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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.

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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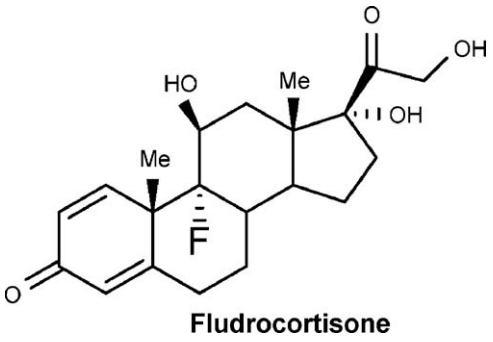


Fig. 1. Fludrocortisone was the first fluorinated pharmaceutical to be developed [1].

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].

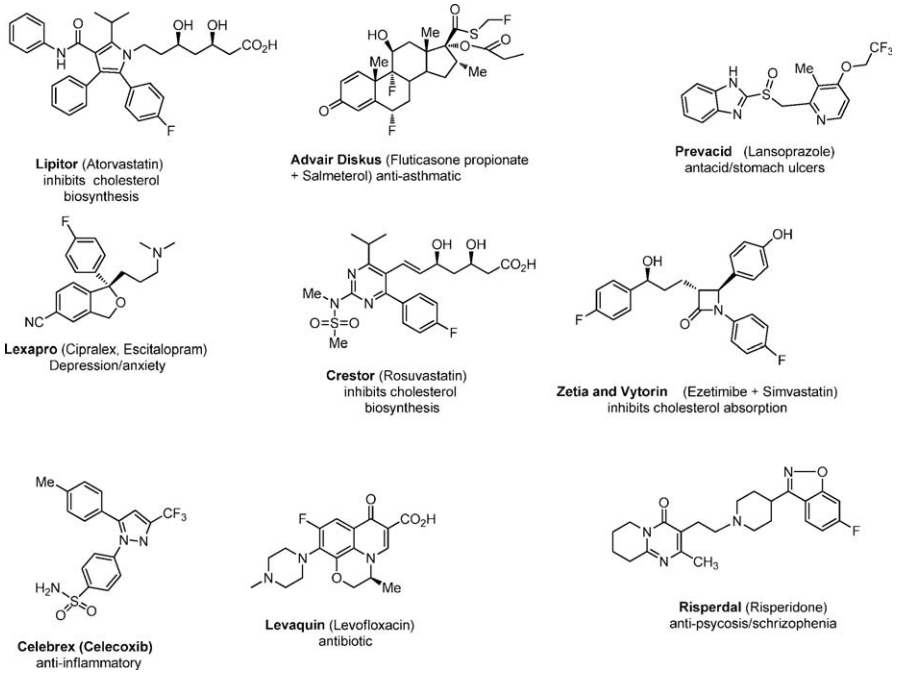


Fig. 2. Structures of the fluorine containing market leading pharmaceuticals.

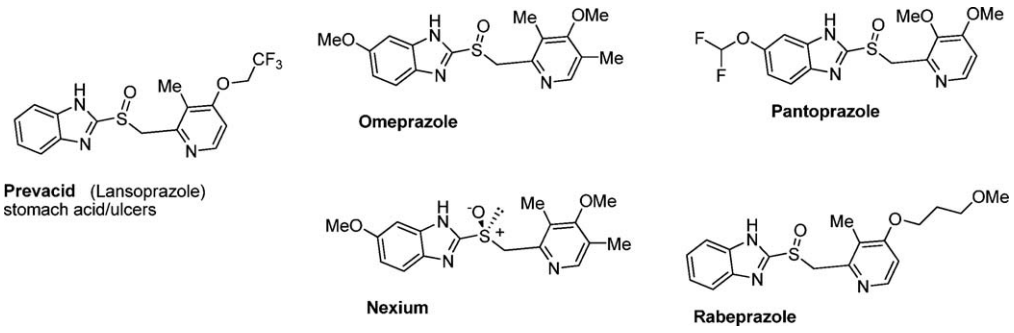
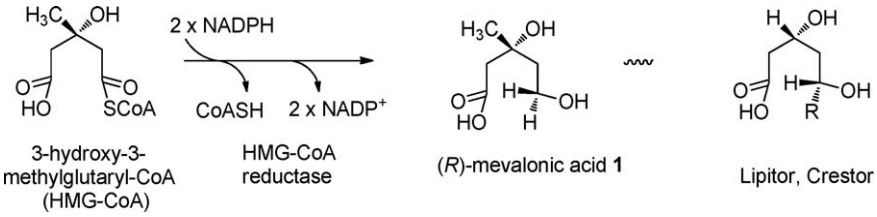


Fig. 3. Antacid drugs of the proton pump inhibitor (PPI) class.

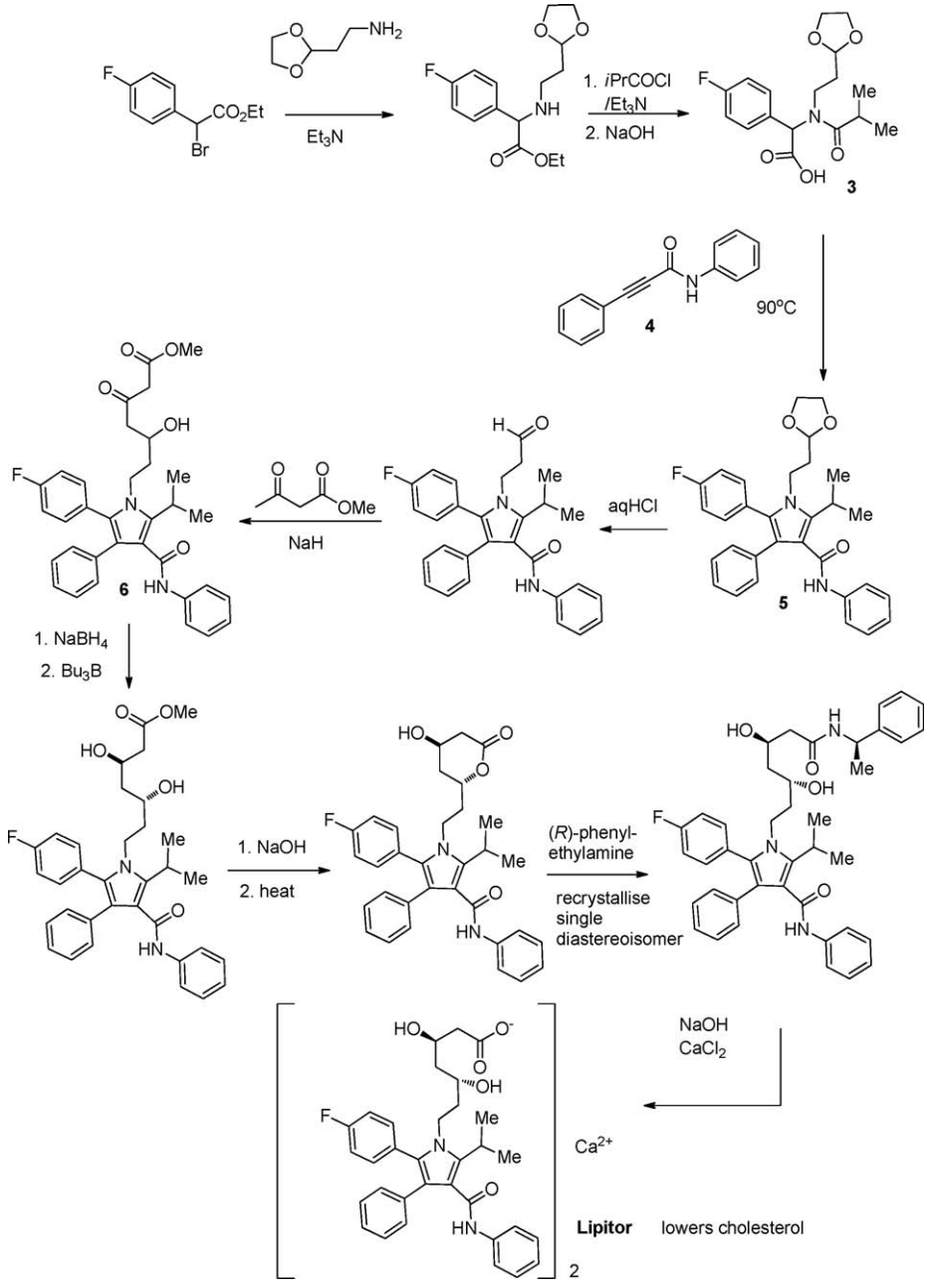


Scheme 1. The reaction of HMG-CoA reductase to generate (*R*)-mevalonic acid, the rate limiting enzyme in steroid/cholesterol biosynthesis. The structural relationship between (*R*)-mevalonic acid and the inhibitory statins, Lipitor and Crestor is highlighted.

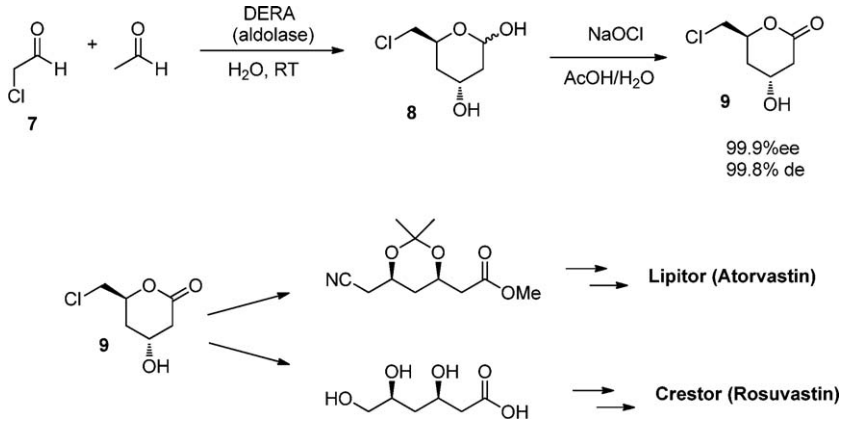
Deoxyribose-5-phosphate aldolase (DERA) can catalyse the aldol condensation between acetaldehyde and chloroacetaldehyde **7** to give the chloromethyl lactol **8** in high enantiopurity. Oxidation gives lactone **9** which is progressed by divergent routes for incorporation into a variety of statins including Lipitor and Crestor.

3. Fluticasone propionate

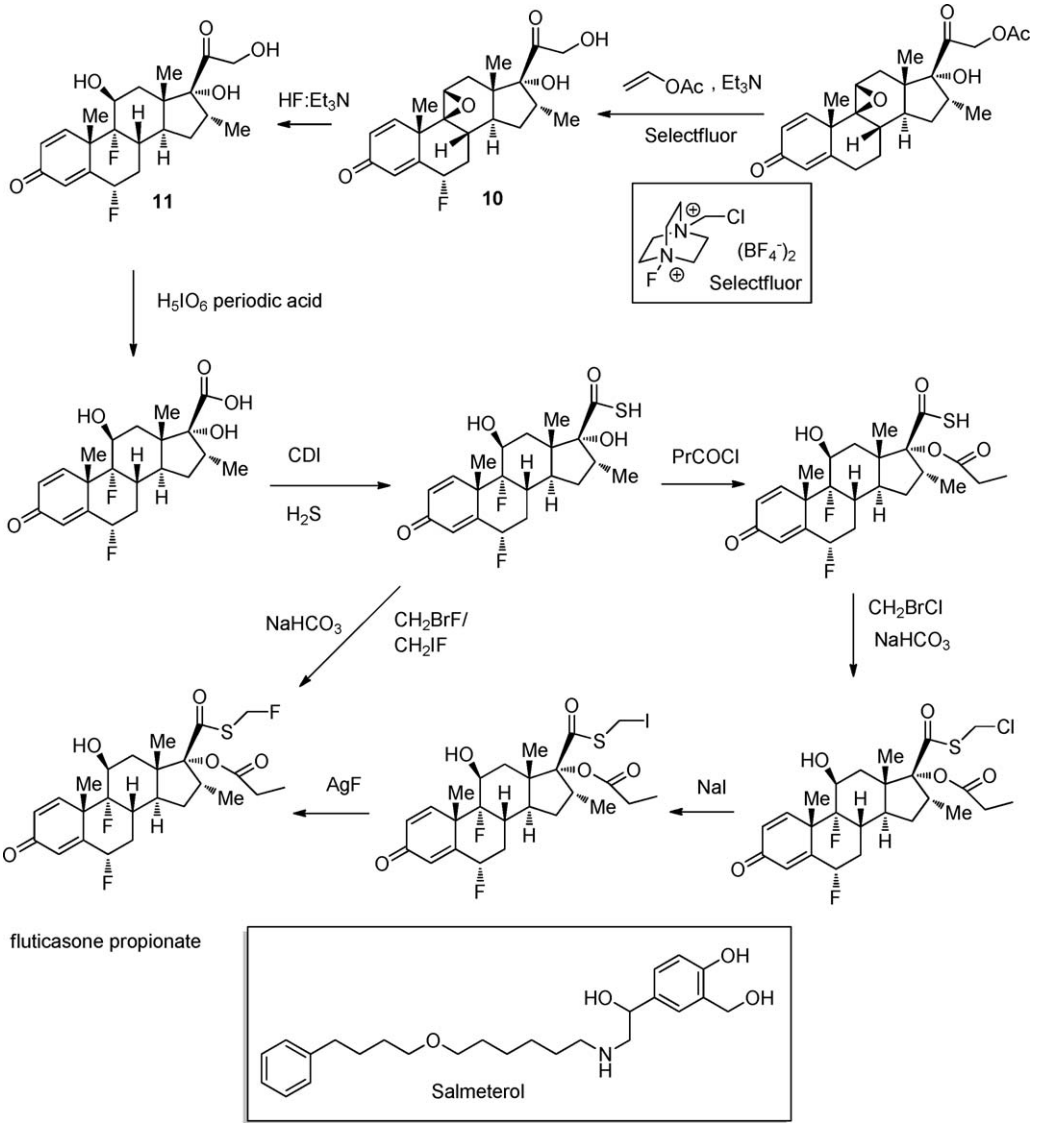
Fluticasone propionate (Table 1) is a steroidal anti-inflammatory used to treat a variety of conditions depending on how it is administered. It is a modern variant of the original Fludrocortisone (Fig. 1) reported by Fried and Sabo in 1954. Fluticasone propionate



Scheme 2. Synthesis and enantiomeric resolution of Lipitor (Atorvastatin) [9].



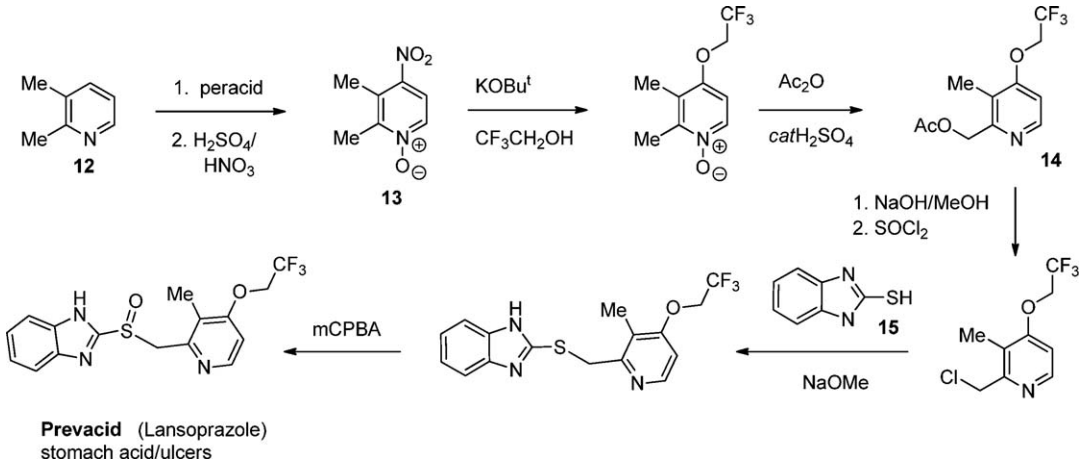
Scheme 3. Enzymatic (aldolase) route to the enantiomerically pure precursors of the side chains of Lipitor and Crestor [10].



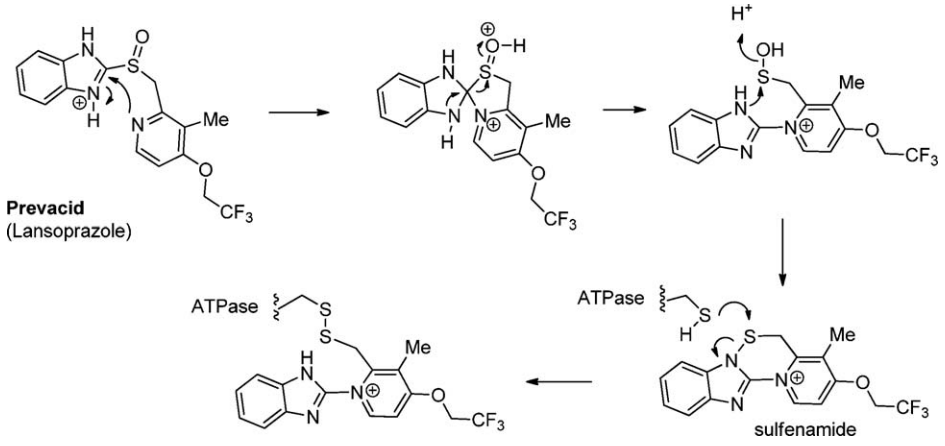
Scheme 4. Synthesis of fluticasone propionate. Fluticasone propionate in combination with Salmeterol are the active components of the Advair Diskus inhaler [12].

can be applied topically to treat inflammation directly associated with dermatoses and psoriasis [11]. However the major market for fluticasone propionate is to treat asthma as the most important member of a large class of inhaled corticosteroids. It is marketed in combination with Salmaterol for asthma treatments, where they are the active components in an inhaler sold as Advair Diskus. Thus the product is the formulation of these two drugs in its inhaler device.

Structurally fluticasone propionate is a complex molecule, certainly for a pharmaceutical product, carrying three separate



Scheme 5. Synthesis of Prevacid (Lanzoprazole).



Scheme 6. An acid catalysed rearrangement of Prevacid takes place in the stomach, to generate a cyclic sulfenamide, which then reacts with a cysteine residue of ATPase and inhibits this enzyme by covalent modification. Inhibition of ATPase inactivates K^+/H^+ exchange in the stomach lining.

fluorine atoms. Two of these fluorines are located at stereogenic centres on the steroidal framework, and the third is incorporated as an unusual fluoromethylthio ester.

This molecule is prepared from a steroidal framework [12]. In the synthesis shown in Scheme 4 the first fluorine is introduced using Selectfluor, an electrophilic fluorination reagent, by reaction with an *in situ* generated, conjugated vinyl enol acetate. Fluorination occurs to the lower 6α face to give epoxy-steroid **10**. Epoxide ring opening with hydrofluoric acid locates the 9α fluorine in **11**. The fluoromethyl group of the thioester is introduced sequentially from the chloro-, then iodo-methyl thioester, by a final fluoride ion (AgF) displacement of iodide to generate the substituent.

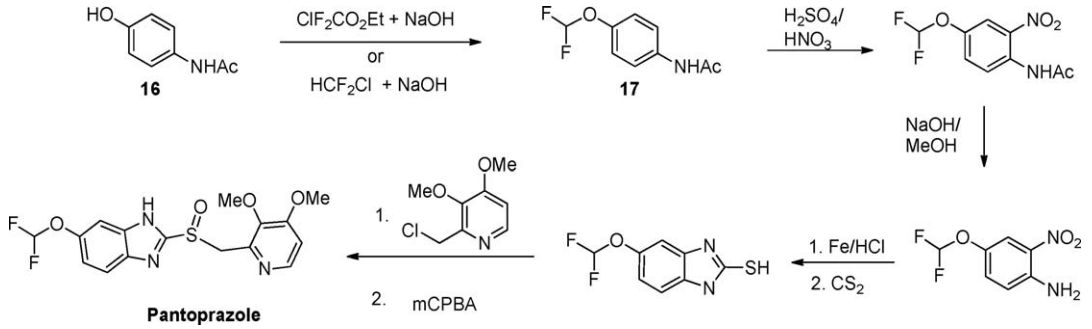
4. Prevacid (Lansoprazole)

Prevacid acid (Lanzoprazole) is currently the most successful commercial drug of its class in regulating gastric acid secretion (Scheme 5) [13]. Other important drugs of this group are Omeprazole, Pantoprazole and Rabeprazole, of which Pantoprazole which contains a difluoromethoxyl group (Scheme 7). They are used to treat heartburn, peptic ulcers and esophagal inflammation. Prevacid (Lansoprazole) is a representative of the 'proton pump inhibitors' (PPI), a group of drugs that inhibit the enzyme that replaces potassium ions (K^+) for protons (H^+) within the stomach lumen, a metabolic process driven by adenosine triphosphate (ATP). Prevacid undergoes an acid catalysed rearrangement in the stomach, in a reaction known as a Smiles rearrangement, to a sulfenamide product that binds irreversibly to this K^+/H^+ ATPase through a cysteine residue [14]. This is illustrated in Scheme 6. As a consequence the drug has a long lasting effect in reducing gastric acid secretion [15].

The sulfoxide residue is a stereogenic centre, however the drugs have been administered as racemates, as the enantiomers do not seem to differentially inhibit acid secretion; however the enantiomers are metabolised at different rates by P-450 enzymes. In the case of Omeprazole, a new (*S*)-(−) enantiopure version has now been marketed as Nexium$^{(R)}$ to target patient populations that have genetic variants and are deficient in certain P-450 metabolising enzymes, and thus achieve longer lasting effects.

Enantiomeric resolution clearly adds a degree of complexity for synthesis in process development [16]. A synthetic route to Prevacid (Lansoprazole) is illustrated in Scheme 5 [17]. It starts by oxidation and nitration of 2,3-dimethylpyridine **12**, and then nucleophilic aromatic substitution of the resultant activated pyridine-N-oxide **13**, by trifluoroethanol under basic conditions. Acetylation, with concomitant acetate migration, in an intramolecular rearrangement, generates the pyridinehydroxymethyl acetate **14**. This intermediate is then taken through to the final drug as the racemic sulfoxide, by nucleophilic substitution with mercaptobenzimidazole **15** and then *m*CPBA oxidation.

Pantoprazole is an important drug of this class which also contains fluorine. The difluoromethyl ether of Pantoprazole is introduced *via* difluorocarbene generation and then reaction with N-acetyl-4-aminophenol **16** to generate the phenol ether **17**, as



Scheme 7. Synthesis of Pantoprazole highlighting difluorocarbene precursors for incorporation of the difluoromethyl ether moiety [18].

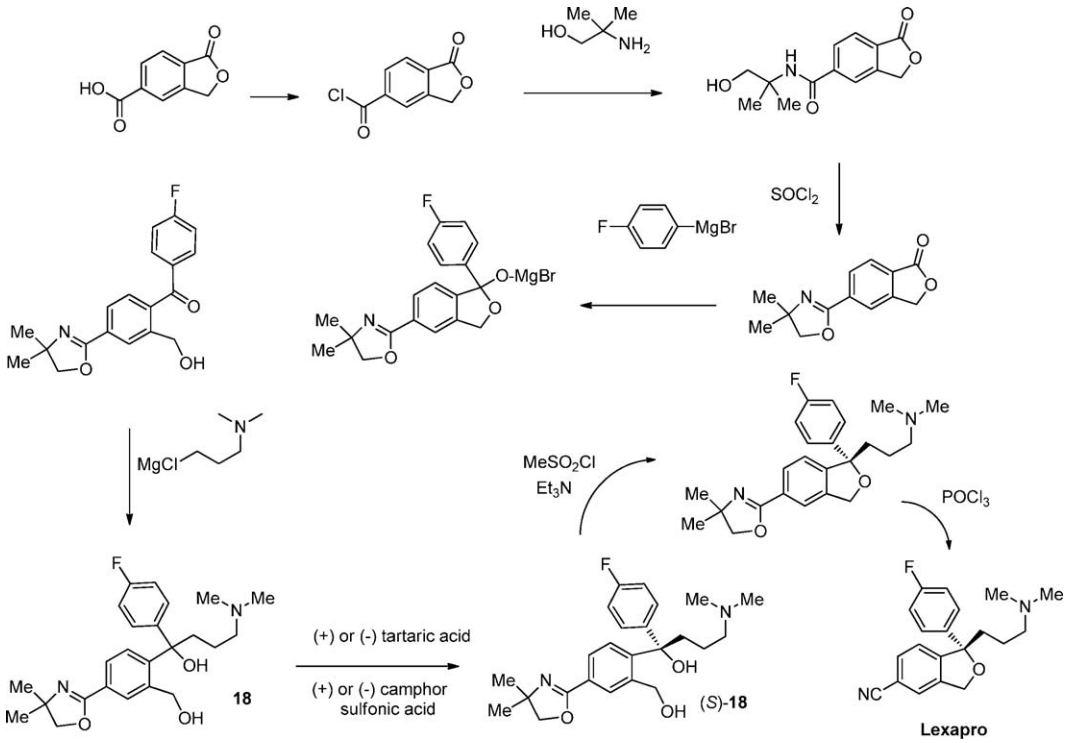
illustrated in Scheme 7 [18]. This moiety is then progressed through to Pantoprazole in a similar manner to that found for Prevacid synthesis.

5. Lexapro (Cipralex, Escitalopram)

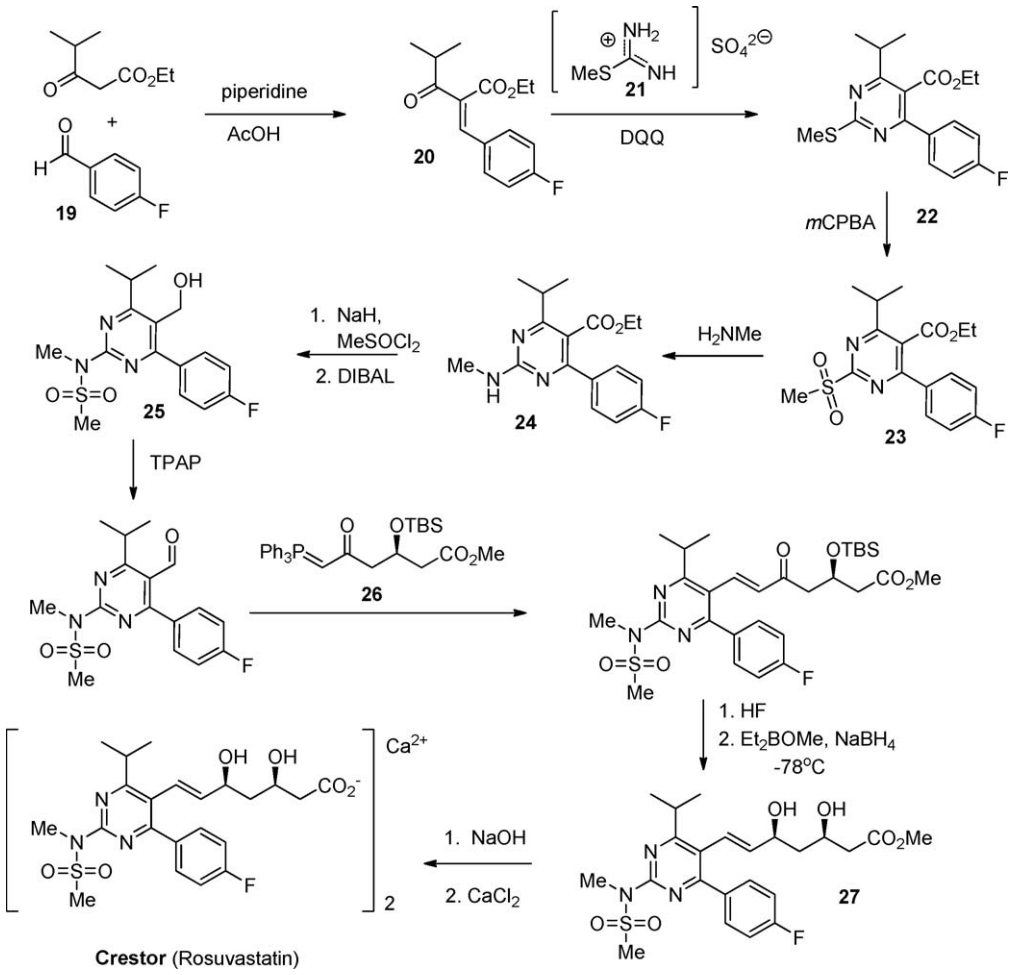
Lexapro (Cipralex, Escitalopram) is an important drug for treating depression and anxiety. It is one of a large class of serotonin selective reuptake inhibitors (SSRIs) [19]. Such drugs act in the brain by blocking the reuptake of the neurotransmitter serotonin, into presynaptic cells. Lexapro is marketed in enantiomerically pure form as its (*S*)-enantiomer as shown. This followed from the racemic drug Citalopram which came to the end of its patent life [20]. The drug was relaunched as a single stereoisomer, and this (*S*)-enantiomer was initially named *es*citalopram, but it is now marketed under the Lexapro trade name. A synthesis of Lexapro is shown in Scheme 8, which incorporates a resolution by crystallisation of the tartaric acid or camphorsulphonic acid salts of dimethylamine **18** to generate (*S*)-**18** [21]. Remarkably the pure enantiomer is also prepared on a multi-ton scale for the clinical market by chiral chromatography resolution, rather than asymmetric synthesis [22].

6. Crestor (Rosuvastatin)

Crestor, like Lipitor (Section 2) is a statin [8]. The structural similarity to Lipitor is obvious in that both have a pendant (3*R*, 5*R*)-dihydroxycarboxylic acid residue. This moiety is important for binding to the enzyme HMG-CoA reductase, the rate limiting enzyme in cholesterol biosynthesis in humans, as described above in Scheme 1 for Lipitor. The synthesis of Crestor, like Lipitor, requires the introduction of two stereogenic centres on the (3*R*, 5*R*)-dihydroxyl carboxylic acid side chain moiety. A synthetic route is illustrated in Scheme 9 [23]. The route introduces fluorine from *p*-fluorobenzaldehyde **19**, in a condensation with a β-keto ester, to generate the conjugated ketone **20**. Reaction with S-methylisothiourea **21** followed by oxidation with DDQ generated the pyrimidine **22**. Oxidation of **22** to methylsulfone **23** rendered it labile to nucleophilic aromatic substitution by methylamine, and then the resultant methylaminepyrimidine **24** was converted to the sulfonamide **25**. Subsequent functional group manipulation leading to a Wittig reaction of a preprepared, enantiomerically pure, side chain phosphonium ylid **26** allowed assembly of the molecular framework. In the final stages the second stereogenic centre was generated by an intramolecularly directed borohydride



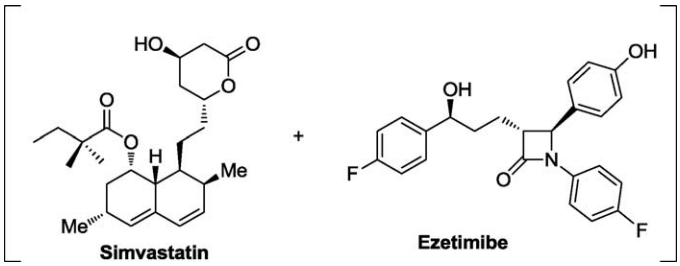
Scheme 8. Synthesis of Lexapro involving resolution by crystallisation of diastereoisomeric salts of dimethylamine **18** [22].



Scheme 9. Synthetic route to the statin, Crestor (Rosuvastatin) [23].

reduction to give the *syn*-diol **27**. The drug is finally formulated as its calcium salt.

7. Zetia and Vytorin



Zetia (Ezetimibe) is a drug prescribed to lower cholesterol levels and to treat obesity [24]. It contains only Ezetimibe and is a complementary therapy to Vytorin. Vytorin is a combination therapy where Ezetimibe and Simvastatin are administered together. The combination is used to lower cholesterol levels in blood to prevent the consequent complications of atherosclerosis, heart disease and stroke. Vytorin like Zetia (Ezetimibe) also has an increasing role in the treatment of obesity. Simvastatin is a semisynthetic 'statin' produced by fermentation of the fungus *Aspergillus terrus* [25,26]. The drug acts by inhibiting HMG-CoA reductase, and lowering *in vivo* biosynthesised cholesterol, in a similar manner to Lipitor and Crestor as discussed in Section 2 and illustrated in Scheme 1 [8]. There is a clear structural similarity between the lactone moiety of Simvastatin and (*R*)-mevalonic acid, and the drug competes with the natural metabolite in binding to HMG-CoA reductase. However Ezetimibe acts in a different manner. It inhibits uptake of dietary cholesterol into blood plasma and it also inhibits the reabsorption of biosynthesised cholesterol into the bile ducts, as cholesterol is reabsorbed by this route back into circulating plasma. Ezetimibe acts by firstly being metabolised to the gluconoride derivative **28** as shown in Fig. 4, and this metabolite becomes localised in enterocytes (absorptive cells) within the intestinal wall and inhibits cholesterol absorption [27]. The metabolite appears to be a better inhibitor than Ezetimibe itself.

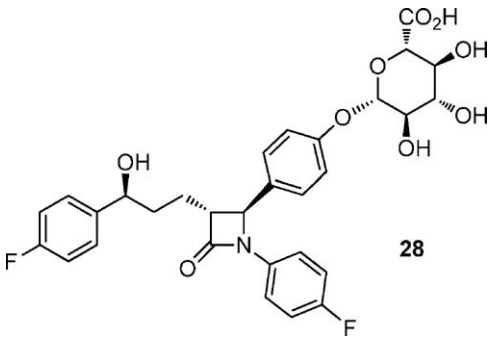
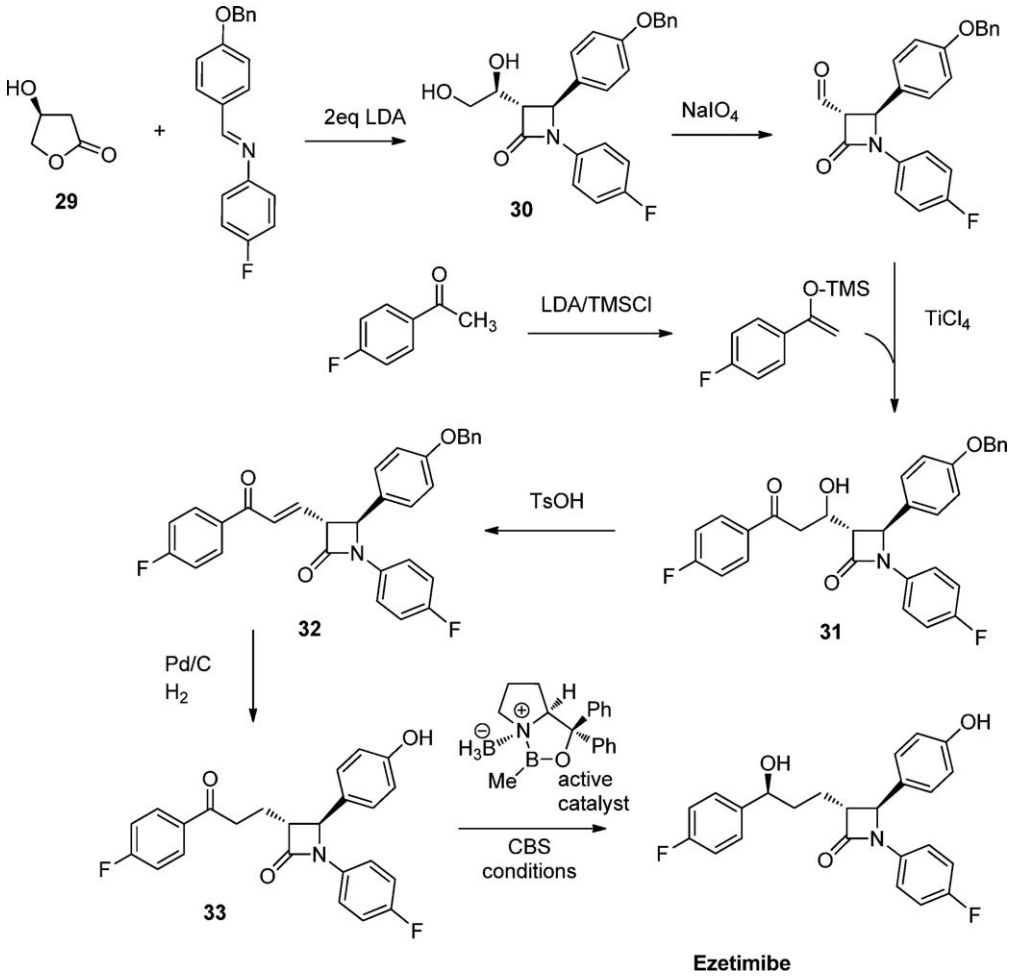
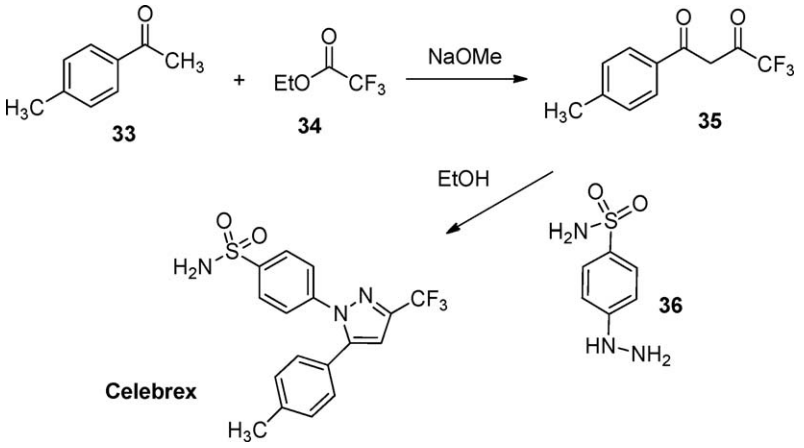


Fig. 4. The gluconoride metabolite **28** of Ezetimibe is thought to be the active agent in inhibiting cholesterol absorption in the gut and bile ducts [27].



Scheme 10. Synthesis of Ezetimbe illustrating β-lactam ring formation and an asymmetric reduction. Ezetimbe is one component in the Vytorin combination administered for lowering cholesterol [28,29].

The Ezetimibe component of Vytorin contains three stereogenic centres and a variety of methods have been explored to assemble this drug in enantiomerically pure form [28]. Scheme 10 illustrates one of the more efficient [29]. The synthesis starts with (*S*)-3-hydroxy-γ-lactone **29**, a reagent commercially available in enantiomerically pure form, and derived by a number of methods including an origin in the chiral pool (L-(*S*)-malic acid). Generation of the dianion of 3-hydroxy-γ-lactone **29** allows an imine condensation, with *in situ* formation of the β-lactam ring of **30**, in high diastereoselectivity. Oxidative diol cleavage and then silyl enol ether condensation generates β-hydroxyketone **31**. Acid promoted dehydration then results in elimination to the α,β-unsaturated ketone **32** side chain which can be hydrogenated, with concomitant benzyl ether



Scheme 11. Two step synthesis route to Celebrex [31].

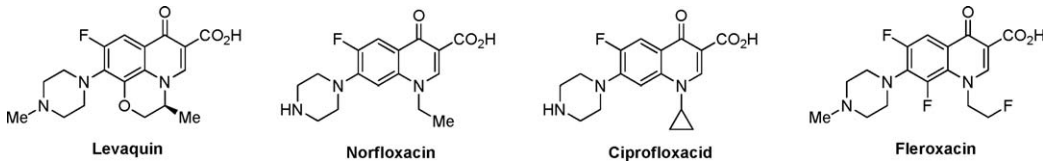


Fig. 5. Representative examples of the fluoroquinolone antibiotics.

deprotection to generate **33**. The final stereogenic centre is efficiently generated by asymmetric ketone reduction (96% de) of **33** using the CBS methodology developed by Corey, Bakshi and Shibata [30].

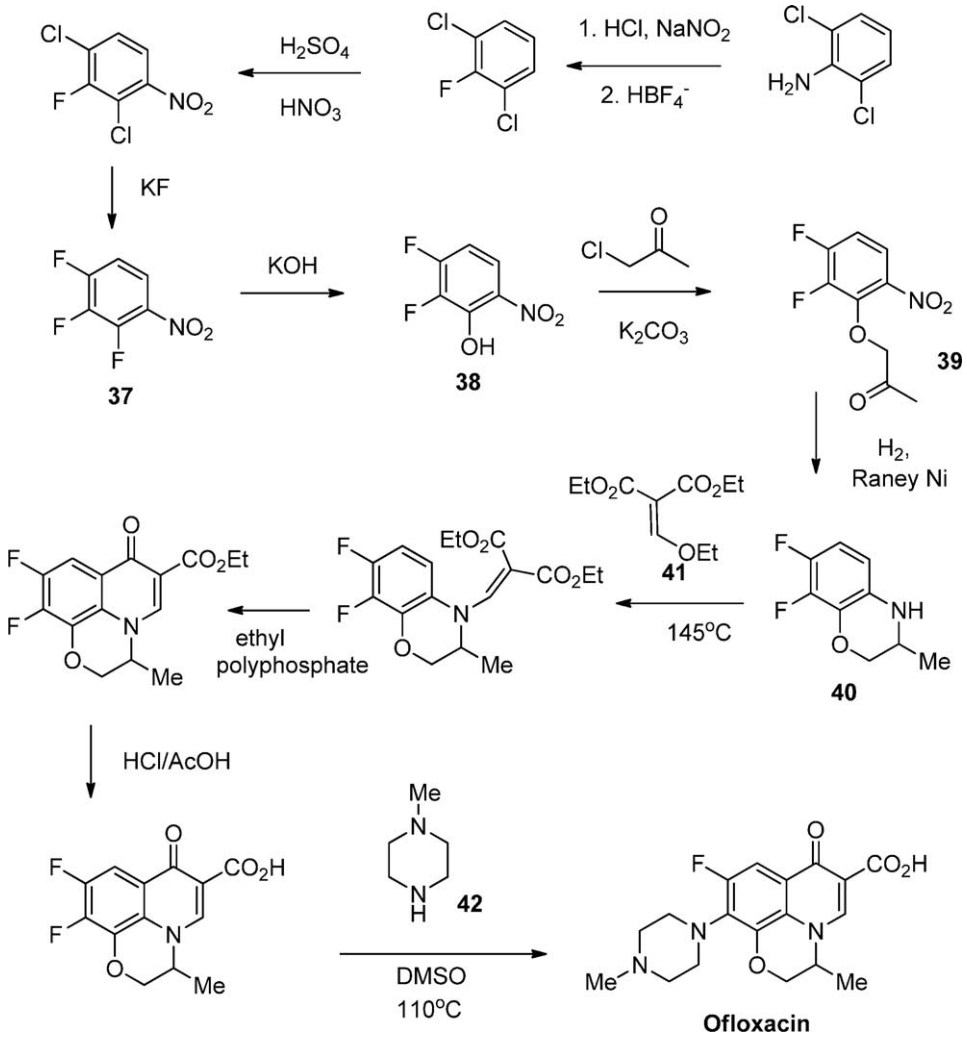
8. Celebrex

Celebrex is used to treat and reduce pain associated with arthritis. It is a non-steroidal anti-inflammatory drug which inhibits prostaglandin biosynthesis. In humans it has selectivity for the inhibition of inducible cyclo-oxygenase-2 (COX-2) over cyclo-oxygenase 1 (COX-1) [31]. The COX-2 enzyme system is responsible for prostaglandin biosynthesis, the inhibition of which reduces the inflammation response [32]. More recently Celebrex is finding a role in the treatment of cancers where it inhibits intracellular levels of the protein cyclin D1, an important protein in cell replication.

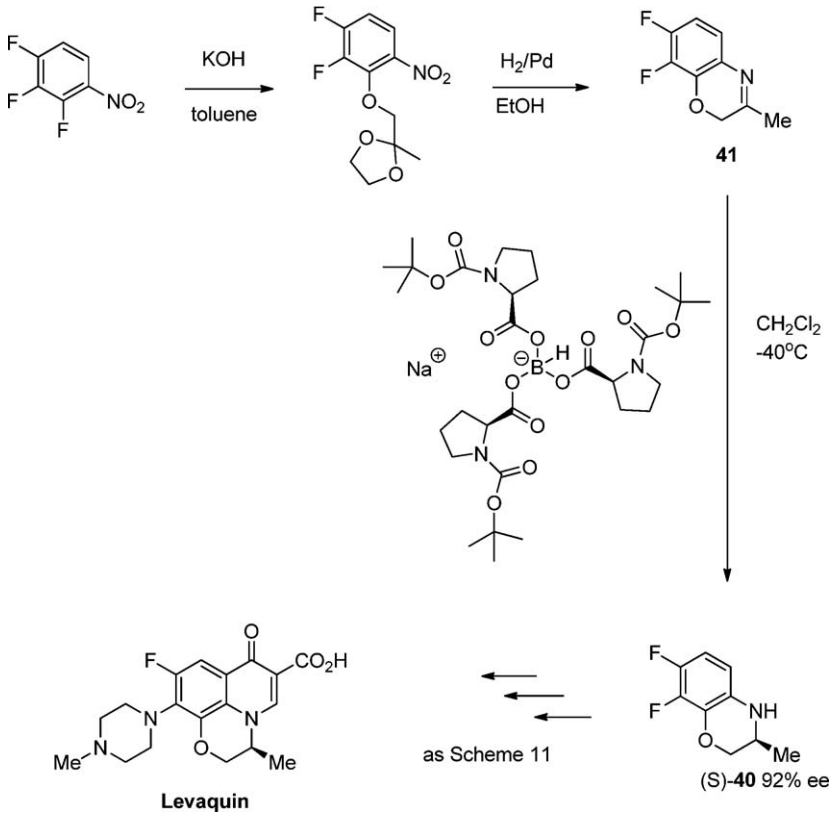
Celebrex emerged as the twentieth best selling drug of 2008 (Table 1). Structurally it is a typical drug like molecule and it is prepared in essentially two steps from straightforward starting materials as illustrated in Scheme 11. A Claisen condensation involving *para*-Me-acetophenone **33** and ethyl trifluoroacetate **34** generates the trifluoromethyl-β-diketone **35**, and then a condensation with the arylhydrazine sulfonamide **36** generates the CF_3-substituted pyrazole ring as the final step in Celebrex synthesis [31].

9. Levaquin (Levofloxacin)

Levaquin is a representative of the very large class of the fluoroquinolone antibiotics. These are probably the most successful non-natural products class of antibiotics, and it has emerged that the fluorine atom at the 9-position of the quinolone ring is essential for good antibacterial activity [33]. Many structural variants have been prepared and marketed and other significant



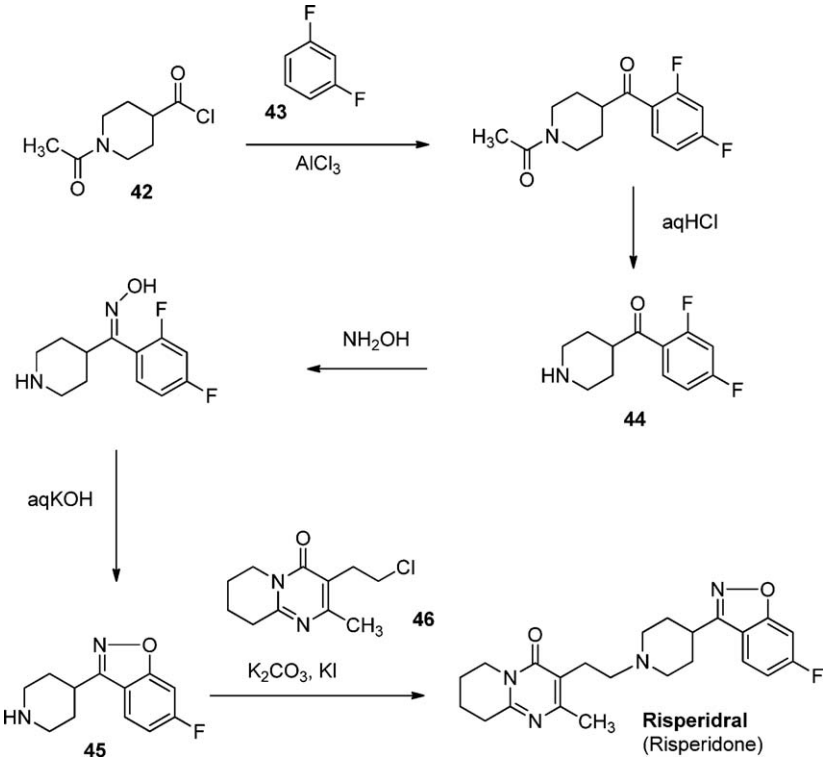
Scheme 12. Synthesis of Ofloxacin *via* 2,3,4-trifluoronitrobenzene.



Scheme 13. Enantiopure synthesis of Levaquin (Levofloxacin) *via* an asymmetric borohydride reduction [35].

representatives of this class are Norfloxacin, Ciprofloxacin, and Fleroxacin (Fig. 5).

Levaquin is the (*S*)-(−) enantiomer of the racemic predecessor Olfloxacin hence the alternative name *Levo*floxacin [34]. The fluoroquinolone antibiotics bind to bacterial DNA gyrase (topoisomerase II), an enzyme that nicks, uncoils and then repairs supercoiled DNA. Inhibition of DNA gyrase inhibits key processes required for rapid cell replication of micro-organisms such as



Scheme 14. Synthesis of Risperdal (Risperidone) starting from 1,3-difluorobenzene.

translation (DNA coding for mRNA) and also DNA repair. The antibiotic can be administered orally or intravenously and is used to treat a wide spectrum of antibacterial infections including pneumonia and bronchial infections.

Racemic Ofloxacin is prepared as shown in Scheme 12, using 2,3,4-trifluoronitrobenzene **37** as a key intermediate. The *ortho* fluorine is displaced by hydroxide and the resultant phenol **38** is used for ether **39** formation. Reductive cyclisation after a Raney nickel hydrogenation then generates the benzoxazine ring system **40**. Construction of the quinolone ring involves a reaction of **40** with diethyl ethoxymethylenemalonate **41** in a two step sequence of condensation and then intramolecular Friedel Crafts acylation. Hydrolysis followed by a nucelophilic aromatic substitution reaction with N-methypiperazine **42** generates racemic Ofloxacin (Scheme 12).

The enantiopure synthesis of Levaquin applies a variant of this route, and relies on an asymmetric synthesis of (*S*)-**40**. One reported method involves imine reduction of **41** using an enantiomerically pure borohydride reducing reagent derived from L-proline as illustrated in Scheme 13 [35]. Other asymmetric hydrogenation methods as well as hydrolytic enzyme resolution methods of carbamates of **40** have been described in the patent and primary literature [36]. With (*S*)-**40** in hand then the synthesis follows that of Ofloxacin as described in Scheme 12.

10. Risperdal (Risperidone)

Risperdal (Risperidone) is a second generation neuroleptic drug used to treat psychotic patients and predominantly to treat schizophrenia. It is also used to treat severe and manic depression and related forms of bipolar disorder. Sales in 2008 (Table 1) were a substantial increase (32%) on the 2007 sales, indicating a surge in its prescription. Risperdal (Risperidone) crosses the blood brain barrier and competes with the neurotransmitter dopamine. The drug acts by binding selectively to, and blocking (antagonist) the dopamine D2 receptor, and shows selectivity with significantly less affinity for dopamine D1 receptors [37]. Risperdal (Risperidone) is also an antagonist of the 5-HT_2 and α_2 adrenergic receptors in the brain. The origin of the reduction in psychotic effects is complex but it appears to be associated with dopamine D2 receptor blockage, and then a compensatory increase in the activity of dopaminergic receptors in peripheral neurons [37].

An important reaction in the early stage of the synthesis of Risperdal is a Friedel Crafts acylation reaction involving 1,3-difluorobenzene **42** with an N-protected-piperidine-4-carboxylic acid chloride **43**, to generate ketone **44** after deacylation. The key 5-membered 1,2-benzisoxazole ring is then generated by oxime generation of ketone **44** and then intramolecular nucleophilic aromatic substitution of the *ortho* fluorine substituent to give **45**. Nucleophilic reaction between the piperidine nitrogen to the pyrimidinone alkylchloride **46** is the last step of the synthesis. The route shown in Scheme 14 represents one of a number of variants in the patent literature [38] where N-protection of the piperidine-4-carboxylic acid chloride can be a carbamate rather than an amide, and the order of oxime preparation/benzisoxazole ring cyclisation and appending the pyrimidinone moiety are reversed

11. Conclusion

This review has highlighted that a large proportion of the leading pharmaceuticals products on the global market contain organic bound fluorine. Of course the commercial fortunes of the selected drugs will rise and fall in future years, as their place in the market matures or as new compounds emerge and compete for the top rank positions. However given the prominent role of fluorine in drug development since the early 1950s, we can be sure that fluorine will continue to be an important element in pharmaceuticals development as long as small molecule therapeutics dominate the pharmaceuticals industry. Thus developments in the chemistry of fluorine and in understanding the particular properties of fluorine when placed in an organic molecule that binds proteins will, remain an important area of chemical research.

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