

Review

Important fluorinated drugs in experimental and clinical use

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Abstract

This reviews details selected fluorine-containing drugs that either have potential for, or are already in, clinical use. Fluorine imparts desirable characteristics to drugs by modulating both the pharmacokinetics and pharmacodynamic properties of a drug. Therefore, incorporation of fluorine into a drug increases the lipophilicity enhancing absorption into biological membranes whereby its small covalent radius can facilitate docking with their drug receptor(s). By emphasising those structural features that modulate the absorption and metabolism of these compounds, when possible, structure–function relationships are discussed. Drug types are classified according to their therapeutic indication and utility rather than structural type and include phosphodiesterase inhibitors, antiparasitic agents (especially antimalarials), anticancer compounds (such as kinases), antibacterials, and selected probes useful for ^{18}F positron emission tomography. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

The low abundance of natural products containing fluorine ensures that drugs containing this element are processed as xenobiotics when they encounter biological systems. An exception is the first fluoro-organic substance extracted from the South African gifblar shrub (*Dichapetalum cymosum*), fluoroacetic acid (**1**), which mimics acetic acid so closely that it can substitute for it in the Krebs cycle. Since then about a dozen natural products containing fluorine have been isolated including the antibiotic nucleocidin (**2**), isolated from *Streptomyces calvus*, which has proved too toxic for clinical use [1].

The incorporation of fluorine into a drug allows simultaneous modulation of electronic, lipophilic and steric parameters, all of which can critically influence both the pharmacodynamic and pharmacokinetic properties of drugs [2]. Bioisosteric substitution for hydrogen by fluorine is, therefore, an important strategy for incorporation of a group capable of reinforcing drug–receptor interactions (electronic modulation) [1], aiding translocation across lipid bilayers or absorption (lipophilic modulation) [3] and inducing conformational change/blocking metabolism (steric parameters) [4]. Fluorine occupies a van der Waals radius (1.47 Å)

positioned between oxygen (1.52 Å) and hydrogen (1.20 Å) allowing it to mimic a hydroxyl group, and to participate in hydrogen bonding interactions [4b]. For instance, PTP1B complexes with bound α,α -difluorinated phosphonate inhibitors, one of the two prochiral fluorines participates in an important hydrogen bonding interaction with the Phe-182 amide NH in the enzyme target [5].

Additionally, chemical and stereochemical transformations are influenced by fluorine when compared to their non-fluorinated counterpart [6].

Fried and Sabo's seminal preparation of 9 α -fluoro-hydrocortisone acetate [7] revealed how judicious introduction of fluorine into an existing biologically active molecule imparted beneficial properties to that compound. Since then, a vast number of fluorinated molecules, including drugs, have been discovered or designed [6]. This review concentrates on recently disclosed compounds that are either advancing to or are in clinical trial. Such compounds have been conveniently segregated according to their therapeutic indication rather than structural type.

2. Phosphodiesterase inhibitors

Second messenger systems involved in regulation of autocoids, drugs, hormones and neurotransmitters include cAMP and cGMP, both of which can be inactivated by

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phosphodiesterase enzymes (PDEs). Ultimately this results in a plethora of effects including reduction of inflammatory cell activity. A particularly well defined and attractive drug target is PDE4 discovered over a decade ago, which can be selectively inhibited by Roflumilast (**3**), a safe and well tolerated fluorinated analogue of Plicamylast, is in phase III clinical trials for asthma [8] and could also be useful for treating allergic rhinitis. Subtypes of this enzyme such as PDE4D can be selectively targeted over other isoforms by an order of two log doses by the *N*-[1-(2-chloro-phenyl)ethyl]-2-(4-fluoro-phenoxy)benzamide enantiomer shown (**4**). These types of compounds are considered useful for the treatment of inflammatory diseases such as asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), pulmonary hypersensitivity, allergic rhinitis, rheumatoid arthritis, psoriasis, and ulcerative colitis, as well as central nervous system (CNS) disorders such as depression and multi-infarct dementia [9,10].

3. Atherosclerosis

Coronary heart disease (CHD) remains the predominant cause of mortality in the developed world. Thickening of the artery wall in this condition leads to both myocardial infarcts and stroke. First generation HMG CoA reductase inhibitors (HMG-CoA) such as Fluvastatin and Lovastatin can inhibit elevated concentrations of low-density lipoprotein cholesterol (LDL-C). Recently, second generation LDL-C inhibitors possessing superior efficacy include a series of fluorinated analogues such as Cerivastatin (**5**) that reduce serum LDL-C by 33–44% in hypercholesterolaemic patients receiving daily sub-miligramme doses. Rosuvastatin (ZD-4522) (**6**), in a clinical trial also decreased total plasma cholesterol concentrations by 34 and 65% for doses of 1 and 80 mg, respectively. Interestingly, this compound is not metabolised by Cyt P₄₅₀ (CYP) 3A4 thereby, diminishing the possibility of drug–drug interactions by this route. However, (**5**) was rapidly withdrawn from market in August 2001 because of its adverse effects on muscle [11]. Statins with good lipid solubility have been postulated to possess increased potential for toxicity because of increased myocyte penetration.

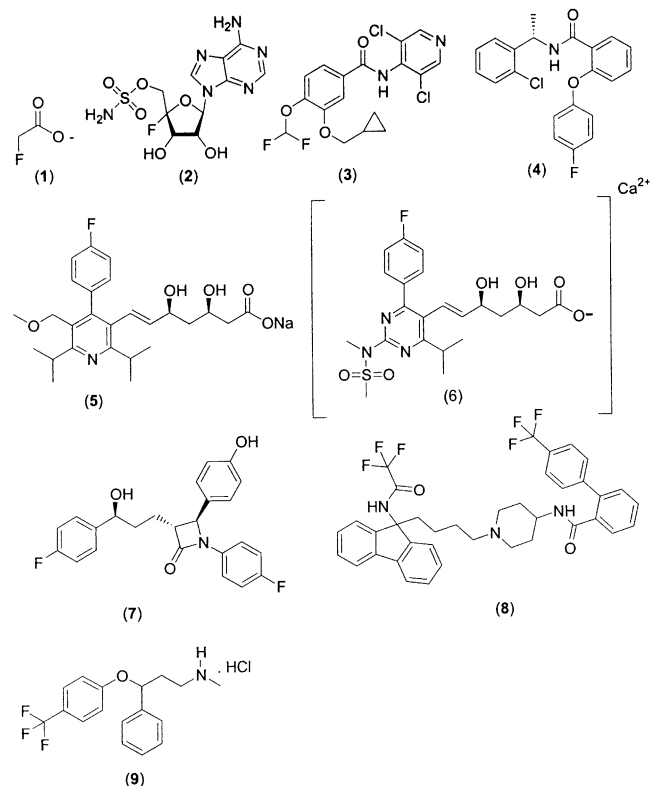
In contrast, cholesterol absorption inhibitors constitute a particularly exciting approach and are exemplified by Ezetimibe (Sch 58235) (**7**), which demonstrates synergistic effects with statins such as Cerivastatin [12]. Ezetimibe can block normal biliary excretion of cholesterol from the gall bladder into the intestine, which is otherwise reabsorbed. Clarification of the exact mechanism of action may lead to further rationally designed drugs.

Microsomal triglyceride transfer protein (MTP) inhibitors transport a variety of lipids including cholesteryl esters and triglycerides into intestinal chylomicrons and hepatic very low-density lipoproteins. The trifluoromethylated containing drug candidate inhibitor BMS 201038 (**8**) is a potent

inhibitor of MTP ($K_i = 0.5$ nM) resulting in a 90% decrease in plasma cholesterol concentrations in hamsters and Watanabe rabbits which lack functional LDL receptors [13]. It is claimed that BMS 201038 can be beneficially used in conjunction with other cholesterol lowering agents in a recent patent [14].

4. Selective serotonin reuptake inhibitors (SSRI's)

These drugs increase the brain's level of serotonin, thus improving mood. SSRI's have also been shown to be useful in the treatment of obsessive–compulsive disorder and some forms of severe shyness and pre-menstrual tension syndromes of which Prozac (fluoxetine hydrochloride) is a representative example (**9**). The trifluoromethyl group probably assists in preventing phase 1 metabolism *para* to the ether linkage.



5. Parasitic diseases

It is estimated that the global incidence of parasitic infections will continue to rise, both for drug sensitive and resistant malaras. Recent, revised estimates indicate that disease burden from malaria has been seriously underestimated and coupled with projected rises in global temperature; the situation is set to worsen [15]. Since an effective vaccine is currently unavailable, considerable effort from various academic and industrial research groups has provided a number of interesting compounds including fluorinated molecules.

In an effort to avoid quinone-imine formation by biosoteric replacement of a sensitive hydroxyl group with fluorine, Park et al. [4] have produced a number of mechanism based, rationally designed compounds which are considered safe and effective substitutes for various antimalarials, including amodiaquine and primaquine. However, in order to avoid bioactivation in vivo to a quinoneimine, the introduction of a 5-fluoro group failed to prevent formation of the 5-glutathionyl metabolite and, therefore, the previously known ejection of a fluoride ion from (10) by cytochrome P₄₅₀ catalysis was invoked.

Bioisoteric substitution of the oxidisable hydroxyl group by a stronger carbon–fluorine bond that can still participate in hydrogen bonding interactions with the drug receptor is exemplified in (11). The primaquine analogue (12) was designed to prevent bioactivation to potentially toxic compounds by incorporating a fluorine on the 6-position but it is inferior to the slow acting Walter Reed Army Institute of Research experimental drug WR 238605 (13), a replacement for primaquine that has prophylactic, treatment and malaria transmission-blocking potential [16]. In this respect, the fluorinated analogue of M6407 (15) 2,6-bis-pyrrolidin-1-ylmethyl-4-(7-trifluoromethylquinolin-4-ylamino)phenol, designed by the Barlin group shows antimalarial activity superior to that of pyronaridine in the *Samiri* ex vivo bioassay model of malaria [17]. Although the azalogue (14) had lowered antimalarial activity its overall toxicity profile was superior to (15).

Introduction of the large trifluorinated methyl group can decrease biological activity compared to the lead compound, possibly by encountering unfavourable steric drug–receptor interactions, as discovered for the trifluoromethyl analogue (16) of the Roche *bis*-quinoline antimalarial Ro 47-7737 [18], several analogues of which are useful in preventative and therapeutic treatments of autoimmune diseases and phenomena, transplant rejection (such as host-versus-graft disease) and sepsis [19b,c]. Similarly, unpublished results indicate similar properties for trifluoromethylated analogues of the highly antimalarial drug Mefloquine (IC₅₀ 1.2 mg/kg, *P. berghei*) [19a,d].

The classic antimalarial Mefloquine (Lariam) (17) is encountering increased drug resistance in endemic areas but has also caused controversy because of its potential adverse reactions in susceptible individuals especially women and those taking recreational drugs causing neuropsychiatric symptoms [20]. Halofantrine (18), which contains a trifluoromethyl group and has proven cardiotoxic to certain individuals and, in at least one instance, has lead to sudden and unexpected mortality [21].

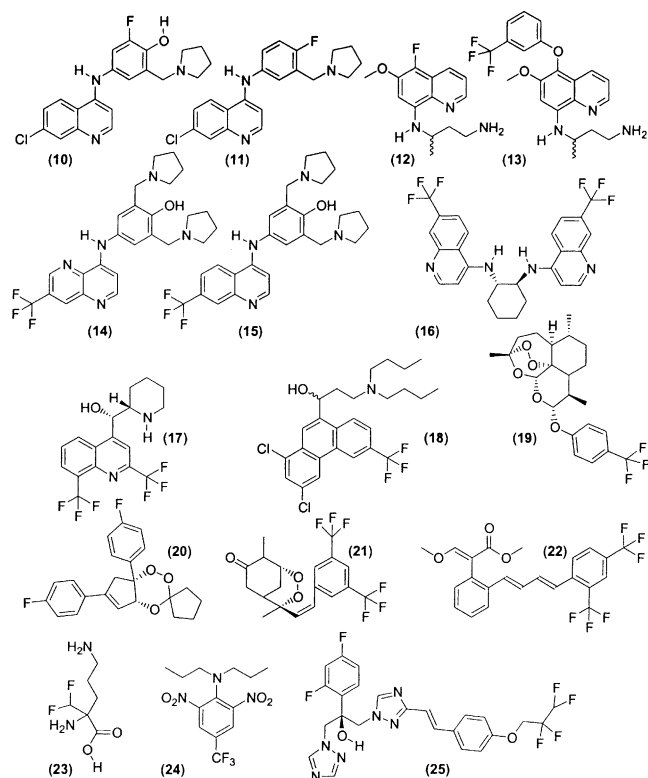
Artemisinin (qinghaosu) extracted from *Artemisa annua compositae* L. Mer. continues to provide inspiration for several new semi-synthetic 1,2,4-trioxane agents. For instance, substitution at C-10 by a fluorinated group improves the in vivo activity by increasing stability towards metabolic inactivation in (19) [22]. Disappointingly, the potent, rationally designed second generation trioxanes, such as Fenozan

BO7, a difluorinated 3,3'-spirocyclopentane 1,2,4-trioxane (20), have yet to be commercialised [23]. Arteflene (21), a fluorinated compound modelled on yingzhaosu A, which contains a 2,3-dioxabicyclo[3.3.1]nonane system, has not been developed further but continues to inspire both mechanistic studies and synthesis of related analogues [24].

Compounds that are structurally unrelated to existing structural types of antimalarial are rare, an exception being the trifluoromethylated phenyl β -methoxyacrylates (22) [25], which may prove useful in avoiding drug resistance.

Eflornithine (23), a rationally designed ornithine decarboxylase inhibitor, can cure infections with *Trypanosoma gambiense* but remains unaffordable by healthcare in endemic areas [26]. The plant microtubule inhibitor trifluralin (24), originally developed as a herbicide, has previously been tested with success against *Leishmania*, *Trypanosoma brucei* and, more recently, *Trypanosoma cruzi*, the causative agent of Chagas disease. Interestingly, this sensitivity has been correlated with the deduced amino acid sequences of α - and β -tubulin of *T. cruzi* compared with plant, mammal and other parasite sequences [27].

Liendo et al. [28] report the in vitro antiproliferative effects, and mechanism of action, of both enantiomers of the *bis*-triazole derivative ICI 195,739 against epimastigotes and amastigotes of *T. cruzi*, the aetiological agent of Chagas' disease. Importantly, the *R*(+) enantiomer, D0870 (25), can induce radical cure of parasite burden in murine models of the acute and chronic forms of the disease. Terminal oxidation (and first pass metabolism) of the ether side chain is probably delayed due to the 2,2,3,3-tetrafluoro blocking group.



6. Kinases as drug targets: anticancer chemotherapy

Bridges has reviewed various chemical inhibitors of kinases, including those containing fluorine substituents, and some of which are currently in clinical trials are illustrated below [29]. ZD1839 (Iressa) is an orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor which blocks signal transduction pathways implicated in the proliferation and survival of cancer cells and other host-dependent processes promoting cancer growth [30]. Unlike Iressa, the quinazoline inhibitor CI-1033, upon binding to the active site of the epidermal growth factor (EGF) receptor, is irreversibly attacked by a thiol at Cys-773 (Michael reaction). When combined with radiation therapy, it acts as a sensitiser resulting in synergistic destruction of erb-B positive breast cancer cells [31]. Similarly, a 4-aryl,3-cyanoquinoline (**28**) has also progressed to the clinic in which bioactivation *in vivo* is blocked by the presence of a fluorine group [32]. ZD6474 (**29**) has particularly good physical properties, is selective for KDR, orally bioavailable and shows potent activity against A459 lung, Calu-6 colon, MDA-MB-231 breast, A431 vulval, SKOV-3 ovarian and PC-3 prostate cancer models in athymic mice, achieving between 92 and 100% inhibition [33].

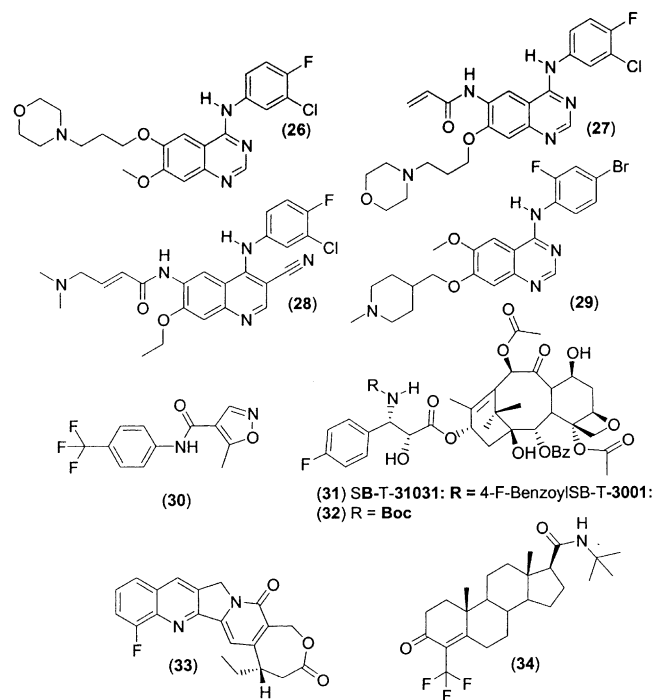
Platelet derived growth factor receptor tyrosine kinase inhibitors are implicated in the uncontrolled proliferation in numerous cell types including glial cells, fibroblasts and smooth muscle cells. Using a combinatorial approach the structurally simple and specific isoxazole SU-101 (**30**) showed activity *in vitro* against various cell types and, importantly exhibited activity in tumour xenograft models at doses of 20 mg/kg per day. Although the trifluoromethyl group retards hydroxylation at the *para* position to the secondary amine group, ring-opening metabolism produces a long-lived metabolite ($t_{1/2} = 19$ days). Phase II clinical trials against an aggressive type of brain tumour (glioblastoma multiforme) proved of little benefit over existing treatments such as procarbazine and were finally discarded, due to an unfavourable metabolic profile [34]. In an attempt to inhibit premature metabolic inactivation of putative topoisomerase II inhibitors, bioisoteric replacement of a chlorine with fluorine in the lead compound lead to a dramatic and unexpected loss of potency in of 4-anilino-2-fluoro-4'-demethylpodophyllotoxin analogues. It is suggested that the unfavourable DNA–fluorine interaction explains the loss of activity [35].

A series of synthetic fluorine-containing analogues of paclitaxel and docetaxel bearing CF_3 or CF_2H at the C-3' position are up to three orders of magnitude more potent than paclitaxel or doxorubin against sensitive and resistant human breast cancer cells. Metabolism studies show that fluorinated taxoids block the action of cytochrome P_{450}S , importantly, a combination of ^{19}F and ^1H NMR analyses coupled with molecular modelling experiments have revealed a novel conformer, which probably undergoes efficient molecular recognition by microtubules and appears

to be tightly bound to the protein. Other fluorine-containing paclitaxel and docetaxel have been synthesised through coupling enantiopure (3*R*,4*S*)-1-acyl- β -lactams with various baccatins. The incorporation of fluorine in such taxoids (**31**, **32**) allows design of an effective probe substance for unravelling their metabolic fate. Such fluorine-containing taxoids block metabolic pathways associated with the cytochrome P_{450} class of enzymes [36,37].

Fluorine substitution in the A-ring of homocamptothecin has a pronounced influence on biological activity, providing several compounds, including (**33**), which show a two-log dose increase in potency over camptothecin. Amongst these compounds, the 10,11-difluoro-hCPT has been selected for further development. The small elemental radius of fluorine is cited as an important requirement when these compounds bind within topoisomerase I, the intended drug target [38].

A novel 5α -reductase steroid inhibitor (**34**) containing a 4-trifluoromethyl group is designed to target benign prostatic hyperplasia. It is more potent *in vitro* than Finasteride and deserves further development [39].



To circumvent deactivating metabolism, Hutchinson et al. [40] have synthesised mono- and difluorinated analogues of 2-(4-aminophenyl)benzothiazoles. 2-(4-Amino-3-methylphenyl)-5-fluorobenzothiazole, because of its resistance to undesired metabolic C-hydroxylation, its potency, and its broad spectrum of action *in vitro*, has emerged as the most potent of the new generation of antitumor benzothiazoles and is currently the favoured clinical candidate. Its L-alanine and L-lysine amino acid pro-drug forms are pharmaceutically robust, water-soluble hydrochloride salts with *in vivo* activity in human xenograft and are, therefore, destined for phase 1 trials.

7. Antibacterials

Infections caused by serious Gram-positive organisms can be treated with Linezolid, the first of a rationally designed [41,42] class of antibacterial agents called oxazolidinones that specifically target early ribosomal protein synthesis “downstream” rather than acting “upstream” on either RNA or DNA. It’s rapid oral absorption and near complete bioavailability is due in part to the presence of a fluorine group and shows activity against vancomycin resistant bacteria [43].

8. Radiolabelled drugs

Although preparation of the ^{18}F analogue of an existing pharmaceutical is challenging, tracking absorption, distribution, site of action, metabolism and finally excretion using positron emission tomography justifies the expense [44,45]. Importantly, the incorporation of the positron emitting nuclide ^{18}F into various drugs has uncovered an important diagnostic tool allowing imaging of cells, nerve tissue and tumours [46], in real time, in vivo. For instance, 6- ^{18}F fluoro-3-(2(*S*)-azetidylmethoxy)pyridine (^{18}F), a novel analogue of the high-affinity nicotinic acetylcholine receptor ligand, A-85380, is a high-affinity radio-ligand for central nicotinic acetylcholine receptors. Due to its short half life it requires extremely rapid synthesis [47]. Automated radiosynthesis of Fluticasone propionate [(*S*)-fluoromethyl-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(propionyloxy)-androstano-1,4-diene-17 β -carbothioate; FP], a potent anti-inflammatory steroid and anti-asthmatic drug, labelled with ^{18}F ($t_{1/2} = 109.6$ min; $\beta(+)=100\%$) using cyclotron-produced no-carrier-added ^{18}F fluoride allows monitoring of deposition in human lung using positron emission tomography (PET) [48]. Fluoroethylthio-2,5-dimethoxyphenethylamine is potentially valuable as a vehicle for ^{18}F studies of brain kinetics in PET studies. In this case, the fluorine atom is claimed to be intrinsic to the expressed central activity [49]. In contrast, pro-drugs can be designed to prevent access to the brain thereby minimising adverse effects including neurotoxicity [50].

9. Conclusion

The expense and method of its insertion into useful bioactive scaffolds currently limit the utility of fluorine. The exciting discovery of an enzymatic reaction that occurs in the bacterium *Streptomyces cattleya*, which catalyses the conversion of fluoride ion and *S*-adenosylmethionine (SAM) to 5'-fluoro-5'-deoxyfluoro-adenosine (5'-FDA), is the first fluorinase enzyme to be identified, a biotechnological discovery that could revolutionise the preparation of organofluorine compounds [51]. Evolution of novel methods of incorporating fluorine into organic molecules will no doubt

continue to increase the abundance of this element into new drugs that require manipulation of all aspects of the journey of a drug through a living organism, namely its absorption, distribution, action, metabolism and elimination profile.

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Further reading

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