BTL NEDERLAND

Insights

Scientific Literature Review

ISSN 2590-0811

July/August 2021 | volume 4 | number 5

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Incorporation of Fluorine Atoms into Molecules: Some Recent Advances

Fluorine atom plays a remarkable role in medicinal chemistry and drug design, owing to its high electronegativity. It has the ability to influence the pharmacokinetic and pharamacodynamics properties of a therapeutic agent. Beyond biologically active compounds, its role in synthetic chemistry paved the way to synthesize compounds that were previously impossible to achieve. This snapshot aims to reflect the extent to which the combination of fluorine atoms in compounds can influence the design and synthesis of drugs, compounds or materials by highlighting some examples of selected recent developments in the field.

KEYWORDS: Fluorine, Metabolic stability, Binding affinity, Fluorinated heterocycles.

Introduction

The incorporation of fluorine atoms into a therapeutic or diagnostic small molecule candidate can lead to a profound pharmacological effect. This is related to the relatively small size and highly electronegativity of fluorine atom, which can influence the pharmacodynamics and pharmacokinetic properties of therapeutically active compounds. Indeed, the introduction a fluorine atom into molecules can improve their metabolic stability due to the resistance of C-F bond to the attack by oxidative metabolism. Such introduction can also influence substitution at adjacent or distal sites of the site of metabolic attack either through conformational or other effects. Moreover, it can tailor pK_a, facilitate cell membrane penetration, and enhance the binding affinity of the compound to the target protein. In fact, the biological activity of fluorinated substituents is a result of both their strong electron-withdrawing effect and their lipophilicity than their analogues as shown in the Table 1.[1]

Table 1. Electronegativities and hydrophobic parameters for various substituents.

Atom/group	Pouling Electronegativity	Hydrophobicity
H	2.10	0.00
F	4.00	0.14
CH_3	2.30	0.56
CF_3	3.50	0.88
OCH_3	2.70	-0.02
OCF_3	3.70	1.04
SCF_3	-	1.44
SF_5	-	1.23

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Looking beyond biological compounds, incorporation of fluorine into molecules has broader application in chemical synthesis, where the ability to prepare fluorinated heterocycles could facilitate the design and synthesis of catalysts or materials with novel properties.

This snapshot is intended to draw the reader's attention to some recent developments in compounds containing fluorine atoms.

1. Enhancing Antimicrobial Potency

Cationic antimicrobial peptides (CAMPs) are short peptides that have a net positive charge and hydrophobic regions and facilitate interactions with membranes. They play a major role in innate immunity of most living organisms and plants, and possess the unique property of non-specific targeting selective to bacterial membranes due to their electrostatic and amphipathic related mode of action towards negatively charged components of bacterial membranes.
In order to improve the antimicrobial efficacy of peptide antibiotics, Glossop *et al.* have synthesized a library of fluorinated *O*-phenyl serine derivatives.[2] As a model ultrashort lipopeptide sequence derived from the octapeptin battacin, these synthetic derivatives were replaced the original D-Phe residue in the middle of the sequence, Leu-D-Phe, as a point of modification considered critical for antimicrobial efficacy. Such a simple modification of the battacin pentapeptide exhibited potent broad-spectrum inhibitory activity against a wide array of pathogenic species, making them a promising class of antibiotic for studying (Figure 1).

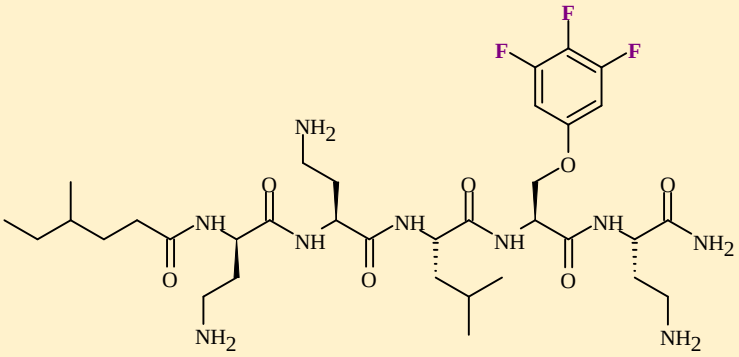

Figure 1. Chemical structure of the model pentapeptide scaffold bearing a fluorinated residue.

2. Improving 2-oxoglutarate oxygenase inhibitor

2-Oxoglutarate (2OG) dependent oxygenases are ubiquitous iron enzymes that catalyzes many biological processes in organisms. In humans, they catalyze hydroxylation and demethylation reactions on multiple substrate. Their roles include collagen biosynthesis, fatty acid metabolism, DNA repair, RNA and chromatin

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modifications, and hypoxic sensing. 2-OG oxygenases catalyze substrate oxidation using 2-oxo-glutarate (2OG), molecular oxygen, and Fe(II) ion as a cofactor, which react to form a reactive Fe(IV)-oxo intermediate that subsequently oxidizes their substrates to yield hydroxylated substrate, and converted into succinate, and CO_2 (Figure 2, A). 2OG-dependent oxygenases are associated with many diseases including anaemia, ischemia-related disorders, and cancer. Improving the selectivity profile of broad spectrum 2OG oxygenase inhibitors may assist in the identification of selective inhibitors for use in functional assignment. Intense efforts have been made to develop therapeutic agents targeted these enzymes. Most current 2OG oxygenase inhibitors are *N*-oxalylglycine (NOG) and 2,4-pyridinedicarboxlic acid (2,4-PDCA) (Figure 2, B).

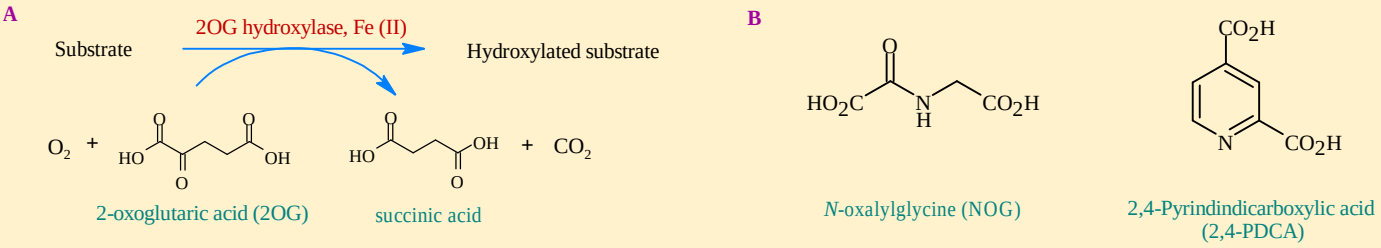
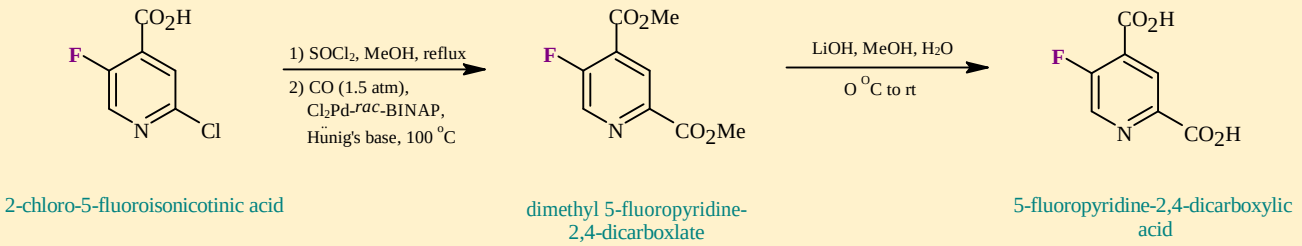


Figure 2. A) 2OG hydroxylases catalyze substrate oxidation; B) the chemical structures of broad-spectrum 2OG oxygenase inhibitors: *N*-oxalylglycine (NOG) and 2,4-pyridinedicarboxylate (2,4-PDCA).

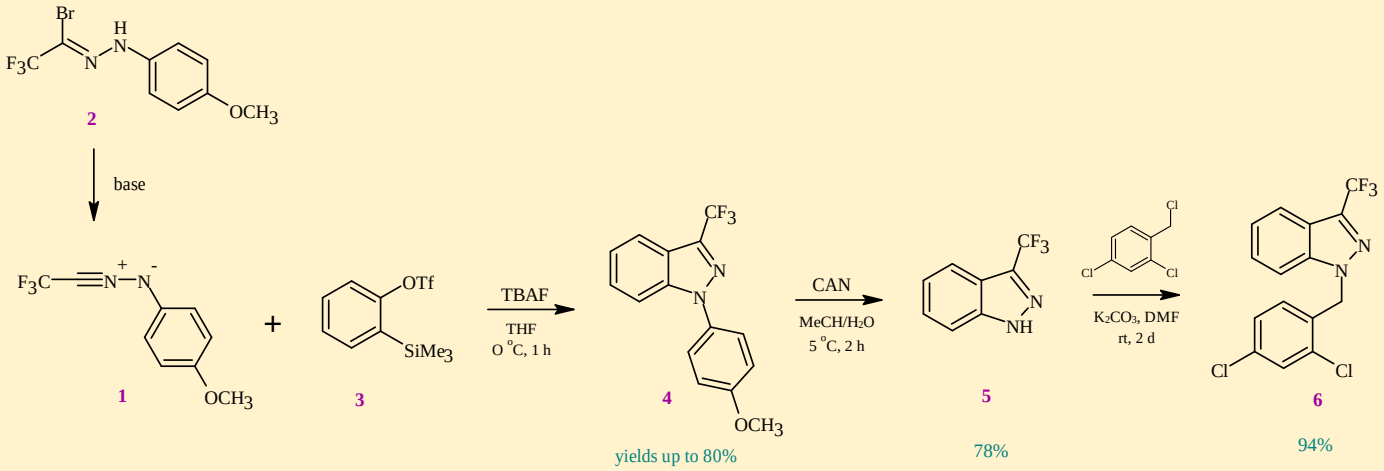
To enhance the inhibitor selectivity of 2,4-PDCA, Brewitz *et al.* demonstrated that the selectivity profile of F- and CF_3-substituted at the C5 position of 2,4-PDCA results in substantial increase in selectivity for 2OG oxygenases aspartate/asparagine-β-hydroxylase (AspH), especially F-substituted derivative, compared to 2,4-PDCA.[3] AspH is reported to be upregulated on the surface of cancer cell potentially obviating the necessity for the 2,4-PDCA derivative to penetrate the cell wall. The F-substituted derivative maintains potent AspH inhibition, owing to the presence of hydrophobic F-substituents on the 2,4-PDCA; an unprecedented observation with respect to 2OG oxygenase inhibition by 2,4-PDCA derivatives. The synthetic pathway of F-substituted 2,4-PDCA derivatives is shown in Scheme 1.



Scheme 1. The preparation of F-substituted 2,4-PDCA derivatives.

3. Synthesis of fluorinated fused heterocycles

Fluorinated indazoles are versatile building blocks for synthesis of potentially biologically active, fluoromethylated *N*-heterocycles, as well as interesting class of organic substrates for further functionalization. The Huisgen [3+2]-cycloaddition of arynes was exploited in a wide scope synthesis of heterocyclic systems, and are also applicable to the synthesis of fused heterocycles such as indazoles and derivatives. This reactive intermediates can be employed as dipolarophiles, and are accessible under mild conditions via fluoride anion-induced elimination from *ortho*-substituted (trialkylsilyl)aryl triflates. Kowalczyk *et al.* have described a fine procedure for the synthesis of 3-trifluoromethyl-1*H*-indazole derivatives **4** via the [3+2]-cycloaddition of *in situ* generated both trifluoroacetonitrile imines **1**, obtained by dehydrobromination of hydrazonoyl bromide **2** with a base, and arynes **3** (Scheme 2).[4] Dearylation of **4** using ceric ammonium nitrate (CAN) gave *N*-unsubstituted indazole **5**, and subsequent alkylation leading to lonidamine analogue **6**. Lonidamine is a medicine used to treat cancer. The procedure demonstrates the high utility of the *in situ* generated arynes as highly reactive dipolarophiles for the synthesis of fused, functionalized nitrogen heterocycles.

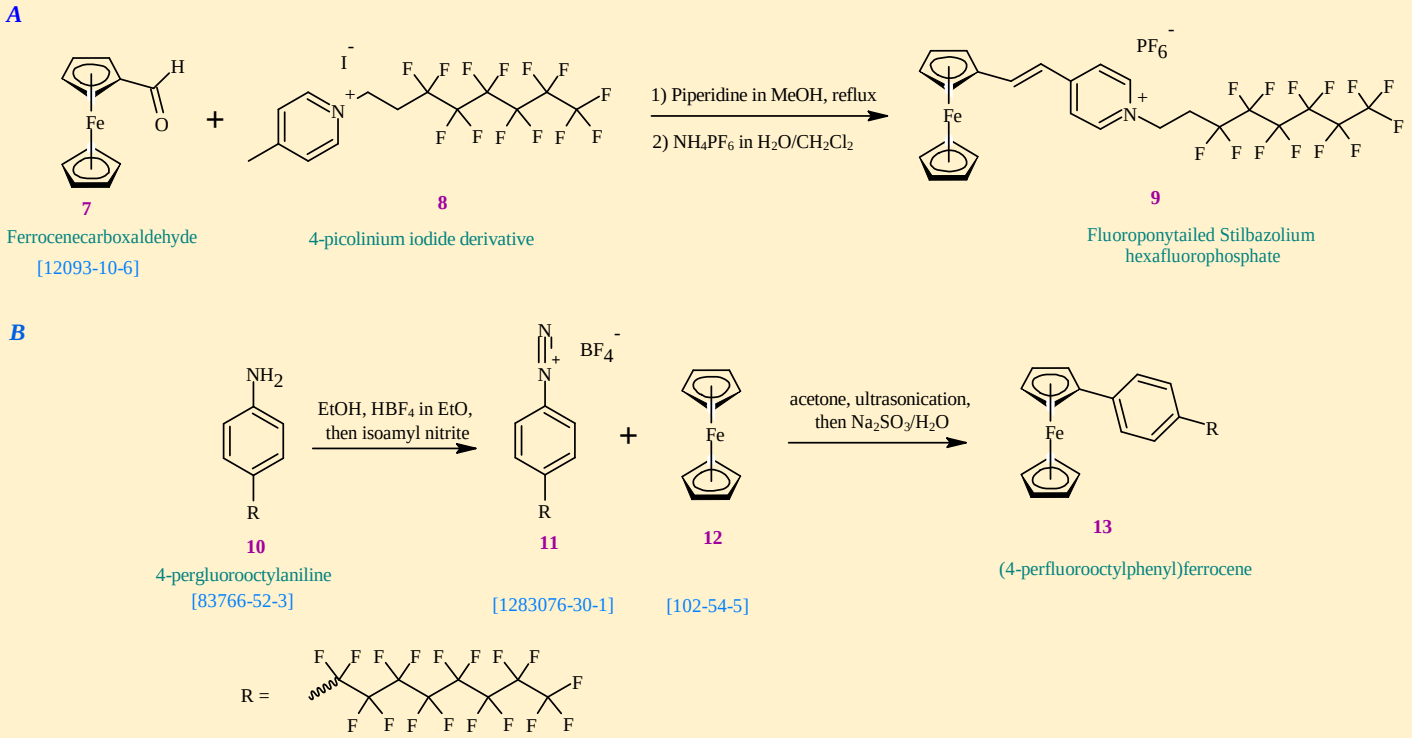


Scheme 2. Synthesis of 3-trifluoromethyl-1*H*-indazole derivatives **4** via the [3+2]-cycloaddition, and lonidamine analogue **6**. TBAF: tetrabutylammonium fluoride.

4. Chromophoric nature of fluorosurfactants containing ferrocene moieties

Fluoroalkylated compounds exhibit supramolecular features in solution. In a study on their surfactant behavior, Fliri *et al.* have prepared two components, an ionic and a neutral ferrocene-containing fluorosurfactant in crystalline form, namely, (*E*)-1-ferrocenyl-2-(1-(1*H*,1*H*,2*H*, 2*H*-perfluorooctyl)-4 -pyridiniumyl)ethylene hexafluorophosphate **9** and (4-perfluorooctylphenyl)ferrocene **13** respectively (Scheme 3), allowing for an investigation of this substance class with single X-ray crystallography for the first time.[5]

They demonstrated that besides a multitude of F···F contacts, no significant intermolecular interactions were observable. Moreover, compound **9** showed interesting deviation in its spectral behavior in four different solvents, with a peak dependent solvatochromism and a concentration dependent fine structure of the absorption, while compound **13** exhibited the common spectral behavior.



Scheme 3. ***A***) Synthesis of crystalline fluoroponytailed stilbazolium hexafluorophosphate (**9**); ***B***) Synthesis of (4-perfluorooctyl-phenyl)ferrocene (**13**) via Gomberg-Bachmann coupling with (11).

5. Intriguing reactivity of potassium acyltrifluoroborates (KATs)

The preparation of compounds with unique optical properties requires a starting building block with characteristic reactivity such as potassium acyltrifluoroborates (KATs). They exhibit interesting reactivity including KATs ligation, resulting in rapid chemoselective amide bond formation with hydroxylamine without the need for coupling reagents or protecting groups owing to their high chemical stability and reactivity. Furthermore, the uitility of KAT has allowed access to the *C,O*-chelated borate luminophore, known as *C,N*-swapped, which exhibits mechanochromic luminescence, that is difficult to constract by conventional methods. This was demonstrated by Ito for the synthesis of *C,N*-swapped boranils **16** through one-pot iminium salt formation/cyclization using KATs **14** and 1,2,3,4-tetrahydroquinolin-8-ol **15** as starting materials (Scheme 4).[6] Compound **16** showed significant luminescence in the solid state, as well as red-shifted mechanochromic luminescence attributable to a crystalline-to-amorphous transition.

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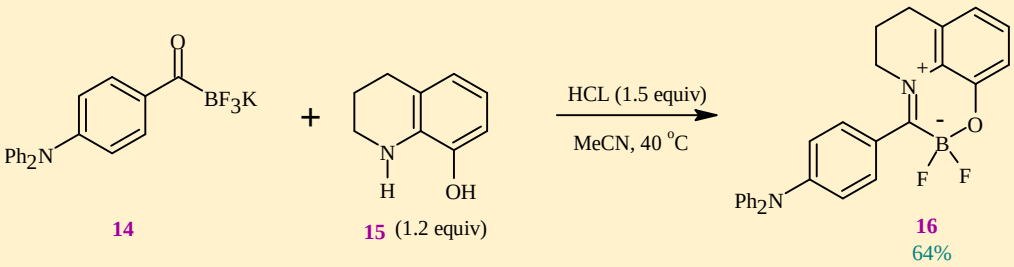

14 15 (1.2 equiv) 16 64%

Scheme 4. Synthesis of *C,N*-swapped boranils **16**.

Conclusion

This snapshot reflects some applications of strategically deposited molecules containing fluorine atoms in medicinal chemistry and drug development. The most important rational features of fluorinated compounds in drug design are to control the physicochemical properties and enhance the metabolic stability and binding affinity of these molecules. Beyond medicinal chemistry, the incorporation of fluorine atoms into compounds is widely applicable in chemical synthesis, where they influence the entire compound, facilitating the design and synthesis of compounds, catalysts or materials with novel properties.

References

1) H. J. Böhn, D. Banner, S. Bendel, M. kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem.*, **2004**, *5*, 637-643.
2) H. D. Glossop, G. H. De Zoysa, L. I. Pilkington, D. Barker, V. Sarojini, *J. Flu. Chem.*, **2021**, *241*, 109685.
3) L. Brewitz, Y. Nakashima, A. Tumber, E. Salah, C. J. Schofield. *J. Flu. Chem.*, **2021**, *247*, 109804.
4) A. Kowalczyk, G. Utecht-Jarzynska, G. Mloston, M. Jasinski, *J. Flu. Chem.*, **2021**, *241*, 109691.
5) L. Fliri, G. Partl, D. Winkler, K. Wurst, T. Gelbrich, T. Müller, H. Schottenberger, M. Hummel, *J. Flu. Chem.*, **2021**, *241*, 109674.
6) H. Ito, *Bull. Chem. Soc. Jpn*. **2021**, *94*, 1547–1552.