Fluorine in Medicinal Chemistry

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Fluorinated compounds are synthesized in pharmaceutical research on a routine basis and many marketed compounds contain fluorine. The present review summarizes some of the most frequently employed strategies for using fluorine substituents in medicinal chemistry. Quite often, fluorine is introduced to improve the metabolic stability by blocking metabolically labile sites. However, fluorine can also be used to modulate the physicochemical properties, such as lipophilicity or basicity. It may exert a substantial effect on the conformation of a molecule. Increasingly, fluorine is used to enhance the binding affinity to the target protein. Recent 3D-structure determinations of protein complexes with bound fluorinated ligands have led to an improved understanding of the nonbonding protein–ligand interactions that involve fluorine.

1. Introduction

Carbon-bound fluorine atoms are unique in organic chemistry. Fluorine is a small atom with a very high electronegativity.[1] With a van der Waals radius of 1.47 Å,[2] covalently bound fluorine occupies a smaller volume than a methyl, amino, or hydroxyl group, but is larger than a hydrogen atom (van der Waals radius of 1.2 Å).

While synthetic fluoro-organic chemistry has matured over recent decades, the specific use of fluorine in small-molecule drug-discovery research is more recent. Traditional medicinal chemistry was very much based on the use of natural compounds or closely related derivatives thereof. Traditional Chinese medicines, for example, do not contain fluorinated molecules.[3] As a consequence, until the 1970s fluorinated compounds were rare in medicinal chemistry.[4] This has changed quite dramatically over the last 20 years, and fluorinated compounds are nowadays synthesized in pharmaceutical research on a routine basis.[5–7] According to the World Drug Index (WDI), there are 128 fluorinated compounds with US trade names.[8] Of the 31 new chemical entities approved in 2002, nine compounds contained fluorine.[9]

In the present contribution, we select a few examples to illustrate how fluorine substitution is used in contemporary medicinal chemistry. We are not attempting to provide an exhaustive review of the subject. Instead, we will discuss representative examples and comment on how we see the use of fluorine evolving.

Current strategies for the introduction of fluorine atoms center on the following topics:

1) Metabolic stability is one of the key factors in determining the bioavailability of a compound. Rapid oxidative metabolism by the liver enzymes, in particular the P450 cytochromes, is often found to limit bioavailability. A frequently employed strategy to circumvent this problem is to block the reactive site by the introduction of a fluorine atom. There are many examples [10–14] illustrating that the replacement of an oxidizable C–H group by a C–F group increases metabolic stability of the molecule.
2) Fluorine can change the basicity of a compound. Highly basic groups can have a limiting effect on the bioavailability. A fluorine atom introduced close to a basic group reduces its basicity; this results in better membrane permeation of a compound and thus improved bioavailability.
3) Increasingly, fluorine substituents are introduced to increase the binding affinity of a compound. For example, most of the NK1 antagonists currently in clinical development contain a 3,5-di(trifluoromethyl)phenyl group to increase binding affinity.[15] In a recent review on the use of QSAR and computer-aided design methods, Wermuth described the 3,5-di(trifluoromethyl)phenyl group as "magic"[16] because it is found in many published NK1 antagonists and classical QSAR does not account for this strong effect of fluorine.

2. Improving Metabolic Stability with Fluorine

Low metabolic stability is a recurring challenge in many drug-discovery projects. Lipophilic compounds have a tendency to be oxidized by liver enzymes, in particular cytochrome P450. There are several strategies to counter this issue. One of them is to make the molecule more polar. An alternative strategy is to block the metabolically labile site with a fluorine substituent and hope that the small fluorine atom will not impair the binding to the target protein. Indeed, this approach is frequently employed and has led to many successful compounds.[10–14]

A particularly nice example is the discovery of the cholesterol-absorption inhibitor Ezetimibe (Scheme 1).[12–13] Starting from the moderately potent compound SCH48461, blockade of two metabolically labile sites in the molecule by fluorine substituents contributed significantly to the discovery of SCH58235 (Ezetimibe), which is a very potent compound that

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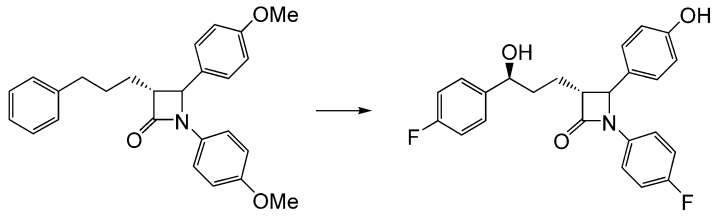
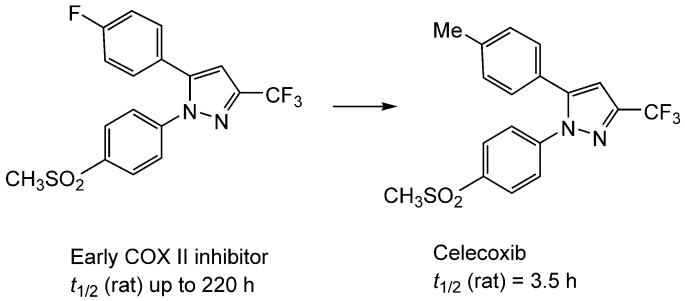


Scheme 1. *Development of Ezetimibe (SCH58235) by optimization of the lead SCH48461.[12,13] As part of the optimization, two metabolically labile sites are blocked by fluorine substituents.*



Scheme 2. *Development of the COX 2 inhibitor Celecoxib.[14] Replacement of a fluorine group by a methyl group reduces the very long half-life to an acceptable level.*

was recently approved by the FDA. Introduction of fluorine atoms prevent oxidation of the phenyl ring to phenol and dealkylation of the methoxy group.

Another interesting recent example demonstrating the strong effect of fluorine on metabolic stability, is the discovery of the cyclo-oxygenase 2 (COX 2) inhibitor Celecoxib (Scheme 2).[10,14] In this case, the extremely high metabolic stability of the lead compound, which results in a very long biological half life, could be reduced to more acceptable levels by replacing a fluorine atom by a metabolically labile methyl group.

Interestingly, there are also a few cases known for which the introduction of a fluorine substituent does not prevent oxidation at that site.[5,17,18] This phenomenon is observed in particular for phenyl rings with a nitrogen substituent in the *para* position to the fluorine substituent. During P450-catalyzed oxidation, a rearrangement takes place in which the fluorine atom moves to an adjacent carbon and the phenol metabolite is formed *para* to the nitrogen substituent.

3. The Effect of Fluorine on Physicochemical Properties

3.1 The effect of fluorine on the pK_a

As the most electronegative atom, fluorine has a very strong effect on the acidity or basicity of nearby functional groups. Depending on the position of the fluorine substituent relative to the acidic or basic group in the molecule, a pK_a shift of several log units can be observed. For example, the pK_a's of acetic acid and its α-fluorinated analogues are 4.76 (CH_3COOH), 2.59 (CH_2FCOOH), 1.24 (CHF_2COOH), and 0.23 (CF_3COOH).[15] Likewise, the basicities of ethylamine and its β-fluorinated analogues, measured by the pK_a's of the protonated amines, decrease in an approximately linear fashion upon introduction of fluorine, the pK_a's being 10.7 ($CH_3CH_2NH_2$), 8.97 ($CH_2FCH_2NH_2$), 7.52 ($CHF_2CH_2NH_2$), and 5.7 ($CF_3CH_2NH_2$).[19] Similarly, a fluorine substituent at the 3 and 4 position of a piperidine ring lowers the pK_a by about 2 log units.[20–21]

Quite often, a change in the pK_a has a strong effect on both the pharmacokinetic properties of the molecule and its binding affinity. For example, a strongly basic group may be required for binding within a certain lead series, but at the same time this basic group may also be found to result in compounds with low bioavailability due to the limited ability of a strong basic group to pass through membranes. The drug discovery project team is then faced with the challenge of finding an optimum between these conflicting effects.

This challenge is very nicely highlighted by the work of van Niel et al.[22] on the discovery of novel fluorinated indole derivatives as selective $5HT_{1D}$ receptor ligands. The incorporation of fluorine was found to significantly reduce the pK_a of the compounds, and this reduction of basicity, with a concomitant weakening of the affinity to the receptor, was shown to have a strong beneficial influence on oral absorption (Figure 1).

3.2 The effect of fluorine on molecular lipophilicity

Lipophilicity is a key molecular parameter in medicinal chemistry. Typically, groups of substantial lipophilicity on the ligand are required to obtain a good binding affinity to the target protein.[23] However, a high lipophilicity typically results in a reduced solubility and a number of other undesirable properties for a compound. Therefore, the right balance between a required lipophilicity and a certain minimal overall polarity of the molecule is one of the recurring challenges for medicinal chemists.

We investigated the effect of replacing a hydrogen by a fluorine atom on the lipophilicity of a compound. We selected 293 pairs of molecules from the Roche in-house database with measured log *D* values that just differ by one fluorine atom. Log *D* is the logarithmic coefficient of the distribution of the compound between octanol and water at a given pH (typically 7.4). A histogram of changes in log *D* upon one H/F exchange is shown in Figure 2. The plot reveals a Gaussian distribution with the maximum slightly higher than 0. On average, the substitution of a hydrogen atom by fluorine increases lipophicity slightly, by roughly 0.25 log units. This is in line with expectations and atomic increments published by others.[24] Interest-

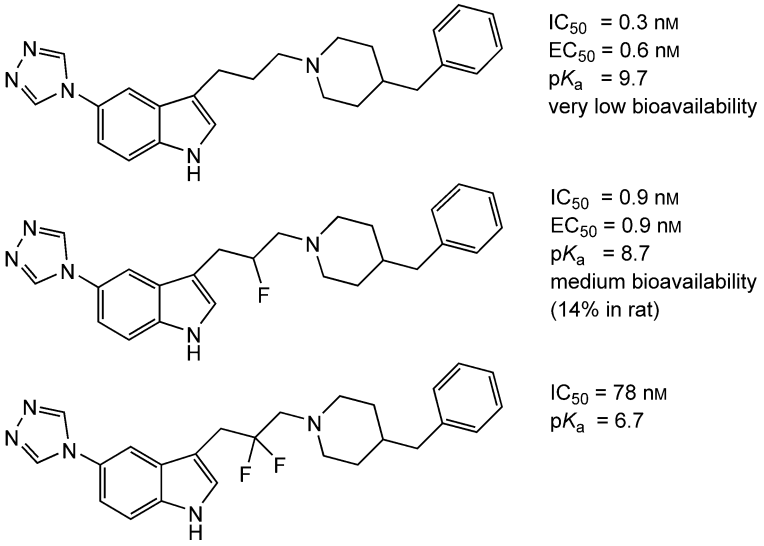


Figure 1. *Effect of pK_a value on the bioavailability and receptor binding for a set of $5HT_{1D}$ agonists.[22] The nonfluorinated parent compound is a very potent receptor ligand, but has a very low bioavailability. The monofluorinated compound has a lower pK_a that is still compatible with the requirements for receptor binding, but now results in a compound of substantially increased bioavaliability. The difluoro compound has a pK_a of 6.7. This compound is no longer basic enough to achieve high binding affinity for the $5HT_{1D}$ receptor.*

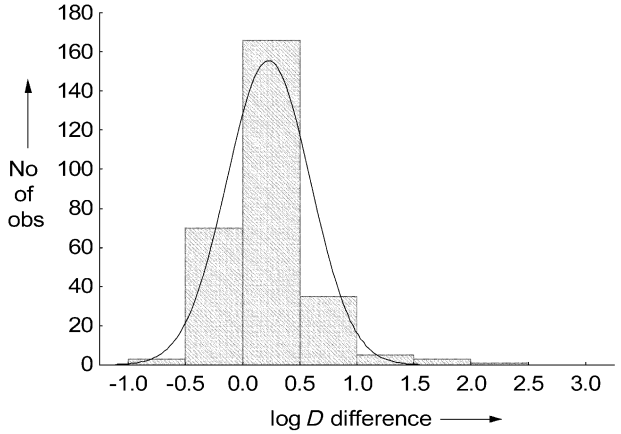
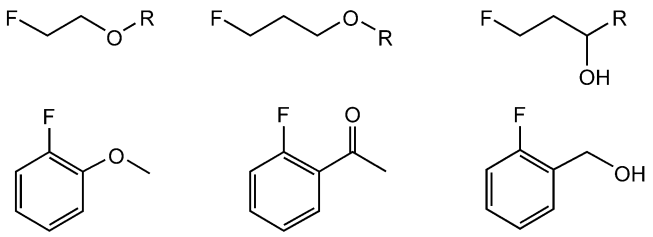


Figure 2. *Histogram of change in log D observed upon substitution of a hydrogen atom by a fluorine atom. On average, log D is increased by roughly 0.25.*

ingly, the tail of the Gaussian distribution extends to values below zero. In other words, there are quite a number of cases for which an H to F substitution decreases lipophilicity. A closer inspection of these cases reveals that there are a few recurring structural patterns that appear to correlate with this effect. The substructures are shown in Scheme 3. At the present, we cannot offer a conclusive explanation for this effect. Interestingly, the compounds are characterized by the presence of an oxygen atom close to the fluorine. We carried out conformational analyses for 14 compounds with a negative log *D* shift associated with one single H/F exchange. All compounds were found to have at least one low-energy conformer with an O···F distance smaller than 3.1 Å. In order to better understand this observation, we calculated the solvation free energies for ethylbenzene, *ortho*-fluoroethylbenzene, acetophenone, and *ortho*-fluoroacetophenone in water and in chloroform (we used chloroform instead of *n*-octanol for technical reasons) by using an ab initio quantum-chemical method.[25] These results indicate that, for ethylbenzene, the fluorine substituent has little effect on the solvation energy both in water and in chloroform, whereas for acetophenone, the fluorine substituent enforces the solvation energy in water more strongly than in chloroform. Taken together with the results from the conformational analysis, one possible explanation, is that fluorine in close vicinity to an oxygen atom increases the overall polarity of the molecule, leading to a more pronounced gain in solvation energy in the polar medium relative to the nonpolar solvent. However, it is also possible that the fluorine polarizes the neighboring oxygen atoms and this leads to stronger hydrogen bonds between the oxygen and neighboring water molecules.

The concept of increased lipophilicity due to H/F exchange does not appear to hold in general and should therefore be used with care. Moreover, our results might point to strategies to reduce the lipophilicity of a compound while, at the same time, increasing its metabolic stability.



Scheme 3. *Chemical substructures observed in compounds for which a fluorine substituent decreases log D.*

We have also examined the other end of the Gaussian distribution shown in Figure 2, which contains compounds with a much stronger positive shift in log *D* than expected for a single H/F exchange. Most of these compounds contain one or more basic nitrogen atoms. The fluorine substituent reduces the basicity of the nitrogen functionality, leading to an increased log *D* which was measured at pH 7.4.

In interpreting the data, we should keep in mind that our data set of 293 molecular pairs might contain a certain structural bias. Therefore, it is very likely that further substructural elements will be discovered that will also give rise to interesting effects of a fluorine substituent on lipophilicity.

4. The Effect of a F Substituent on Molecular Conformation

A fluorine substituent can lead to a change in the preferred molecular conformation. Again, this effect can be explained by

the size and electronegativity of fluorine. Based on a van der Waals radius of 1.47 Å for fluorine, the volume of a trifluoromethyl group is roughly twice that of a methyl group. As a result, the effect of fluorine substitution on molecular conformation is quite subtle and sometimes difficult to predict.

For example, methoxybenzenes without *ortho* substituents favor a planar conformation. We have carried out a search for trifluoromethoxybenzenes without substituents in the *ortho* positions using the November 2003 release of the Cambridge Structural Database (CSD)[26] and found six entries.[27] None of them has the $-OCF_3$ group in the plane of the phenyl ring. For five entries, the dihedral angle C–C–O–C is around 90°, while for one crystal structure the dihedral angle is about 36°. Interestingly, similarly twisted conformations are also found for aryl-bound difluoroalkyloxy groups. Spectroscopic studies and high-level quantum-mechanical calculations further show that preference for the planar arrangement in anisole ($\Delta E \sim 3$ kcal mol^{-1}) is inverted to the orthogonal orientation in trifluoromethylanisole ($\Delta E \sim -0.5$ kcal mol^{-1}).[28]

These observations can have important consequences in a lead-optimization program. Clearly, the OCF_3 group is not just a simple isosteric replacement of a OCH_3 group, because it adopts a different conformation. The R group in Ph–OCF_2–R will point in a different direction from that of the R group in Ph–OCH_2–R. A nice example illustrating this point is the work by Massa et al.[29] on inhibitors of cholesteryl ester transfer protein (CETP) containing 3-tetrafluoroethoxy substituents. This paper suggests that the steric and electronic properties of Ph–OCF_2CF_2H are very similar to 2-phenyl-furan, which according to Massa et al.[29] is also nonplanar. From a medicinal chemistry perspective, this is a very interesting finding because monosubstituted furan is generally considered to be an undesirable group due to its metabolic instability and its potential to generate reactive metabolites. The OCF_2CF_2H side chain is therefore a promising route forward to converting a biologically active furane into a more stable group.

5. The Role of Fluorine in Protein–Ligand Interactions

Fluorine can have significant effects on the binding affinity in protein–ligand complexes. This effect can be direct by interaction of the fluorine with the protein, or it can be indirect by modulation of the polarity of other groups of the ligand that interact with the protein.

Frequently, it is found that a fluorine substituent leads to a slight enhancement of the binding affinity due to an increased lipophilicity of the molecule (see section 3.2) that results in an increased (nonspecific) affinity for the protein. If F increases the affinity by lipophilic interactions, then one will typically see a gradual increase of the affinity for the series H–F–Cl–Br. Indeed, such behavior has been frequently reported, for example, in ref. [30], and it is indicative of unspecific lipophilic interactions of fluorine. However, sometimes within the H–F–Cl–Br series, the observed binding affinity is maximum for F, for example in ref. [31]. This behavior may be consistent with the occurrence of specific polar interactions involving F or simply indicate that only limited space is available in the protein cavity.

Probably the strongest indirect effect of fluorine on binding affinity is the change of basicity or acidity of the ligand molecule. One example is the set of $5HT_{1D}$ agonists described by van Niel et al. [22] discussed above (Figure 1). Another striking example is the binding of $CX_3SO_2NH_2$ (X = H or F) to carbonic anhydrase II (CA II).[32] CA II is a metalloenzyme with a zinc cation in the active site. It is known from 3D X-ray structure determination that the deprotonated sulfonamide group binds at the active site through a direct interaction of the negatively charged R–SO_2NH^- group and the positively charged Zn^{2+} cation. $CH_3SO_2NH_2$ is an extremely weak acid with a pK_a of 10.5 and binds to CA II with $K_i = 100\,\mu M$. $CF_3SO_2NH_2$ is much more acidic due to the electron-withdrawing effect of the three fluorine atoms and has a pK_a of 5.8; at neutral pH, $CF_3SO_2NH_2$ is dissociated. As an anion, it binds to carbonic anhydrase more strongly with $K_i = 2\,nM$. This simple fluoroaliphatic sulfonamide is thus almost as potent an inhibitor of carbonic anhydrase as some more complex heteroaromatic compounds that have been in use for the treatment of glaucoma for more than 50 years. That the binding affinity to carbonic anhydrase is directly linked to the pK_a of the sulfonamides is evidenced by a linear correlation between the acid pK_a (ranging from 5.8 to 11.1) and the binding constant K_i (ranging from 2 nM to 250 μM).[32]

Benzylic α,α-difluorophosphonates, α,α-difluorosulfonates, and α,α-difluorocarboxylates have been described as inhibitors of the protein tyrosine kinase 1B (PTB1B).[33,34] Difluoro compounds are relatively good inhibitors of PTB1B, while the non-fluorinated counterparts are very poor inhibitors. X-ray crystallographic and kinetic studies suggest that this effect is due to direct interactions of at least one of the fluorine atoms with the enzyme active site. The effect appears not to be attributable to pK_a shifts.[33,34]

The enzyme carbonic anhydrase II has also been used to study direct protein–ligand interactions involving fluorine.[35–38] Abbate et al.[35] synthesized analogues of the CA II inhibitor methazolamide. The perfluorobenzoyl analogue binds almost ten times more strongly to CA II than methazolamide. The X-ray crystallographic structure determination reveals a stacking interaction between the perfluorophenyl ring of the inhibitor and the aromatic ring of Phe131.

A similar interaction of fluoroaromatic inhibitors of human CA II was studied by Doyon et al.[36] and by Kim et al.[37–38] Fluorination of a phenyl side chain interacting with the side chain of Phe131 improves the binding affinity.

5.1 The role of F in polar interactions

Olsen et al. have demonstrated for a set of fluorine-substituted thrombin inhibitors that C–F···C=O interactions can play an important role in protein–ligand interactions and can lead to significantly increased binding affinities.[39] A fluorine scan of thrombin inhibitors led to the discovery of a monofluorinated compound that binds five times more strongly to thrombin

than the nonfluorinated parent compound. The binding mode of the fluorinated compound was determined by X-ray structure analysis and shows that the F atom is in remarkably close contact with the H–C_α–C=O moiety of Asn98 of thrombin. The authors suggest that this H–C_α–C=O fragment should be considered fluorophilic because it offers several favorable polar interactions with F.

Interestingly, a very similar structural arrangement has also been observed in some other protein–ligand complexes with fluorinated ligands, for example in many fluorinated inhibitors of p38 kinase.[40–42] One example[42] is shown in Figure 3. A similar interaction pattern for fluorine was also observed for a factor Xa inhibitor.[43]

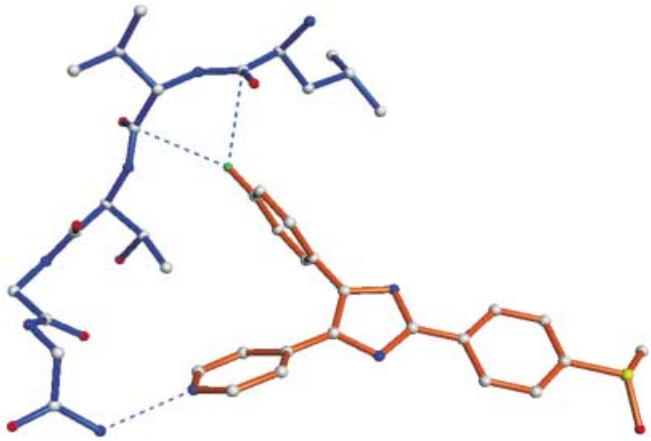


Figure 3. *Binding of a fluorinated inhibitor to p38 kinase (pdb refcode 1au9[41]). The fluorine is in close proximity to two carbonyl groups of the protein. The distances between the fluorine atom and the carbon atoms of the C=O units are 3.21 and 3.47 Å. Oxygen atoms are in red, nitrogen atoms in blue, carbon atoms are light gray, fluorine atoms are green, and sulfur atoms are shown in yellow.*

5.2 Does fluorine form hydrogen bonds?

The question of whether covalently bound fluorine atom engages in hydrogen bonds in protein–ligand complexes has been the subject of quite a considerable debate. Dunitz[44] has pointed out that the number of cases in small-molecule crystal structures in which a covalently bound fluorine atom engages in a nonbonding interaction that could legitimately be termed a hydrogen bond is very small. In most cases, the interactions of C–F units appear to be better described in terms of weak polar interactions.

We would like to report one example from our own work. In our effort to discover novel serine protease inhibitors with antithrombotic activities, we synthesized a pair of molecules (Figure 4) that differ just by one fluorine atom. The fluorinated

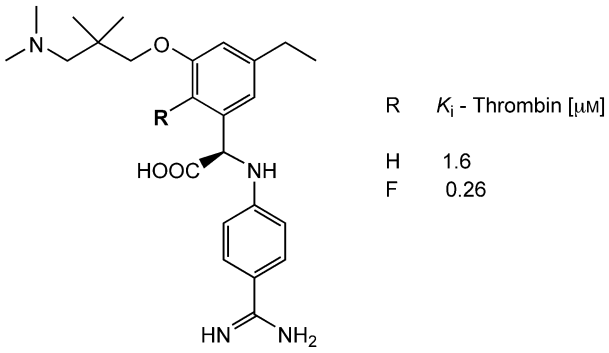


Figure 4. *Structure and binding affinity of a pair of thrombin inhibitors with and without fluorine substituent.*

compound is a good inhibitor of thrombin with $K_i = 260$ nM. The compound without fluorine is six times less potent ($K_i = 1.6$ μM). We determined the X-ray structures of both compounds bound to human thrombin. They are shown side-by-side in Figure 5. Interestingly, there is a conformational change of the ligand on going from R=H to R=F. In the fluorinated compound, the fluorine is within hydrogen-bonding distance of the N–H group of Gly216 of thrombin, although the distance is somewhat at the upper end of what would be considered to be geometrically compatible with a hydrogen bond ($R_{F,N} = 3.47$ Å). Therefore, this interaction mode certainly constitutes a favorable dipolar interaction. Whether one wants to call this a hydrogen bond remains a matter of personal taste.

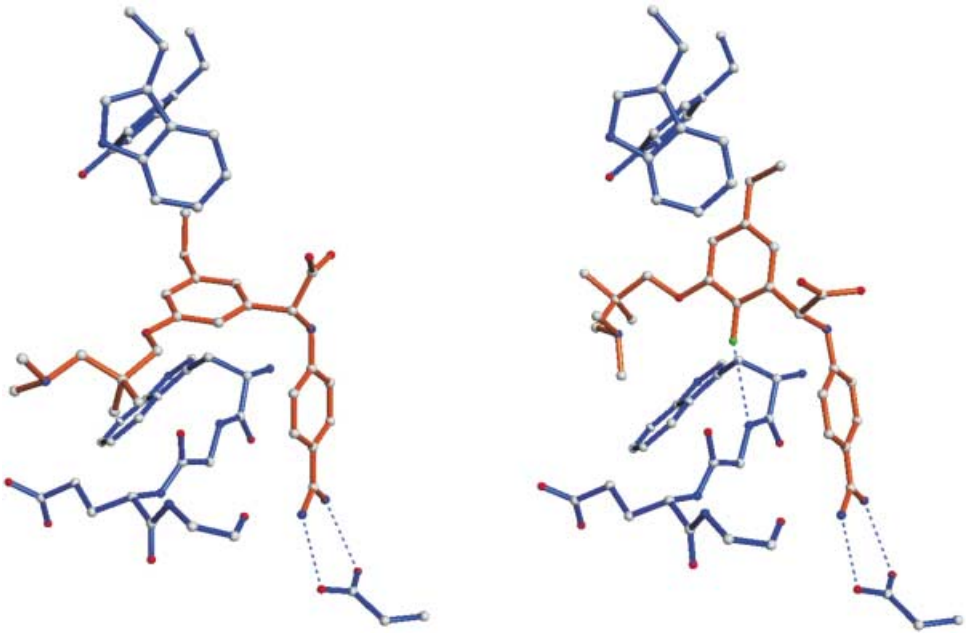
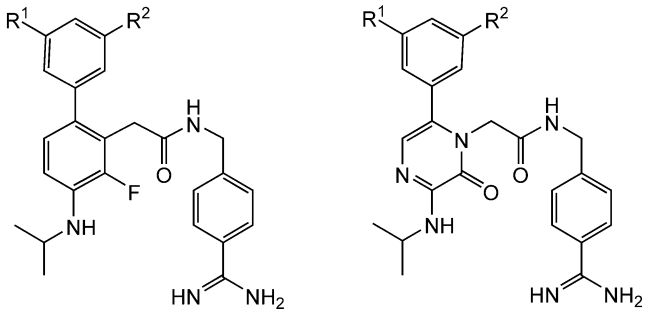


Figure 5. *Structure of two inhibitors with and without fluorine bound to thrombin. In the right-hand structure, the F···N distance is 3.47 Å.*

A similar interaction of fluorine with a protein N–H group in a series of inhibitors for the serine protease complex Tissue Factor/Factor VIIa (TF/VIIa) has been described by Parlow et al.[45–47]. They report a fluorinated compound (Figure 6) with



K_i - Tissue Factor VIIa = 0.34 μM
(R^1=NH_2, R^2=H)

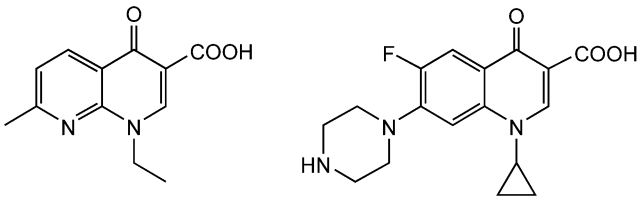
Figure 6. *Structure of two inhibitors of the serine protease factor VIIa with pyrazinone and benzene core structures.*

a benzene core that is a good inhibitor of TF/VIIa with K_i = 340 nM.[45] The X-ray structure of the protein–ligand complex reveals a hydrogen bond between the fluorine and the N–H group of Gly216 of the protein with ($R_{F,N}$ = 3.4 Å). However, Parlow et al. also report that the fluorinated compound has a weaker binding affinity than the pyrazinone inhibitors, which form strong hydrogen bonds to the N–H group of Gly216 through the pyrazinone carbonyl group.[46]

6. Fluorine as Key Component in Drugs

As indicated in the Introduction, there are now many marketed drugs containing one or more fluorine atoms. In many cases, fluorine was introduced to modulate the molecular properties, for example, as described in Section 2 for Ezetimibe.[12–13] In the case of fluorouracil,[48] the unique properties of fluorine are exploited to generate a potent irreversible inhibitor of thymidylate synthase (actually, the active compound is a metabolite that is formed in vivo).

The discovery of the fluoroquinolones as antibacterials is a striking example of the strong effect of fluorine atoms on molecular properties.[31,49,50] Fluoroquinolones are highly active and safe antibacterial agents that are widely used. The usage of a first generation of molecules, exemplified by nalidixic acid (Scheme 4), was limited by a rather narrow antibacterial spectrum and a comparatively weak activity. These problems could be overcome by the discovery of the fluoroquinolones such as ciprofloxacin (Scheme 4). The role of the fluorine atom has been investigated in detail by Domagala et al.[49] A comparison of several fluoroquinolones and their nonfluorinated parent compounds revealed that i) F increases binding affinity by a factor of 2–17, ii) F reduces plasma protein binding leading to a higher free fraction of the drug, and iii) F increases cell penetration by a factor of 1–70. The combination of these effects results in a dramatically improved antibacterial activity. Interestingly, the same effect is also found when the fluorine atom is introduced into the first generation compound nalidixic acid.[50]



Scheme 4. *Chemical structures of the DNA gyrase inhibitors nalidixic acid (left) and ciprofloxacin (right).*

Conclusion

Fluorinated compounds are frequently synthesized in modern medicinal chemistry and have led to a large number of highly effective drugs. Most frequently, fluorine is introduced to block a metabolically labile site in the molecule. Increasingly, fluorine is also introduced to modulate the physicochemical properties and to increase binding affinity by exploiting specific interactions of F with the target protein.

Modern fluorine-organic chemistry has dramatically widened the synthetic repertoire for the specific introduction of fluorine into organic molecules. Our continuously improving understanding of the diverse physicochemical, biophysical, and pharmacological effects of H/F substitution offers interesting new opportunities in medicinal chemistry.

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Keywords: basicity · fluorine · lipophilicity · metabolic stability · protein–ligand interactions

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