Medicinal Chemistry Research (2023) 32:1231–1234
https://doi.org/10.1007/s00044-023-03094-y

MEDICINAL CHEMISTRY RESEARCH

COMMENT

Future challenges and opportunities with fluorine in drugs?

David O'Hagan[1] · Robert J. Young[1,2]

Received: 25 April 2023 / Accepted: 25 May 2023 / Published online: 15 June 2023

Contributed comment to the special Issue of *Medicinal Chemistry Research* marking the retirement of Dr Nicholas Meanwell from Bristol Myers Squibb.

The increasing incorporation of fluorine into bioactive molecules is attributable to the profound effects this substitution has on their activity and disposition. Nick Meanwell is an avid proponent of the "enchanted atom" and contributed much to furthering our understanding of its impacts in drug discovery through authoritative and highly cited reviews on applications [1], isosterism [2, 3] and metabolic/pharmaceutical [4] aspects of fluorination. The reviews were received widely by the community in no small part reflecting the importance that fluorine has assumed in medicinal chemistry. Figure 1 taken from one of these reviews [4] illustrates the increasing prevalence of fluorinated drugs in approvals since the steroidal anti-inflammatory fludrocortisone was licenced in 1955 [5]. Drugs such as 5-fluorouracil and atorvastatin have saved lives on a global scale whilst over 300 others, in the purported 20% of recent molecules [5], contributed much to reductions in disease prevalence and improvements in well-being.

The unique properties of fluorine in terms of its steric compactness and its ability to form stable bonds to carbon contribute to its versatility, whilst its high electronegativity inductively tunes the electronic profile of a molecule thus modulating basicity/acidity and other physical characteristics. Contrary to these profound intramolecular effects, its poor propensity to hydrogen bonding means that it does not generally promote strong intermolecular interactions, although di- or multipolar interactions in the desolvated binding sites of proteins can improve molecular affinities. In pharmaceuticals, fluorine is often strategically placed on a molecule to supress metabolism, modulate physical properties, and consequently increase in vivo half-lives. Aryl-fluorinations and higher levels of fluorine such as the introduction of the CF_3 group can have these effects too and can increase lipophilicity without metabolic vulnerability. An appreciation of subtle stereoelectronic effects controlling intramolecular interactions has been exploited to bias conformations and rigidify structures [1, 2]. Taken together, fluorine has proven to be remarkably successful, and most drug development programmes will at least explore fluorine during optimisation of a lead compound, increasingly enabled by developments in synthesis methods and technologies that now facilitate fluorination through nucleophilic, electrophilic, and deoxyfluorination protocols [6].

The impact of natural recognition is a subject of increasing interest in drug discovery [7], and it follows that the selective introduction of fluorine into natural products or accessing fluorinated'pseudo' natural products (defined by their connectivity/scaffolds being unknown to nature) is an attractive prospect in pharmaceutical innovation [7]. Although only a limited number of fluorinated natural products are currently characterised [8], the genes and enzymes that produce them are being prospected for new biotechnologies enabling the synthesis of fluorinated natural product analogues [9]. In the medium- to long-term, synthetic and biosynthetic prospects in selective fluorination should address unsolved synthesis challenges, thereby enabling introduction of fluorine into drug scaffolds at will. Furthermore, judicious fluorination holds promise in the era of artificial intelligence when the notion of making desired, not just easily synthesisable, molecules is again coming to the fore.

In reviewing metabolic and pharmaceutical aspects of fluorinated compounds, Nick et al. reflected on the "potentially problematic outcomes with some fluorinated motifs and [how they] are enhancing our understanding of how fluorine should be deployed" [4]. This referred to in vivo toxicity rather than environmental concerns. The comment focussed on metabolism and warned that despite the strength of the C-F bond it is often readily liberated in metabolic processes, generating reactive intermediates that can have undesirable consequences (Fig. 2). In recent conversations, Nick

✉ Robert J. Young
rob@blue-burgundy.co.uk

[1] School of Chemistry and Centre for Biomolecular Sciences, University of St Andrews, St Andrews KY16 9ST, UK

[2] Blue Burgundy Limited, Ampthill, Bedfordshire MK45 2AD, UK

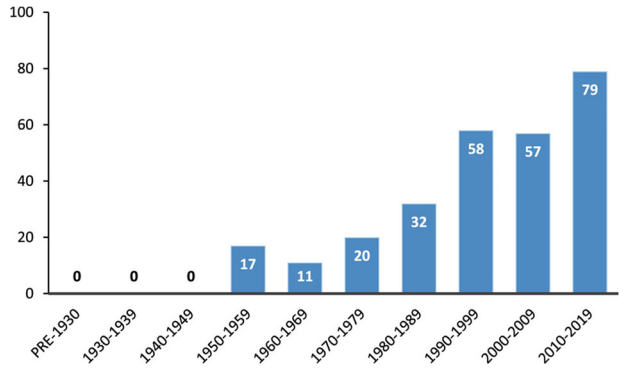


Fig. 1 Fluorine-containing drugs approved by the U.S. Food and Drug Administration through the end of 2019, Reprinted with permission from ref [4]. Copyright 2020 American Chemical Society

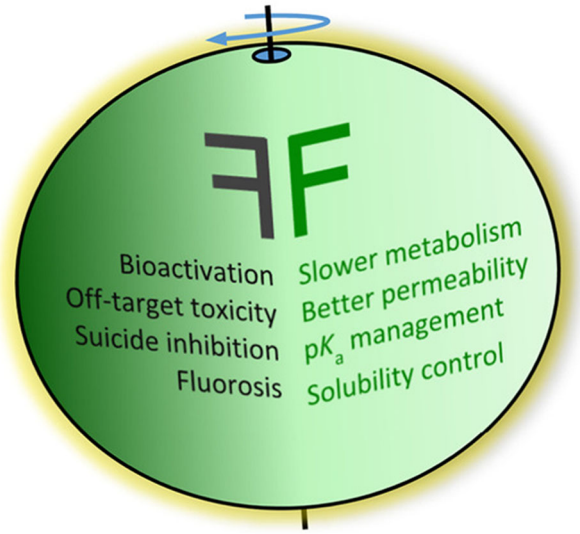
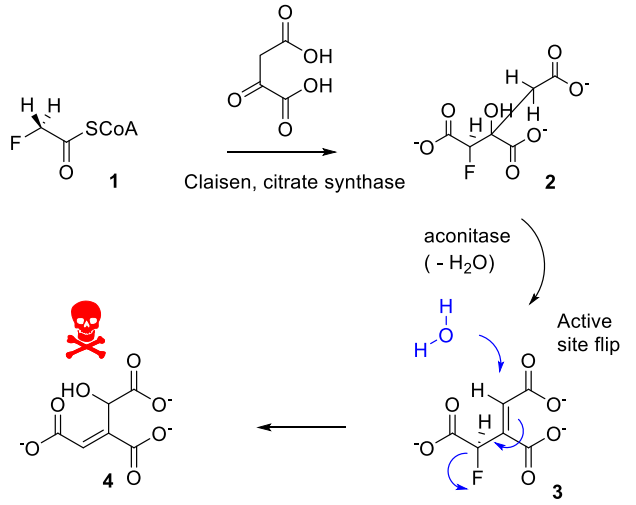


Fig. 2 The conflicting behaviours of fluorine, reprinted with permission from ref [4]. Copyright 2020 American Chemical Society

considered the repercussions of "good fluorine and bad fluorine," topics of profound importance to drug hunters [10]. In their extensive review of the metabolism of fluorinated compounds a plethora of degradation pathways are evident; the peculiar and chameleonic properties often contributing to complex and unexpected outcomes.

The toxicity of fluoroacetate is the most prominent example of adverse metabolism and this occurs via an indirect mechanism through inhibition of the Krebs cycle. This acute toxicity is a perennial risk known to Medicinal Chemists, whether it be fluoroacetates themselves or an origin via metabolism of terminal fluoro- aliphatic lipids, ethers or amines. In the context of unexpected metabolites, Scheme 1 illustrates the ultimate production of 4-hydroxy-trans-aconiate, a potent and tight-binding inhibitor of aconitase, the ultimate toxicant from fluoroacetate metabolism. Despite the strength of the C-F bond, such reactivity in biological systems is well-characterised [10].

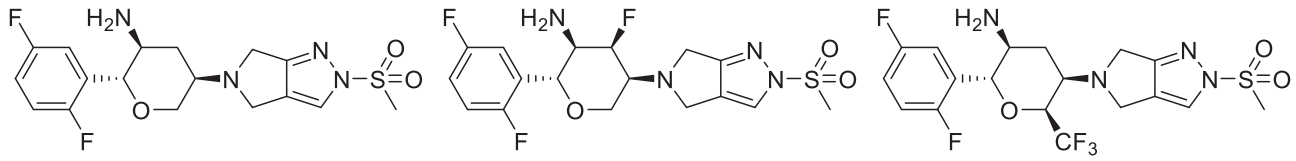


Scheme 1 The indirect toxicity of fluoroacetate is manifested through its acetyl-CoA derivative **1** that undergoes a stereospecific Claisen condensation to give *erythro*-(*2 R,3 R*)-2-fluorocitric acid **2** that dehydrates through the action of aconitase, yielding **3** which flips in the active site prior to the addition of water to yield 4-hydroxy-trans-aconitate **4**, a potent, tight-binding inhibitor of aconitase

The Paracelsus edict "*dosis sola facit venenum*"—or the dose makes the poison is a central facet of drug discovery, but in the "toxicophoric" [11] age of medicinal chemistry further research into lability and understanding of these mechanisms would be useful in guiding the choice of fluorinated motifs. But, like all Janus-faced phenomena, the flip side has resulted in fluorine-facilitated selective toxins, such as fluoro-ornithines and 4-fluorothreonine, potentially useful as anti-cancer, antibiotic or anti-trypanosomal agents [4, 8].

Catabolic processes in the breakdown of drug molecules involved in returning fluoride or fluorinated by-products are not so well-characterised. It can take 30 years for micro bacteria to evolve in response to environmental challenges [12], so the colloquial analogy of "Teflon®-coating" pharmaceuticals with multiple fluorinations could be a recipe for extending half-lives at the expense of environmental persistence or inadvertent/indirect release of toxicants. Fig. 3 illustrates just how much impact fluorinations can have on the half-lives of bioactive molecules, which may also contribute to their persistence.

It is understood that the fate of many trifluoromethylated drugs, such as fluoxetine [13], is ultimately to release trifluoroacetic acid (TFA) into the environment, a molecule of increasing environmental concern [14]. TFA is a highly persistent compound in water courses and has no apparent degradation pathways. There was a discussion that TFA may have a natural source in the deep oceans suggesting a geothermal origin, however recent revisions have challenged this assessment and conclude that it is most likely that TFA in the environment is entirely of anthropogenic origin. The refrigerants industry has progressed to its third generation of



Omarigliptin
DDP-4 IC_{50} 3 nM
Mouse PK
Cl 7.4 ml/min/kg
$t_{1/2}$ 4.7h
AUC 4095 ng.h/ml

F-Omarigliptin
DDP-4 IC_{50} 22 nM
Mouse PK
Cl 0.7 ml/min/kg
$t_{1/2}$ 19 h
AUC 23,500 ng.h/ml

CF_3-Omarigliptin
DDP-4 IC_{50} 4 nM
Mouse PK
Cl 2.6 ml/min/kg
$t_{1/2}$ 30 h
AUC 8,000 ng.h/ml

Fig. 3 The Merck DDP-4 inhibitor Omarigliptin, itself formulated for once weekly dosing, and two further fluorinated analogues [16] that showed profoundly longer half-lives (indicative of *once-monthly* dosing) and increased exposure because of fluorination

fluorocarbon products, after ozone depleting chlorofluorocarbons (CFCs) and then high global warming potential (GWP) hydrofluorocarbons (HFCs). The current low GWP product 1234yf, a hydrofluoro-olefin (HFO), is now a major source of anthropogenic TFA. 1234yf is removed rapidly from the upper atmosphere by photo-oxidation and is converted to TFA, which, in global rainwater monitoring, has been observed above acceptable guidelines during some events. Concerns around TFA accumulation in the environment are accelerating unease in agrochemicals and pharmaceuticals regarding a future for fluorine and particularly substituents such as ubiquitous -CF_3 containing products. Aryl-CF_3 compounds are widely represented in bioactives and their production as well as the intermediates used to prepare them on scale, present additional, although relatively minor environmental sources of TFA. This is compounded by the perfluoroalkyl sulfonate (PFAS) crisis which recognises that this persistent class of molecules are accumulating in environmental water sinks and surreptitiously appearing in the blood of the human population and mammals on all continents at ppb levels. The developing regulation around perfluoro-organics may extend to CF_3 containing compounds, with TFA the shortest chain PFAS, although it is a reasonable assumption that many configurations such as N-CF_3 and O-CF_3 compounds will ultimately degrade to fluoride. The deployment of certain classes of fluorine-containing motifs in the search for new drugs may be expected to decline in popularity in the face these challenges, however it is anticipated that 'Essential use' regulations [15] will offset a significant decline in the bioactives arena, and the judicious incorporation of non-persistent fluorine remains a powerful approach for developing new products for enhanced societal benefits.

Conclusion

The selective introduction of fluorine into bioactive molecules has had an impressive impact in medicines and global food production in products associated with agrochemicals. However, the presence of fluorine in all products is receiving critical scrutiny due to environmental concerns regarding persistence chemicals. Despite the self-evident positives of 'good fluorine,' if it is to continue as a design tool then relevant motifs will have to be compatible with evolving environmental legislation. In particular, products that degrade to TFA or other persistent end products will likely feel regulatory pressures, whereas products that biodegrade to fluoride will have more satisfactory prospects. Such awareness and change present new challenges and we anticipate a surge in fluorination innovation around next generation approaches aimed at exploiting the exquisite properties of this unique element.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Gillis EP, Eastman KJ, Hill MD, Donnelly DJ, Meanwell NA. Applications of Fluorine in Medicinal Chemistry. J Med Chem. 2015;58:8315–59. https://doi.org/10.1021/acs.jmedchem.5b00258

2. Meanwell NA. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. J Med Chem. 2018;61:5822–80. https://doi.org/10.1021/acs.jmedchem.7b01788
3. Mei H, Han J, White S, Graham DJ, Izawa K, Sato T, et al. Tailor-Made Amino Acids and Fluorinated Motifs as Prominent Traits in Modern Pharmaceuticals. Chem – A Eur J. 2020;26:11349–90. https://doi.org/10.1002/chem.202000617
4. Johnson BM, Shu Y-Z, Zhuo X, Meanwell NA. Metabolic and Pharmaceutical Aspects of Fluorinated Compounds. J Med Chem. 2020;63:6315–86. https://doi.org/10.1021/acs.jmedchem.9b01877
5. Inoue M, Sumii Y, Shibata N. Contribution of Organofluorine Compounds to Pharmaceuticals. ACS Omega. 2020;5:10633–40. https://doi.org/10.1021/acsomega.0c00830
6. Caron S. Where Does the Fluorine Come From? A Review on the Challenges Associated with the Synthesis of Organofluorine Compounds. Org Process Res Dev. 2020;24:470–80. https://doi.org/10.1021/acs.oprd.0c00030
7. Young RJ, Flitsch SL, Grigalunas M, Leeson PD, Quinn RJ, Turner NJ, et al. The Time and Place for Nature in Drug Discovery. JACS Au. 2022;2:2400–16. https://doi.org/10.1021/jacsau.2c00415
8. Chan KKJ, O'Hagan D. Chapter Eleven—The Rare Fluorinated Natural Products and Biotechnological Prospects for Fluorine Enzymology. In: Hopwood DA, editor. Methods Enzymol. Cambridge MA: Academic Press; 2012. p. 219–35.
9. Sirirungruang S, Ad O, Privalsky TM, Ramesh S, Sax JL, Dong H, et al. Engineering site-selective incorporation of fluorine into polyketides. Nat Chem Biol. 2022;18:886–93. https://doi.org/10.1038/s41589-022-01070-y
10. Pan Y. The Dark Side of Fluorine. ACS Med Chem Lett. 2019;10:1016–9. https://doi.org/10.1021/acsmedchemlett.9b00235
11. Kalgutkar AS. Designing around Structural Alerts in Drug Discovery. J Med Chem. 2020;63:6276–302. https://doi.org/10.1021/acs.jmedchem.9b00917
12. Udiković-Kolić N, Scott C, Martin-Laurent F. Evolution of atrazine-degrading capabilities in the environment. Appl Microbiol Biotechnol. 2012;96:1175–89. https://doi.org/10.1007/s00253-012-4495-0
13. Khan MF, Murphy CD. Bacterial degradation of the anti-depressant drug fluoxetine produces trifluoroacetic acid and fluoride ion. Appl Microbiol Biotechnol. 2021;105:9359–69. https://doi.org/10.1007/s00253-021-11675-3
14. Sun M, Cui JN, Guo J, Zhai Z, Zuo P, Zhang J. Fluorochemicals biodegradation as a potential source of trifluoroacetic acid (TFA) to the environment. Chemosphere. 2020;254:126894. https://doi.org/10.1016/j.chemosphere.2020.126894
15. Garnett K, Van Calster G. The Concept of Essential Use: A Novel Approach to Regulating Chemicals in the European Union. Transnatl Environ Law. 2021;10:159–87. https://doi.org/10.1017/S2047102521000042
16. Zhang C, Ye F, Wang J, He P, Lei M, Huang L, et al. Design, Synthesis, and Evaluation of a Series of Novel Super Long-Acting DPP-4 Inhibitors for the Treatment of Type 2 Diabetes. J Med Chem. 2020;63:7108–26. https://doi.org/10.1021/acs.jmedchem.0c00374