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# Modulation of drug pharmacokinetics and pharmacodynamics by fluorine substitution

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**ABSTRACT** Fluorine substituents have become common drug substituents due to the availability of safe, regioselective and economic fluorinating agents. Fluorine bioisosteres can simultaneously modulate the electronic, lipophilic and steric parameters of the drug molecule. Such modulation can profoundly affect the physical and pharmacokinetic properties of drug molecules. In this review, past, present and future drugs, including various antimalarial compounds, serve as examples of what can be achieved by incorporating fluorine into both experimental scaffolds and compounds in current clinical use. Drugs that form toxic quinone-imines, for example amodiaquine, can be rationally re-designed to strengthen desired pharmacodynamic and pharmacokinetic properties, whilst depressing undesired reactions which lead to toxicity in the patient. In contrast, introduction of the trifluoromethyl group into artemisinin slows drug metabolism, imparting a superior pharmacokinetic profile whilst maintaining high antimalarial potency *in vivo*.

## INTRODUCTION

An abundance of methods for safely incorporating fluorine into organic compounds now exists, which do not always require Haselloy-lined pressure vessels. Importantly, nickel micro-reactors using diluted elemental fluorine can be used for direct functionalisation (1). The common isotope of fluorine (<sup>19</sup>F) is second only to nitrogen (van der Waals radius 1.55 Å) as a favourite hetero-atom for incorporation into drugs (2). Judicious incorporation of fluorine into a lead compound to alter its pharmacokinetic and/or pharmacodynamic properties has become a powerful tool in bioorganic and medicinal/pharmaceutical chemistry (3-7). Estimates suggest that between 5-15 percent of new introductions approved for clinical use contain fluorine (3, 7). Halogenation of drugs is commonly used to enhance membrane binding and permeation. The effect of regiospecific replacement of a hydrogen atom by chlorine or, more importantly, a trifluoromethyl residue has been discussed elsewhere (2). Organofluorine can also act as an important donor atom in the coordination

chemistry of biorelevant metal ions such as Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup> and Ca<sup>2+</sup> although it can also interact with aluminium to provide a phosphoryl transfer transition state analogue, thereby activating G proteins undesirably (8).

Well documented instances of metabolic instability, particularly quinone-imine formation or the release of fluoride, in a minority of individual compounds dictate that appropriate toxicological testing be conducted before the widespread clinical use of such molecules (8). For instance, defluorination mediated by enzymatic action has led to the withdrawal of some compounds from clinical use. An early casualty was methoxyfluran (Figure 1); its biotransformation to oxalic acid and fluoride caused renal failure which was sometimes fatal (9). Despite these early setbacks and the expense of producing such compounds, introducing fluorine into compounds usually produces appreciable benefits. Sevoflurane, for example, is a safe and versatile inhalational anaesthetic compared with currently available agents. Occasionally it appears obvious that a particular position or substituent will be susceptible to nucleophilic activation (resulting in the release of fluoride) or the formation of toxic products. Nevertheless, in bioorganic chemistry, fluorination at certain positions ablates peptide degradation and the more transient isotope <sup>18</sup>F has enjoyed enormous success in tracking real-time kinetics of a molecule containing this isotope (10).

## EARLY HISTORY OF FLUORINE CONTAINING COMPOUNDS OF COMMERCIAL INTEREST

Gerhard Schrader was given the project of developing synthetic insecticides at Germany's I.G. Farben (Leverkusen) and this laid the foundation for modern fluorine containing pharmaceuticals (11). Industrial production of hydrogen fluoride at the company provided a convenient source of fluorine. For instance, fluorine was also an important component (4,4'-difluorobiphenyl) of the ointment, Epidermin, used to treat burn wounds (11) but its mechanism of action remains unknown. This suggested that fluorine was incorporated for the sake of novelty rather than as the consequence of a rational drug design strategy.

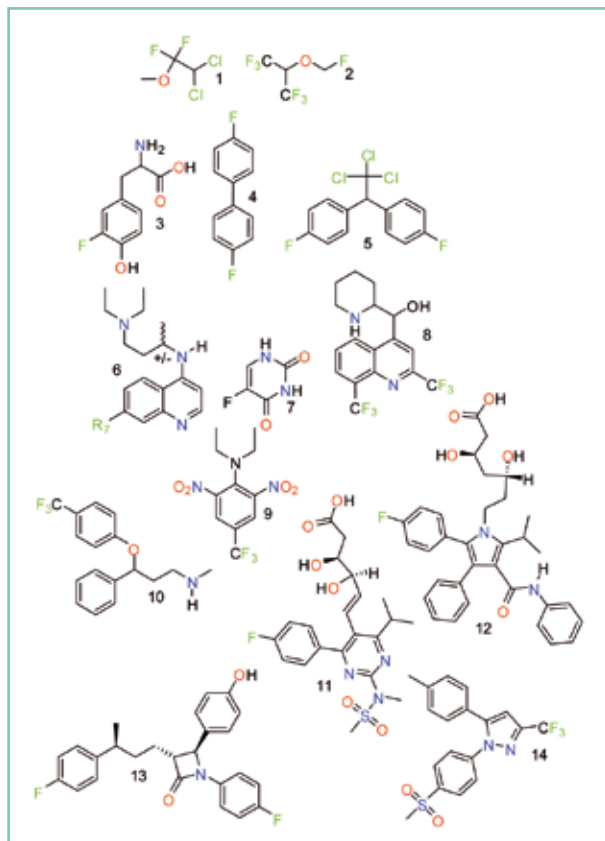


Figure 1. 1: Methoxyflurane; 2: Sevoflurane; Important fluorinated pharmaceuticals. 3: 3-fluorotyrosine (an early but toxic treatment for hyperthyreosis) (11); 4: Epidermin, 4,4' difluorobiphenyl; 5: GIX, 6:  $R_7 = \text{Cl}$ , Chloroquine; 6:  $R_7 = \text{CF}_3$ , Trifluoroquine; 7: fluorouracil; 8: Mefloquine (Lariam); 9: Trifluralin, pre-mergent herbicide; 10: Fluoxetine; 11: Rosuvastatin (Crestor); 12: Atrovastatin (Lipitor); 13: Ezetimibe; 14: Celecoxib.

By World War II, 20 tonnes of fluorobenzene were used to manufacture the DDT insecticide analogue, GIX (1,1'-(2,2,2-trichloroethylidene)-bis-(*p*-fluorobenzene)) at I.G. Farben for mosquito control. Notably, the trifluoromethyl analogue of the antimalarial chloroquine (Figure 1, 6) (12, 13) failed to attract attention primarily because chloroquine was easier to produce and the development of chloroquine-resistant *Plasmodia*, the causative organism of malaria, had not yet been fully appreciated. It was in fact known to Bayer investigators that halogens could alter and retard premature metabolism of a drug (so called obstructive halogenation) and for this reason chloroquine has a halogen at its 7-position (14).

Compounds of medicinal interest containing trifluoromethyl substituents, including anaesthetics, antipsychotics, antibiotics and a few antimalarials, though small in number, were reviewed in 1958 (Figure 1) (12). Some of the landmark compounds in the history of fluoropharma are illustrated in Figure 1. Apart from the inhalational general anaesthetics (e.g. enflurane, fluoxetine, halothane), it was not until hydrocortisone-like drugs and 5-fluoro-uracil (Figures 1 and 2) exceeded the potency of existing pharmaceuticals that industry was persuaded to use expensive, corrosive and potentially toxic precursors to design fluorine containing drugs. A notable example is the drug mefloquine, developed just after the Vietnam War, which was useful against resistant strains of malaria but its efficacy has been eroded in recent years. (Figure 1, 8). Since then methods of introducing fluorine have become routine so much so that many agrochemicals, such as trifluralin (Figure 1, 9), can

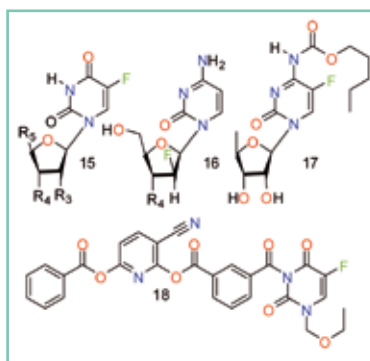


Figure 2. Superior fluorouracil analogues 15) a) Floxuridine where  $R_3 = \text{H}$ ;  $R_4 = \text{OH}$ ,  $R_5 = \text{CH}_2\text{OH}$ ; 15) b) Tegafur where  $R_3 = R_4 = R_5 = \text{H}$ ; 15) Furtulon where  $R_3 = \text{OH}$ ;  $R_4 = \text{OH}$ ,  $R_5 = \text{CH}_3$ ; 16) Gemicitabine; 17) Xeloda; 18) Emitetur (33, 34)

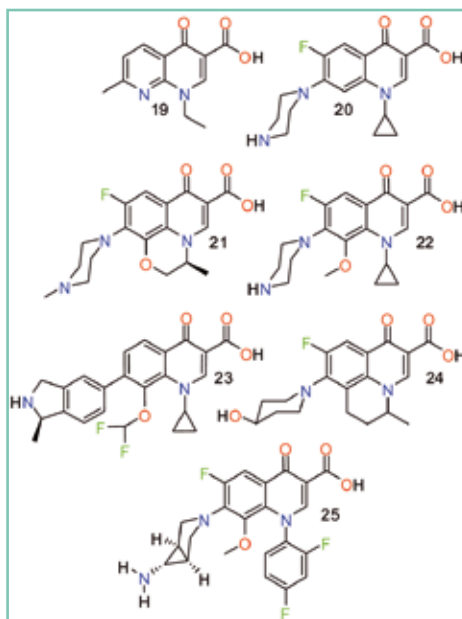


Figure 3. Fluoroquinolones used in clinical practice. Note the fluorine situated para- to the activating quinoline ring nitrogen induces a toxic liability when irradiated. Consequently, patients are advised to avoid excessive sunlight. Nadifloxacin is effective against skin infections including Acne vulgaris. 19: Nalidixic acid; 20: Ciprofloxacin; 21: Levofloxacin; 22: Gatifloxacin; 23: Garenoxcin; 24: Nadifloxacin; 25: Trovafoxacin.

be produced cheaply. It is active *in vitro* against *Plasmodium falciparum*, but not *in vivo* against *Plasmodium berghei*.

Antibiotic multi-drug resistance is a major and continuing public health concern and some clinicians are switching to replacements such as the fluoroquinolones. Developed initially from Leshers's nalidixic acid, inspired by an impurity isolated from chloroquine production, this class of bacterial type-2 topoisomerase (gyrase and topoisomerase IV) inhibitors are still being refined. Seminal modifications to the lead substance (nalidixic acid) were the incorporation of fluorine at position 6 of the 4-quinolone and replacement of the 7-methyl substituent with a piperazine group to significantly enhance antibacterial activity. Greater bio-availability was achieved by the addition of a cyclopropyl group to produce compounds such as ciprofloxacin (Figure 3, 20). Modifications made in the piperazine group resulted in third and fourth generation compounds with superior activity against streptococcal organisms. Prominent clinically useful fluorine-containing agents include ciprofloxacin for the treatment of Gram-negative and urinary tract infections, gatifloxacin, moxifloxacin, and levofloxacin for the treatment of respiratory tract infections as well as skin and soft tissue infections caused by *S. aureus*.

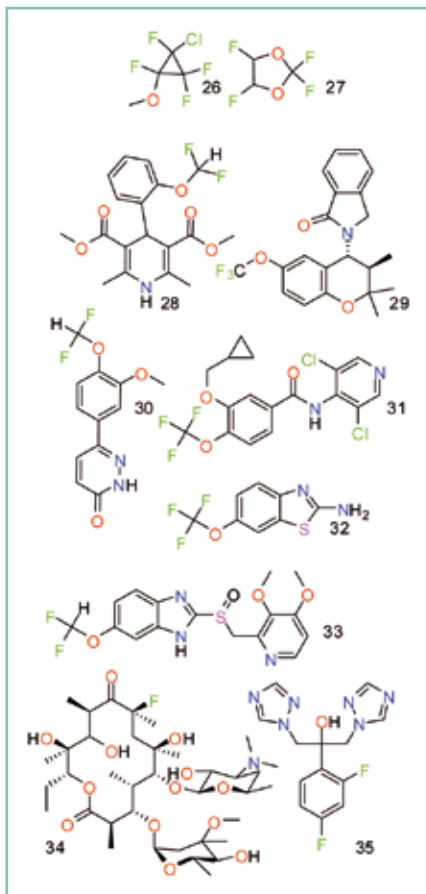


Figure 4. Newer fluoropharmaceuticals (17). **26**: Alifurane; **27**: Dioxchlorane; **28**: Riodipine; **29**: Celkalim; **30**: Zardaverine; **31**: Roflumilast; **32**: Riluzole; **33**: Pantoprazole; **34**: Ritro; **35**: Fluconazole.

Addition of the 8-methoxy group (e.g. gatifloxacin, Figure 3, **22**) enhanced activity against anaerobes. Amongst newer agents is garenoxacin (geninax, (Figure 3, **23**), which is useful against both Gram-positive and Gram-negative bacterial infections. Many of these compounds have also been tested against *Plasmodia*, and both liver and blood stages of *Plasmodium Spp.*, and their inhibitory effects were increased with prolonged incubation. Grepafloxacin trovafloxacin, and ciprofloxacin were the most effective drugs, with 50 percent inhibitory concentrations of <10 µg/ml against both strains. Only grepafloxacin, piromidic acid, and trovafloxacin (Figure 3, **25**), had an inhibitory effect against hepatic stages of *P. falciparum* and *P. yoelii yoelii*; this effect combined reductions of the numbers and the sizes of schizonts in treated cultures (15). However, trovafloxacin has revealed hepatotoxicity which will prevent the use of this drug for antimalarial prophylaxis. Further important drugs, shown in Figures 4 – 6, illustrate the fact that drugs containing CF<sub>3</sub> and aryl substituted fluorines outnumber those with CHF<sub>2</sub> substituents which remain in a minority (3-9).

### PHYSICAL ORGANIC CHEMISTRY OF FLUORINE

In medicinal chemistry, the fluorine atom (van der Waals radius 1.47 Å) often replaces a labile hydrogen atom (1.20 Å) when the pharmacokinetic profile of a compound requires modulation. The larger fluorine group more closely

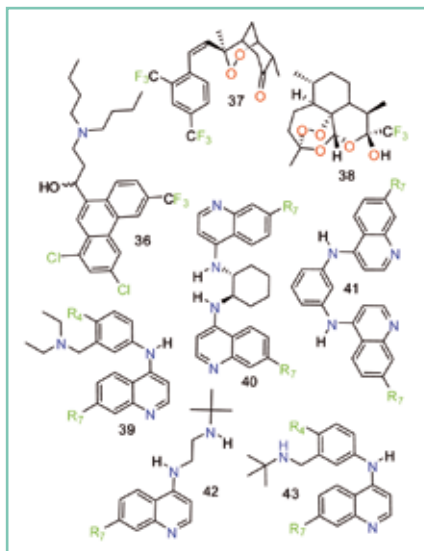


Figure 5. Experimental and clinically useful fluorinated antimalarials. **36**) Halofantrine (20); **37**) Arteflene (22); **38**) BB101: Ismail, Bonet-Delphon, Bisby unpublished work; (21, 29); **39**) a) Amodiaquine where R<sub>4</sub> = OH; fluoroamodiaquine where R<sub>4</sub> = F, R<sub>7</sub> = Cl (23); **40**) Ro 47-7737 where R<sub>3</sub> = Cl; (1R,2R)- N<sup>1</sup>,N<sup>2</sup>-bis(7-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,2-diamine where R<sub>3</sub> = CF<sub>3</sub>; **41**) Metaquine where R<sub>7</sub> = Cl (31); Trifluorometaquine R<sub>7</sub> = CF<sub>3</sub>; R<sub>5</sub> = CH<sub>3</sub>; **42**) N<sup>1</sup>-tert-butyl-N<sup>2</sup>-(7-(trifluoromethyl)quinolin-4-yl)ethane-1,2-diamine. **43**) Fluoro analogue of GSK369796: N-(3-((tert-butylamino)methyl)-4-fluorophenyl)-7-chloroquinolin-4-amine (26).

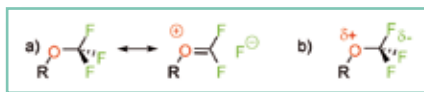


Figure 6. a) Hard ion mesomeric representation of the CF<sub>3</sub>O- group. The anomeric effect apparently manifests itself by acceptor bond elongation and donor bond contraction (See (2)). However, it may be more appropriate to depict this structure as b) partial charges; See O'Hagan (16).

resembles oxygen (1.52 Å) than hydrogen both in size and polarity and often serves to modulate interactions within drug receptor sites. Introducing fluorine into a molecule can lead to unexpected effects. For instance, diethyl ether has anaesthetic properties i.e. depresses neuronal activity, but perfluoroethyl ether (synonym bis(pentafluoroethyl) ether) causes violent convulsions in mice at concentrations as low as 30 ppm (12), although convulsions could be due to neuronal disinhibition rather than direct stimulation. The high electronegativity of fluorine (Pauling scale = 4.0) modulates the reactivity pattern of the host molecule. Leroux et al. (2) have emphasized that the increased oxidative stability of fluorinated molecules is not associated with the greater strength of the C-F bond relative to the C-H bond since biological oxidation does not involve the homolysis of C-H or C-F bonds. It is the bond energies and heats of formation of H-O and C-O bonds relative to those of the F-O bond which are important. Since the latter are unfavourable, all alternative mechanisms which evade attack at fluorine always take precedence in biological systems (2). Both the trifluoromethyl and the trifluoromethoxy groups are strongly electron-withdrawing and so have an activating effect over multiple bonds. The trifluoromethoxy group is referred to as a super- or a pseudo- halogen, which is also more lipophilic. In terms of lipophilicity, the trifluoromethoxy group resembles either a chlorine or fluorine atom. The effect on the C-C bond length of substituting a trifluoromethyl moiety for a methyl group reflects the "anomeric effect" shown in Figure 6 and is dictated by substituent electronegativity of the atom to which it is attached. A useful qualitative description of the effects of fluorine substitution has been provided by O'Hagan (16). Acceptor bond elongation and donor bond contraction have little effect on the carbon fluorine bond length. By contrast, the carbon-oxygen bond contraction is almost 0.1Å. A recent review (2) has highlighted pesticides containing the CF<sub>3</sub>O group, and its authors have argued that a CF<sub>3</sub>O substituent can advantageously replace a fluorine atom in most molecules with the benefit of increased lipid solubility. Many drugs with enhanced effectiveness and selectivity contain the CF<sub>3</sub>O moiety (Figure 4, e.g. **29**, **31** & **32**). The unusual electron distribution of CF<sub>3</sub>O, which possesses geminal combination of an alkoxy or aryloxy group with a fluorine atom, encourages bonding/non-bonding resonance and has formally depicted by superposition of both a covalent and an ionic limiting structure (Figure 6a) (2) but is better represented by the partially polarised model depicted in Figure 6b (16).

The CF<sub>3</sub>O group is sufficiently robust to resist chemically and thermal attack by acids, bases, organometallic reagents as well as oxidizing or reducing agents. Aromatic rings bearing the CF<sub>3</sub>O group parallel the alkoxy group with respect to electron withdrawal, whilst also serving to deactivate the aromatic ring system thereby imparting superior stability to drugs containing such substituents (Figure 4, e.g. **29** & **31**) (17).

### FLUORINE SUBSTITUTION MODULATES DRUG RECEPTOR INTERACTIONS

Since the 1990s, research emphasis has shifted to neglected areas of fluorine containing pharmaceuticals. Exploring carbon-fluorine single bonds on docking interactions, either through space with drug-receptors or by stereoelectronic effects on molecular conformation of drugs, is attracting considerable attention (16). Sometimes these effects are useful and contain special motifs including fluorines that are weak hydrogen-bond acceptors (2, 3), which can be studied by X-ray crystallography, spectroscopy or combined with molecular modelling, especially quantum mechanical approaches (e.g. Density Functional Theory). When considering drug receptors, these effects provide powerful opportunities for drug design (18, 19). A good example in terms of medical need is the long sought after docking of haem, which is the drug target for many quinoline based antimalarials. This interaction has been initially explored by molecular modelling (19) (Figure 7), but has recently also been characterized by X-ray crystallography for halofantrine (Figure 5, **36**) (20) shown in Figure 8. Such approaches led to understanding the mechanism of action by exploring close contacts, including van der Waals interactions and hydrogen bonding (16, 19). Exploration of the unstable intermediates such as those generated from arteflene and BB 101 (Figure 5; **37**, **38**) (21) can be reliably studied using fast reaction techniques (pulsed radiolysis) complemented by DFT calculations (22). The two trifluoromethyl groups in the aromatic portion of arteflene (Figure 5; **37**) retard undesired phase I, first pass metabolism in the host liver, improving the pharmacokinetic profile when compared to non-fluorinated analogues. By contrast, inductive effects caused by fluorine bearing substituents have been thoroughly explored, for example, by reducing the basicity of neighbouring amines to enhance bioavailability (6). Thus a shift in pK<sub>a</sub> from 4.95 to 2.17 was obtained by systematically increasing the number of fluorine substituents into the aryl side chain of amodiaquine

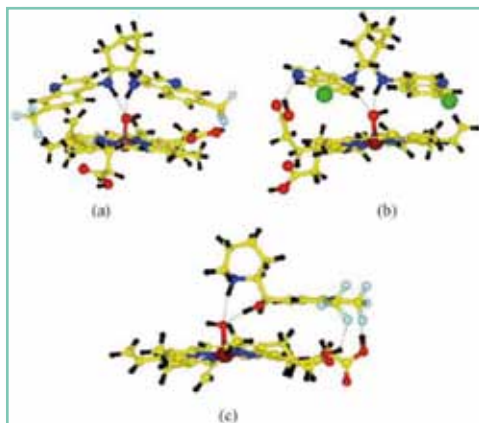


Figure 7. Structures indicating putative hydrogen bond interactions with hematin. Hydrogen bonds shown as dotted lines. (a) 40: (±) *trans*-N<sup>1</sup>,N<sup>2</sup>-bis-7-(trifluoromethyl-quinolin-4-yl) cyclohexane-1,2-diamine depicting hydrogen bond to the CF<sub>3</sub> in position 7 (19, 30); (b) (±) *trans*-N<sup>1</sup>,N<sup>2</sup>-bis-7-(trifluoromethyl-quinolin-4-yl) cyclohexane-1,2-diamine showing a hydrogen bond to endo-cyclic nitrogen atom (c) 8: mefloquine, indicating hydrogen bonds to CF<sub>3</sub> in both positions 2 and 8 (19,30). All structures were generated using molecular mechanics (Cerius2).

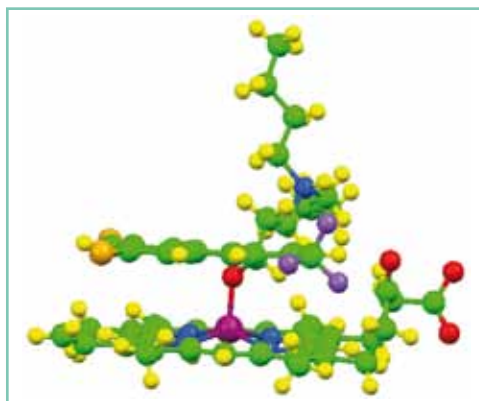


Figure 8. Crystal structure of Halofantrine bound to heme. (20). Water molecule and solvent removed to clarify drug receptor interactions. The aromatic ring of the drug forms  $\pi$ - $\pi$  interactions parallel to the mean plane of the heme  $\sim$ 3.5 Å apart. Colour key: green: carbon; yellow: hydrogen; orange: chlorine; red: oxygen; heme: magenta; nitrogen: blue; fluorine: purple.

(23) (Figure 5). These pK<sub>a</sub> values can be predicted accurately via quantum mechanics calculations. Effects on electrostatic potential, dipole moments and other physical properties have been discussed elsewhere (6). Biffinger et al. have suggested that since the C-F bond possesses an unusual combination of polarity with non-polarizability (hardness), it engenders fluorinated compounds with polar hydrophobicity (24). Consequently, desolvation of fluorinated surfaces (and functional groups) and weak dipolar interactions in organized media facilitate molecular recognition which, if important in receptor interactions in biological systems, justifies its popularity in medicinal compounds.

### ELIMINATING STRUCTURAL ALERTS: QUINONE IMINES IN ANTIMALARIALS

A labile OH group has proven especially dangerous when present either *ortho*- or *para*- to a primary or secondary aryl amine group, for instance amodiaquine (Figure 5; **39** where R<sub>4</sub> = OH, R<sub>7</sub> = Cl) (23). Subsequent oxidation can generate either an *ortho*- or a *para*-quinone-imine, a grouping that is associated with toxicity *in vivo*. Hence, the fluoro analogue of amodiaquine (Figure 5; **39** where R<sub>4</sub> = F, R<sub>7</sub> = Cl), which cannot form the toxic quinone-imine associated with hepatotoxicity, was first synthesised by VanderWerf in a US Navy sponsored study, but it showed inferior antimalarial activity when

compared with amodiaquine in animal models (25). More than 40 years later, a Liverpool University team undertaking a toxicologically driven, rational drug design approach, reported the antimalarial activity against malaria parasite clones *in vitro* (23). It took another 15 years using a public-private partnership to find a rationally designed compound with good *in vivo* activity, (Figure 5) (26). Not only does this compound possess a bioisosteric fluorine replacing the structural alert (i.e. -OH) in amodiaquine, it contains a *t*-butyl side chain instead of the metabolically unstable diethylamine side chain (Figure 5; **43**). Preliminary testing shows it has an acceptable safety profile but does not overcome all of the side effects associated with chloroquine. Although more expensive to produce, it is considered a "back up" to GSK369796 by these workers (26).

### RECENT DEVELOPMENTS

A similar approach of using fluorine to replace a bioisosteric OH group susceptible to quinone-imine formation was applied to the ParkeDavis compound

tebuquine, a potent antimalarial compromised by its propensity to cause foamy macrophages. The fluoro analogue appeared safe, but it lacked suitable antimalarial potency *in vivo* (27). Recently, a study has shown enhanced activity of mefloquine and artesunic acid against *P. falciparum in vitro* and *P. berghei in vivo* (in mice) by combination with ciprofloxacin. These investigators suggest that ciprofloxacin, in combination with antimalarials, may be useful in the treatment of chloroquine-resistant human malaria, allowing the use of lower doses of these drugs (28). Semi-synthetic modification of the natural product artemisinin (19) with various trifluoromethyl groups (Figure 5) can be used to produce potent antimalarials which are metabolically stable and possess superior pharmacokinetic profiles i.e. show good potential for clinical use (29). The trifluoromethyl group remains popular and has been incorporated in a number of experimental antimalarials (Figure 5, 40-42) which show useful activity *in vitro* and *in vivo* (30-32). Given the rising global threat caused by malaria (30-32), the use of fluorine containing pharmaceuticals in the development of new antimalarials seems assured for now.

## CONCLUSIONS

In the field of fluorinated drugs, single fluorine atoms, trifluoromethyl or trifluoromethoxy groups are usefully employed to modulate pKa values, modulate lipophilicity and thus improve the bioavailability and metabolism of pharmaceuticals. These features of established fluoro substitutions to tailor the pharmacokinetic properties of drug molecules are now being supplemented by an increasing awareness of the subsequent impact of the fluoro substitution on the pharmacodynamic activity and toxicity of the compounds.

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