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# METABOLISM OF FLUORINE-CONTAINING DRUGS

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■ **Abstract** This article reviews current knowledge of the metabolism of drugs that contain fluorine. The strategic value of fluorine substitution in drug design is discussed in terms of chemical structure and basic concepts in drug metabolism and drug toxicity.

## INTRODUCTION

Fluorine substitution can alter the chemical properties, disposition, and biological activity of drugs (1). Many fluorinated compounds are currently widely used in the treatment of disease. These include antidepressants, antiinflammatory agents, antimalarial drugs, antipsychotics, antiviral agents, steroids, and general anaesthetics (2). The chemistry and medicinal chemistry of fluoro-organic compounds and drugs have been reviewed (1, 3–5). The development of new fluorinating agents has vastly increased the potential for synthesis of novel fluorinated drugs. In addition, the development of sophisticated noninvasive analytical techniques based on fluorine nuclear magnetic resonance (NMR) and positron emission topography has transformed the study of fluorinated drugs in man and animals (6–8).

The inclusion of a fluorine atom in a drug molecule can influence both the disposition of the drug and the interaction of the drug with its pharmacological target (Figure 1). For example, the effects of fluorine substitution on the inter- and intramolecular forces that affect binding of ligands, and thus introduce receptor subtype selectivity, at cholinergic and adrenergic receptors are now well understood (9–11). Fluorine substitution can also have a profound effect on drug disposition, in terms of distribution, drug clearance, route(s), and extent of drug metabolism (12). Such changes can be used constructively by medicinal chemists to improve both the safety and the efficacy of a drug. Therefore, the purpose of this review is twofold. First, to outline the chemical basis of changes in drug disposition that can be achieved by the introduction of fluorine. Second, to consider the pharmacological and toxicological implications of such changes with respect to drug response.

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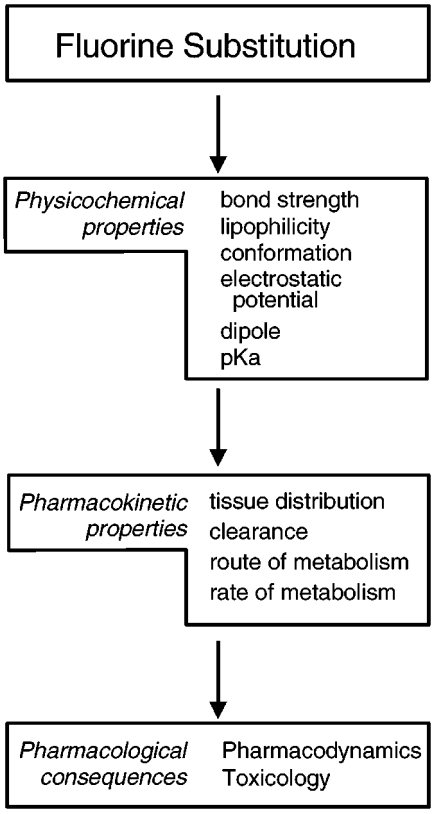


**Figure 1** Flow diagram illustrating the effect of fluorine substitution on drug response.

## PHYSICOCHEMICAL PROPERTIES OF FLUORINATED DRUGS

The replacement of a hydrogen atom or hydroxyl group by a fluorine atom is a strategy widely used in drug development to alter biological function. Although it is generally thought that fluorine for hydrogen substitution causes minimal steric effects at receptor sites, the actual van der Waals radius of fluorine (1.47 Å) lies between that of oxygen (1.57 Å) and hydrogen (1.2 Å) (Table 1). Despite the fact that fluorine has a greater size than hydrogen, several studies have demonstrated that it is a reasonable hydrogen mimic and exerts only a minor steric demand at receptor sites, at least for monofunctional analogues (3).

In contrast to their slight differences in size, hydrogen and fluorine have quite different electronic properties. Fluorine is the most electronegative element in the periodic table (Table 1). The resulting change in the electron distribution in a molecule, following the replacement of a hydrogen atom for fluorine, can alter the $pK_a$, the dipole moments, and even the chemical reactivity and stability of neighboring functional groups. The magnitude of the change in these electronic

**TABLE 1** Physiochemical properties of the carbon-fluorine bond

| Element | Electro-negativity | Bond length ($CH_2X$, Å) | Van der Waals radius (Å) | Bond energy (kcal/mol) |
|---|---|---|---|---|
| H | 2.1 | 1.09 | 1.20 | 99 |
| F | 4.0 | 1.39 | 1.35 | 116 |
| O(OH) | 3.5 | 1.43 | 1.40 | 85 |

properties is often determined by the bonding between the fluorine atom and the functional group. Thus, the presence of a fluorine atom *ortho* to a phenolic group is associated with a reduced $pK_a$ of 1.2, whereas *meta* and *para* fluoro substitutions have much less effect. The incorporation of two fluorine atoms at the 2- and 6-positions of phenol leads to a reduction of $pK_a$ of 2.7 U. Based on this effect, the 2,6-difluorophenol group has been used as an isostere of a carboxylic acid in a series of GABA aminotransferase inhibitors (13). These compounds were shown to inhibit the aminotransferase enzyme demonstrating the potential of this bioisosteric replacement.

The presence of a single fluorine, adjacent to a carboxylic acid function in aliphatic systems, can also have pronounced effect on the $pK_a$. This fact was used to rationalize the decrease in toxicity of new monofluorinated analogues of methotrexate. The incorporation of a fluorine atom adjacent to the glutamic carboxyl acid function results in an increase in the acidity. As a result, these new analogues are less toxic than methotrexate because they do not form polyglutamates, metabolites associated with undesirable prolonged cellular retention (14).

Fluorine forms a strong bond with carbon (bond energy C-F = 116 kcal/mol), which has an increased oxidative and thermal stability compared with the carbon-hydrogen bond (C-H = 99 kcal/mol). The carbon-fluorine bond is one of the strongest known in organic chemistry. In addition to the formation of covalent bonds, a fluorine atom present in a molecule can also form reversible, electrostatic bonds with certain functional groups.

The isosteric replacement of the hydroxyl group is a commonly used strategy in medicinal chemistry. This substitution is usually based on the premise that the fluorine can hydrogen bond accept in a manner similar to the oxygen of a hydroxyl function. However, the higher electronegativity and lower polarizability of fluorine over oxygen has a major influence on the ability of fluorine to mimic a hydroxyl group (15, 16). Recent calculations have measured the strength of an optimum F...H bond (1.9 Å) to be 2.38 kcal $mol^{-1}$ in an adduct between fluoromethane and water. Therefore, the F...H bond is clearly much weaker than the corresponding O...H (conservatively estimated to be ca 5 kcal $mol^{-1}$). The carbon-fluorine bond also has a strong dipole, and this may interact, either positively or negatively, with other dipoles. For example, it is thought that in fluorinated derivatives of noradrenaline, interactions between a ring carbon-fluorine bond and the hydroxyl group on the beta-carbon in the side chain determine the conformation of the molecule, and hence, the

position of the fluorine atom in the aromatic ring can determine receptor selectivity (17). Fluorine also has a number of specific stereoelectronic effects, such as the fluorine anomeric effect in carbohydrates, the Anh-Eisenstein stabilization effect in lipase-mediated kinetic resolutions, and the *cis* effect in difluorinated alkanes (3).

In contrast to the single replacement of a hydrogen for fluorine, replacement of a methylene function with a difluoromethylene function ($CF_2$ for $CH_2$) can have a significant effect on both conformation and physical properties (3). The difluoromethylene moiety has in fact been used as an electronic mimic of labile oxygen atoms in phosphate esters ($R\text{-}CF_2\text{-}PO_3^{2-}$ vs $R\text{-}OPO_3^{2-}$). This functional group has found extensive use in the design of inhibitors of enzymes that hydrolyze or bind phosphate esters (18). The $CF_2$ has been proposed as a reasonable isosteric and isopolar replacement for the hydroxyl group because of their size, electron distribution, and ability to act as a hydrogen bond acceptor (19–21). The $CF_2H$ group is particularly favored because of its ability to act as a hydrogen donor (22), potentially allowing interaction with solvent and biological molecules. Further introduction of fluorine causes even greater steric restrictions. The frequently used trifluoromethyl group ($-CF_3$) is closer in size to an isopropyl group (23). Indeed, several workers have suggested that the $CF_3$ group can exert an effect comparable to a phenyl ring or even a *tert*-butyl function (24).

The presence of a fluorine atom can influence the lipophilicity of a molecule and hence affect the partitioning of the drug into membranes, and also facilitate hydrophobic interactions of the drug molecule with specific binding sites, on either receptors or enzymes. The replacement of a single aromatic hydrogen atom usually results only in a modest increase in lipophilicity, whereas the $CF_3$ group is among the most lipophilic of all substituents.

The fluoride ion is a good leaving group, being the conjugate base of a strong acid. Therefore, the fluoride ion can be lost, in both displacement and elimination reactions, and this aspect of fluorine chemistry can be utilized in the design of drugs or chemical agents that form stable covalent bonds with target receptors or enzymes as part of their pharmacological response. This is the basis of the "lethal synthesis" concept (25). More recently, fluorinated inhibitors of GABA aminotransferase have been synthesized as potential mechanism-based inhibitors (13).

The presence of fluorine can alter the oxidation potential of an aromatic system, and thus alter the rate of autoxidation and formation of quinones and quinoneimines. Sequential introduction of fluorine atoms into the nucleus of paracetamol produced an increase in the oxidation potential of the molecule, as measured by cyclic voltammetry (26).

Before embarking on fluorination as a synthetic strategy to alter drug disposition, it is imperative to determine whether the changes in the physicochemical properties will diminish the inherent pharmacological activity of the drug. Molecular modeling techniques can, in theory, be used to examine (*a*) the importance of the group to be replaced in the drug-receptor interaction and (*b*) whether the resulting C-F bond can provide the same chemical interaction with the receptor. However, it must be stressed that modeling of the C-F bond in drug-receptor interactions

is not a trivial task, even for very simple molecules in an aqueous environment (27).

## STRATEGIES FOR THE USE OF FLUORINE SUBSTITUTION TO ALTER DRUG DISPOSITION

The introduction of fluorine into a molecule can be used to alter the rate, route, and extent of drug metabolism. Fluorine substitution can also be used to dissociate the pharmacological and toxicological properties of a drug when a toxic metabolite has been identified.

Such alterations are most commonly achieved by fluorine substitution at the site of metabolic attack, based on the premise that the carbon-fluorine bond is much more resistant to direct chemical attack by cytochrome P450, in comparison to the carbon-hydrogen bond. In addition, substitution at sites adjacent to and, in some instances, distal to the site of metabolic attack can also affect drug metabolism, by either inductive/resonance (through bond) effects or conformational and electrostatic (through space) effects. The presence of a fluorine atom adjacent to a site of metabolic attack could, in theory, either increase or decrease the rate of biotransformation, depending on (*a*) whether the metabolic attack is nucleophilic or electrophilic in nature and (*b*) inductive or resonance effects of the fluorine atom predominate in the reaction. For example, in a simple saturated system, the inductive effect of fluorine should reduce the susceptibility of adjacent groups to attack by P450 enzymes. In contrast, it might be anticipated that the presence of fluorine *ortho* to a phenolic group might increase its reactivity as a nucleophile in methylation and glucuronidation reactions, and there is some evidence to support this hypothesis (28, 29).

Fluorine substitution can therefore have complex effects on drug metabolism. The framework outlined in Figure 1 is used to consider the importance of the role of fluorinated subgroups on various aspects of drug disposition, and the consequent impact on drug efficacy and drug toxicity.

## THE EFFECT OF FLUORINE SUBSTITUTION ON DRUG DISTRIBUTION

The inclusion of fluorine in a molecule has two benefits with respect to drug distribution. First, certain fluorine-containing functional groups enhance lipophilicity and therefore passive diffusion of drug across membranes. Second, noninvasive techniques can be used to assess penetration of the drug to the site of action, whether brain, tumor, or site of infection (30–32).

Centrally acting drugs must pass through the blood brain barrier in sufficient concentration to elicit their pharmacological effect. For example, there are three categories of neuroleptics that act by blocking dopamine receptors in the central nervous system (CNS): tricyclics, butyrophenones, and diarylbutylamines. Many of these drugs contain either a $CF_3$ group or a fluoro-phenyl group, which

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