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Fluorine in health care: Organofluorine containing blockbuster drugs

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ABSTRACT

Organic fluorine compounds have had a profound impact on the development of bioactives for the modern pharmaceuticals market. It is estimated that up to 20% of pharmaceuticals prescribed or administered in the clinic contain a fluorine atom and 30% of the leading 30 blockbuster drugs by sales contain a fluorine. In this *Highlight* review, the top 10 fluorine containing pharmaceuticals (by US Sales in 2008) are highlighted. By this measure, these are currently the most significant fluorinated compounds impacting on health care. They embrace statins (Lipitor, Crestor, Vytorin, Zetia/Ezetimibe), anti-inflammatories (fluticasone propionate, Celebrex), antacids (Prevacid), antidepressants (Lexapro), neuroleptics (Risperdal) and antibiotics (Levaquin). In each case the structures and modes of action of these important drugs compounds are reviewed and representative synthetic routes are highlighted.

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1. Introduction

In 1954 Fried and Sabo [1] showed that the introduction of a fluorine atom to the 9α position of cortisol, improved its therapeutic index as an anti-inflammatory by an order of magnitude. Historically the development of Fludrocortisone (Fig. 1) was the first example of the introduction of fluorine into a pharmaceuticals product. A recent review by Hagmann [2] retrospectively illustrates that over the subsequent 60 years, fluorine has been found in around 15–20% of all new chemical entities (NCIs) licensed each year for the clinical market. The element generally finds its way into the organic framework during lead optimisation studies, and particularly as a strategy to block metabolism, for example by hydroxylation enzymes, to increase lipophilicity (logP) or to tune pharmacokinetic properties [3,4,5]. The impact of fluorine in this context has been dramatic. Of the top 30 best selling pharmaceutical products (US Sales in 2008), 10 have at least one fluorine atom [6]. Thus 30% of the leading blockbuster pharmaceuticals contain fluorine. This *Highlight* profiles these compounds (Table 1) and illustrates by association the impact of organic fluorine chemistry in the development of high end of the market, health care products. The review provides some commentary on the modes of action of these leading drugs and illustrates synthetic routes, although in individual cases the actual industrial route to these compounds is not always clear (Figs. 2 and 3).

2. Lipitor (Atorvastatin)

Lipitor (Atorvastatin) is currently the biggest selling pharmaceutical globally [7]. It holds the most prominent position in the blockbuster league table (Table 1) with sales of $5.9 billion ($\$5.9 \times 10^9$) dollars in 2008. It is commercially the most significant drug of the 'statin' class. The statins [8] are cholesterol lowering drugs which are prescribed to reduce the amount of biosynthetic cholesterol produced by the patient, to offset plaque accumulation and then vascular constriction with the consequent problems associated with increased blood pressure. Lipid particles can also become released from the vascular coating and move in the blood stream resulting in stroke or heart attacks.

Lipitor has two rather conspicuous stereogenic centres in its structure. These are crucially important to the mode of action of Lipitor. The drug is a potent competitive inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), the rate limiting enzyme of cholesterol biosynthesis in higher mammals [8]. HMG-CoA reductase reduces HMG-CoA to (*R*)-mevalonic acid, an important intermediate in steroid biosynthesis. There is a clear stereochemical relationship between the pendant (3*R*)-hydroxyl of the (3*R*, 5*R*)-3,5-dihydroxycarboxylic acid moiety of Lipitor and (*R*)-mevalonic acid (Scheme 1). This is also the case for Crestor (Section 6), which has a similar mode of action. The pendant (3*R*, 5*R*)-3,5-dihydroxycarboxylic acid moiety is recognised by HMG-CoA reductase, essentially acting as a (*R*)-mevalonic acid mimetic. This is recognised by the active site and inhibits the enzyme and blocks *in vivo* cholesterol biosynthesis.

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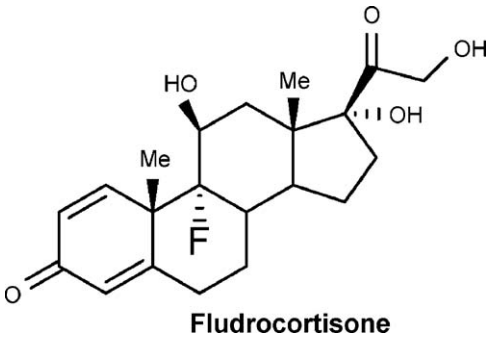

Fig. 1. Fludrocortisone was the first fluorinated pharmaceutical to be developed [1].

Table 1
Top 10 selling organofluorine containing pharmaceuticals (USA, 2008).

Position by sales (2008) relative to all pharmaceuticals	Trade name (see text for associated names)	US Sales in 2008 ($\$ \times 10^9$)
1	Lipitor	5.9
4	Advair Discus	3.6
5	Prevacid	3.3
11	Lexapro	2.4
17	Crestor	1.7
18	Vytorin	1.5
20	Celebrex	1.5
22	Levaquin	1.5
28	Risperdal	1.2
30	Zetia	1.2

Ten of the top 30 best selling products in health care are organofluorine compounds [6].

Lipitor is synthesised as a single enantiomer for the clinic. One route is outlined in Scheme 2 [9]. A key reaction involves the generation of the central pyrrole ring system by addition of a protected 4-fluorophenylglycine **3** to a conjugated acetylenic amide **4**, a process that occurs with concomitant decarboxylation to give pyrrole **5**. The 3,5-dihydroxycarboxylic acid side chain is prepared firstly as a racemic single diastereoisomer. This is accomplished by stereoselective borohydride reduction of the 3-keto-5-hydroxy precursor **6**. An enantiomeric resolution is then carried out using (*R*)-phenylethylamine to generate separable diastereoisomeric amides as illustrated in Scheme 2. Recrystallisation allows separation of the two diastereoisomers, and the desired one is hydrolysed to the enantiomerically pure drug, which is formulated as its calcium salt.

More recently an improved enzymatic method has been described for the synthesis of the side chain of Lipitor and also for Crestor (see Section 6) as illustrated in Scheme 3 [10].

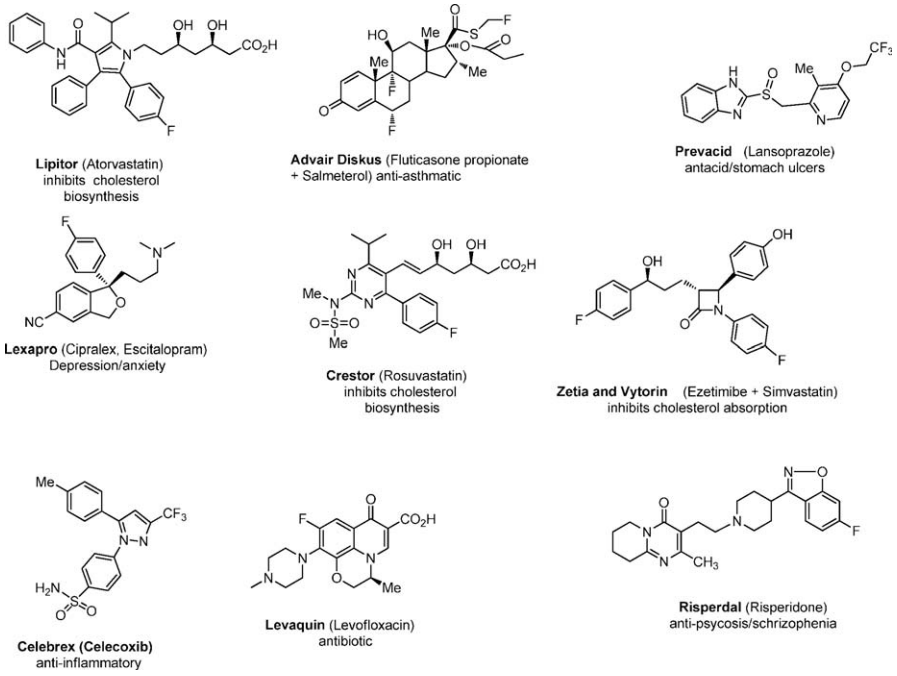

Fig. 2. Structures of the fluorine containing market leading pharmaceuticals.

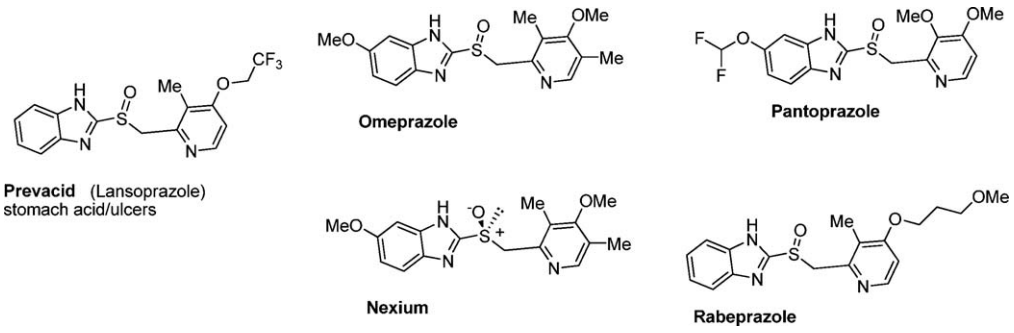

Fig. 3. Antacid drugs of the proton pump inhibitor (PPI) class.

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