorinated compounds are already in use as pharmaceuticals (and agrochemicals), and more and more are being developed? According to a recent book, by 1990 around 220 fluorinated drugs were on the market, representing 8 per cent of launched synthetic drugs, and at the time of its publication around 1,500 were under development (1). Three general answers may be given: a) the fluoro-organic compound has inherent biological activity; b) the introduction of fluorine into a biologically active compound improves its pharmacological properties; and c) what has been described as 'patent jumping' (2).

The pharmacological superiority of fluorinated compounds over their non-fluorinated analogues may be rationalised as follows. Although, contrary to popular misconceptions, covalently bound fluorine (C-F bond length 138 pm) has a significantly larger steric requirement than hydrogen (C-H bond length 109 pm), fluorinated compounds usually have a sufficient similarity in size and shape to their non-fluorinated analogues to fit a given enzyme receptor, so that they tend to have similar inherent biological activity. On the other hand, the carbon-fluorine bond is very strong (485 KJ mol^{-1}, compared with C-H, 416 KJ mol^{-1}), so the fluorinated compounds tend to be more resistant to metabolic degradation. The introduction of fluorine also generally confers increased lipophilicity.

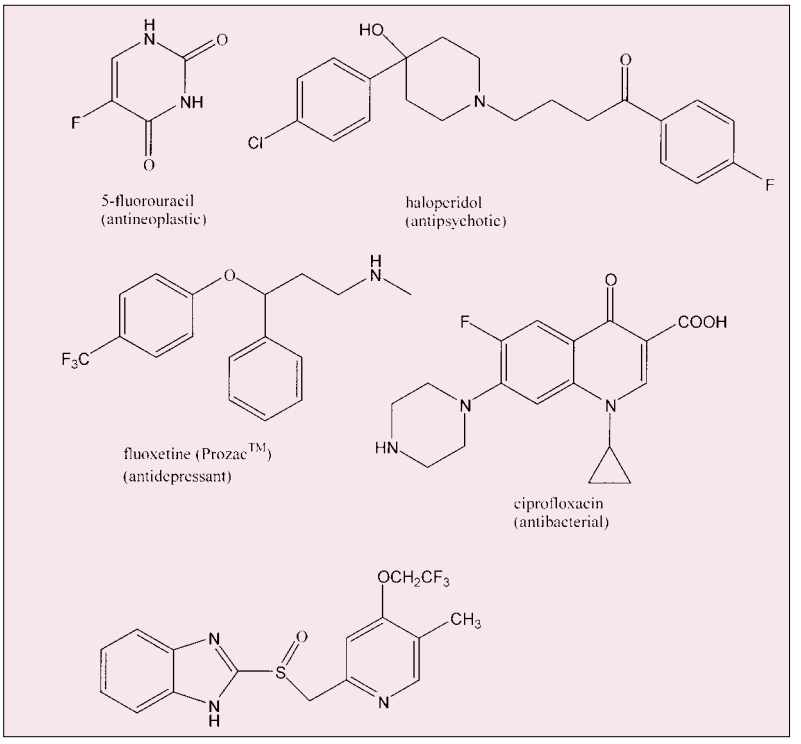

Figure 1. Some fluorinated aromatic and heterocyclic pharmaceuticals.

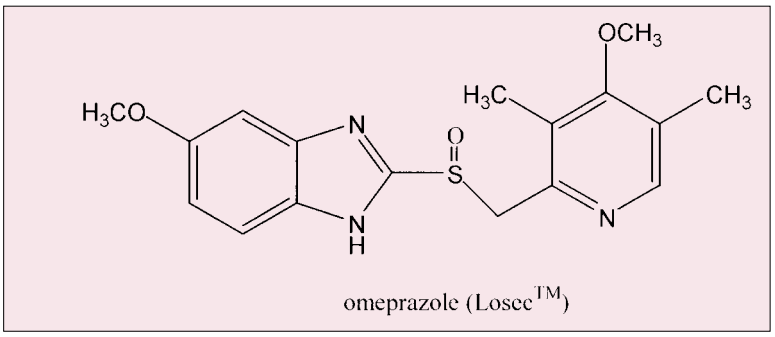

Figure 2. The structure of the proton pump inhibitor, omeprazole (Losec, Astra).

Pharmaceutical properties of organofluorine compounds

As so many fluorine-containing drugs are on the market, only a small selection can be mentioned. Some well-known examples are shown in Figure 1, which displays the variety of both chemical structures and types of pharmaceutical activity, and also illustrates some of the reasons for the popularity of fluorinated pharmaceuticals.

5-Fluorouracil is an example of a fluorinated compound with inherent pharmaceutical activity, and is one of the longest established fluorinated pharmaceuticals. It interferes with DNA and RNA synthesis by blocking the action of thymidylate synthetase, and is thus cytotoxic. However, it acts preferentially in fast-growing (cancerous) cells, which consume it rapidly (3).

Another long-established fluorinated pharmaceutical is haloperidol (4), which is used to treat a number of psychoses, in particular Gilles de la Tourette's syndrome. This example is unusual in that little is known about its mode of action and the non-fluorinated analogue has not been reported. However, it was the forerunner of a long line of fluorinated psychoactive compounds, of which perhaps the best known is the antidepressant, fluoxetine (Prozac™) (5). Details of the mode of action of this compound are still unclear, but it functions as a selective inhibitor of serotonin re-uptake. 5-Fluorouracil and haloperidol possess monofluorinated rings, but fluoxetine exemplifies the large number of biologically active trifluoromethylaromatic compounds.

Another important kind of biological activity is shown by another monofluorinated aromatic compound, the antibacterial, ciprofloxacin (6). Numerous non-fluorinated quinolone antibacterials have been made, and many marketed, but the fluorinated compounds appear to have superior properties, so that several are on the market and more are under development. Ciprofloxacin is active against both Gram-positive and Gram-negative bacteria.

Lansoprazole might be regarded as an example of 'patent jumping'. It was introduced by Takeda as a rival to Astra's 'blockbuster' proton pump inhibitor, omeprazole (Figure 2). Inevitably,

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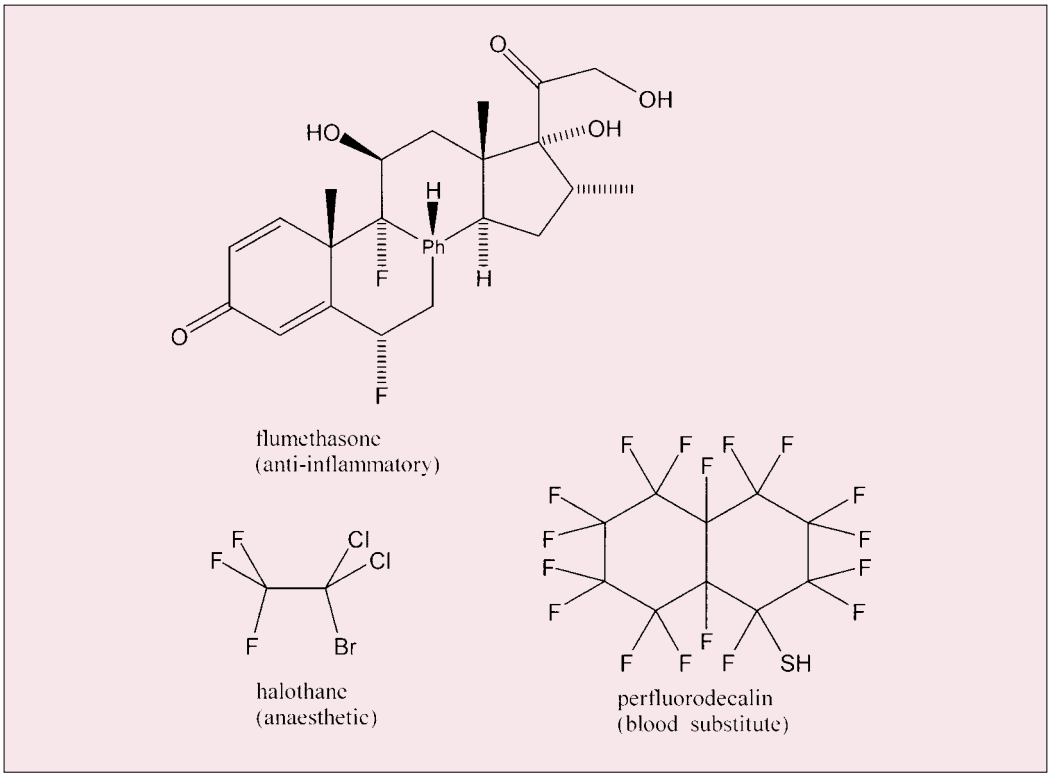

Figure 3. Some fluoroaliphatic and alicyclic pharmaceuticals.

patent litigation ensued! The Astra-Hässle patent (7) covered compounds with a 4-ethoxy substituent in the pyridine ring, and a key dispute was whether this covered a 2,2,2-trifluoroethoxy substituent. Since the dispute was settled out of court, the argument is still not legally resolved.

Almost all the compounds listed in reference (1) are aromatic compounds bearing fluoro or trifluoromethyl substituents. Fluorinated aliphatic compounds are much less widely used as pharmaceuticals but two categories are important: steroids and anaesthetics (see Figure 3). Fluorinated steroids are exemplified by flumethasone. Fluorine-substitution in steroids has been found beneficial in blocking metabolic pathways (particularly hydroxylation), and also in modifying the reactivity of adjacent oxygen functions. Anaesthetics are exemplified by halothane. Despite some disadvantages, halothane is still one of the most widely used inhalation anaesthetics, although various fluorinated ethers have been introduced as alternatives (see Ref 1, p 891). (It is noteworthy that although halothane is both an ozone destroyer and a greenhouse gas, there has not been an outcry against its use on these grounds.) Finally noteworthy are perfluorocarbons such as perfluorodecalin. These compounds can dissolve large volumes of oxygen and, following successful animal trials, have met with some clinical success as 'artificial blood' (see Ref 8, p369 for reviews).

Synthesis of fluorinated pharmaceuticals

Organic fluorine chemistry has its own characteristics; the organic chemistry of the other halogens can *not* be extrapolated to fluorine. Furthermore, although methods for introducing fluorine into organic molecules have been developed over many years (8), many of the earlier laboratory techniques are not suited to industrial production. Accordingly, the high level of interest in fluorinated pharmaceuticals has led to corresponding activity in the development of improved methods for synthesising these compounds. As a result, useful fluorinated building blocks (most of them fluoroaromatic compounds) are now offered on a large scale (1), and new reagents and techniques are available (9). Some of these recent advances are highlighted below.

- The classical method for preparing fluoroaromatic compounds was the thermal decomposition of aryldiazonium tetrafluoroborates (the Balz-Schiemann reaction). Various modifications have been made to this unpredictable and sometimes hazardous process, but the preferred industrial method is now diazotisation in anhydrous hydrogen fluoride. Hydrogen fluoride is of course very hazardous, but it is readily handled on a large scale provided that proper precautions are taken.

- Chlorinated and brominated organic compounds are comparatively easily prepared, so exchange of fluorine for the other halogens is attractive. Once again, anhydrous hydrogen fluoride has been used as combined solvent and source of fluoride (either alone or in conjunction with compounds such as antimony pentahalides). Another widely used source of fluoride ions is potassium fluoride, which must be anhydrous and preferably finely divided. By the use of spray-dried potassium fluoride, usually in an anhydrous dipolar aprotic solvent such as sulfolane, multiple replacements of chlorine by fluorine are achievable.

- Hydrogen fluoride and other sources of fluoride have been used to replace hydroxyl and selected ether functions by fluorine. Probably more important is the replacement of carbonyl functions: aldehyde and ketone groups by gen-dimethyl and carboxylic acid groups by trifluoromethyl. The former transformation is accomplished by sulfur tetrafluoride (hazardous), by diethylaminosulfur trifluoride (DAST; less hazardous though less reactive) or by bis (2-methoxyethyl)aminosulfur trifluoride (Deoxofluor®, claimed to be a safe replacement for DAST (8)).

Figure 4. Laboratory-scale use of fluorine using the Fluorodec® LT generator (reproduced by permission of Fluorogas Ltd).

The above may be regarded as indirect methods for introducing fluorine, involving F^-. For 'direct' introduction of fluorine, by replacement of hydrogen, sources of $F^\bullet$ or F^+ are required.

- Elemental chlorine and bromine may be used for radical halogenation (for example, via photo-dissociation). In the case of fluorine, such reactions proceed only too well. As a consequence

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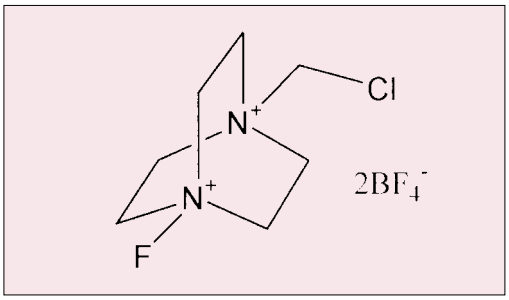

Figure 5. Selectfluor® reagent.

of the very weak F-F bond (dissociation energy only 159 KJ mol^{-1}) and the very strong C-F bond (485 KJ mol^{-1}), radical chain fluorination by elemental fluorine is so exothermic that incautious experiments on reactions of fluorine with hydrocarbons led to ignition or worse (9). Some of the methods for overcoming this problem are the use of high dilution in inert gases, low temperatures and moderators, and 'slow release' techniques such as electrochemical generation of fluorine in situ and the use of high-valent metal fluorides as fluorine carriers. All of these required special know-how and equipment, so they tended to be confined to specialised laboratories. Such laboratories continue to be invaluable, but equipment for generating and handling fluorine is now more generally available. Work with fluorine should still not be undertaken lightly and requires rigorous safety evaluation, but it can now be carried out in a 'normal' laboratory environment (see Figure 4).

• Fluorine is the most electronegative element, so the design of reagents capable of furnishing electrophilic fluorine - $F^{\delta+}$, let alone F^+ - has required considerable invention. Perchloryl fluoride, $FClO_3$, worked fairly well but proved hazardous, and xenon difluoride is useful but very expensive. However, rationally designed reagents containing fluorine bonded to other electronegative atoms, oxygen and nitrogen, are now available (10). Fluoroxy-compounds, such as fluoroxytrifluoromethane, CF_3OF, and acyl hypofluorites, RCOOF, have to be prepared *in situ* (using fluorine), but studies on a large number of N-fluoro-compounds (11) have led to the development of some stable, crystalline reagents for electrophilic fluorination. These include the commercially available Selectfluor® reagent, Figure 5.

A short article can only give an over-simplified and highly selective account of fluorinated pharmaceuticals. However, I hope to have demonstrated that, rather than being viewed as unusual and esoteric, organofluorine compounds should be regarded as important mainstream pharmaceuticals, and advances in synthetic methodology now make them readily available.

After graduating from Imperial College, London, (BSc and PhD), postdoctoral research in the USA (Louisville, Ky) and the UK (Reading) and a period in industry (Courtaulds), Dr Basil Wakefield spent most of his career at the University of Salford, where his research interests included polyhalogenated aromatic and heteroaromatic compounds. In 1984, he was a co-founder with Feodor Scheinmann of Ultrafine, which arose from a university company set up to carry out custom syntheses for industry. On his retirement from the university, he joined the company - which now has a staff of almost 30 and offers a comprehensive chemical service to pharmaceutical and biotechnology companies.

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