

Key Benefits to Adding Fluorine to Pharmaceutical Compounds

How did something that is so rare in nature – fluorine – become so common in medicines? A fundamental strategy for medicinal chemists when inventing new drugs is to take a molecule, frequently from nature, and make modifications to its structure to alter its activity. Replacing hydrogen and other functional groups with fluorine can have a dramatic effect on biological activity. It is much more strongly electronegative than hydrogen, and so swapping a fluorine atom for a hydrogen atom can be expected to exert a large electronic effect on neighbouring carbon centres, altering both the dipole moment and the pKa of the molecule. It can also have a knock-on effect on the stability and reactivity of other functional groups in the compound.

Fluorine's van der Waals radius of 1.35Å may appear significantly larger than that of hydrogen, 1.10Å, but studies have shown that, size-wise, fluorine is actually a good hydrogen mimic, adding only limited extra steric demand at receptor sites.¹ In addition, its bond length to carbon of 1.26–1.41Å is reasonably similar to that of a carbon–hydrogen bond, which is in the region of 1.08–1.10Å. Therefore, replacing hydrogen with fluorine gives little change in the overall steric bulk of the molecule.

Fluorine substitutions may greatly increase a molecule's lipophilicity, an important consideration when making molecules that are designed to be active in vivo. Incorporating fluorines increases fat solubility, improving its partitioning into membranes and hence increasing bioavailability. Fluorination can also aid hydrophobic interactions between the drug and binding sites on receptors or enzymes. Carbon forms some of its strongest bonds with fluorine, with a higher oxidative and thermal stability than a carbon–hydrogen bond. The fluorine can also make reversible electrostatic bonds with some other functional groups. Despite the strength of the carbon–fluorine bond, however, as the conjugate base of a strong acid, fluoride is a good leaving group, and this can be factored into the design of drugs which are intended to form stable covalent bonds with their targets.

Since the advent of 5-fluorouracil, fluorine substitution has become a common strategy in the drug discovery process, whether by modifying natural molecules, as in the case of 5-fluorouracil, or as part of a systematic search for more active analogues of existing drugs. A good example of the latter is flunitrazepam (Rohypnol, Roche), which is more effective than its non-fluorine containing parent, nitrazepam (Mogadon, also Roche). The only structural difference between the two drugs is an ortho fluoro phenyl substituent.

Therefore it is hardly a surprise that so many common drugs contain fluorine. This includes three of the top ten best selling drugs in 2003. The best seller, Pfizer's cholesterol lowering agent atorvastatin (Lipitor), has an aromatic fluorine substituent. The proton pump inhibitor lansoprazole (Prevacid) from TAP contains a difluoromethylene unit. And the fluticasone component in GlaxoSmithKline's combination asthma treatment Seretide has three separate aliphatic fluorine substituents.

However, the selective fluorination reactions to make these drugs are rarely straightforward. They often use dangerous or expensive reagents. Therefore, the best route is often to let someone like Halocarbon Products worry about introducing the fluorine and build the drug molecule around one of their commercially available fluorinated intermediates.

¹ *R. Duschinsky, E. Plevin and C. Heidelberger, J. Am. Chem. Soc. 1957, 79, 4559*