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Mini-Review

Contribution of Organofluorine Compounds to Pharmaceuticals

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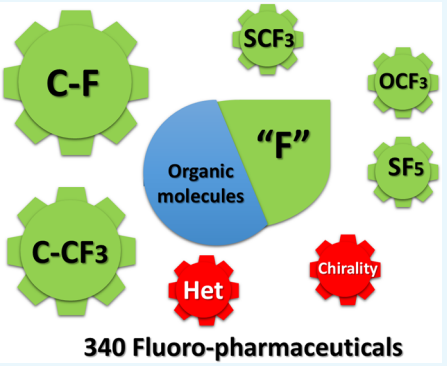
ABSTRACT: Inspired by the success of fluorinated corticosteroids in the 1950s and fluoroquinolones in the 1980s, fluorine-containing pharmaceuticals, which are also known as fluoro-pharmaceuticals, have been attracting attention for more than half of a century. Presently, about 20% of the commercial pharmaceuticals are fluoro-pharmaceuticals. In this mini-review, we analyze the prevalence of fluoro-pharmaceuticals in the market and categorize them into several groups based on the chemotype of the fluoro-functional groups, their therapeutic purpose, and the presence of heterocycles and/or chirality to highlight the structural motifs, patterns, and promising trends in fluorine-based drug design. Our database contains 340 fluoro-pharmaceuticals, from the first fluoro-pharmaceutical, Florinef, to the latest fluoro-pharmaceuticals registered in 2019 and drugs that have been withdrawn. The names and chemical structures of all the 340 fluorinated drugs discussed are provided in the Supporting Information.



INTRODUCTION

Small organic molecules have traditionally maintained a central position in drug discovery and development in the 20th century.[1] Small-molecule drugs are typically characterized by molecular weights <500 g/mol, allowing them to easily penetrate cell membranes to reach, e.g., target proteins and DNA in order to exert biological activity. Their chemical structures are relatively simple, and they can be synthesized from simple starting materials or natural products using established chemical reactions. However, over the past decade, the pharmaceutical industry has changed rapidly, and focus has increasingly shifted from small organic molecules to bio-pharmaceutical products (biologics).[2] Biologic drugs such as monoclonal antibodies are much larger and can be obtained using biotechnology or related methods. Due to their very high molecular weights, biological medical agents principally act on proteins on the cell membrane and targets outside the cell. Although many technological issues with the use of biological medicines remain, biologics have substantial advantages over small drugs, particularly in terms of selectivity, side effects, and toxicity. Indeed, biologics are currently the fastest-growing class of pharmaceuticals and have recently been among the highest-selling drugs on the market.[2]

Interestingly, the situation is somewhat different for fluoro-pharmaceuticals,[3] i.e., small organic pharmaceutical drugs that contain at least one fluorine atom or a fluorinated functional group (e.g., trifluoromethyl, CF_3). In recent years, an estimated 20% of the marketed drugs have been fluoro-pharmaceuticals. The first fluoro-pharmaceutical was fludrocortisone, Florinef (Florinef acetate), which was brought to market in 1954 (Figure 1a). Florinef is a synthetic corticosteroid that contains a fluorine atom at the stereogenic 9α-position. It exhibits potent

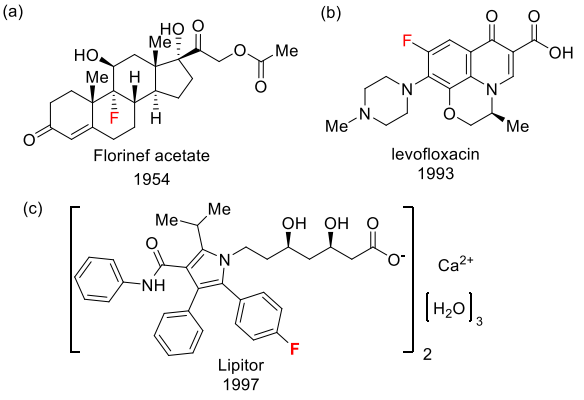


Figure 1. Selected landmark fluoro-pharmaceuticals: Forinef acetate, levofloxacin, and Lipitor.

mineralocorticoid properties and high glucocorticoid activity for the treatment of adrenogenital syndrome, adrenal insufficiency, and postural hypotension. Fluoroquinolones (new quinolones), such as ciprofloxacin, norfloxacin, and levofloxacin, were introduced in the 1980s and represent a second historically significant group of fluoro-pharmaceuticals (Figure 1b). Fluoroquinolones act as potent antibacterial agents by inhibiting the activity of DNA gyrase and topoisomerase, and

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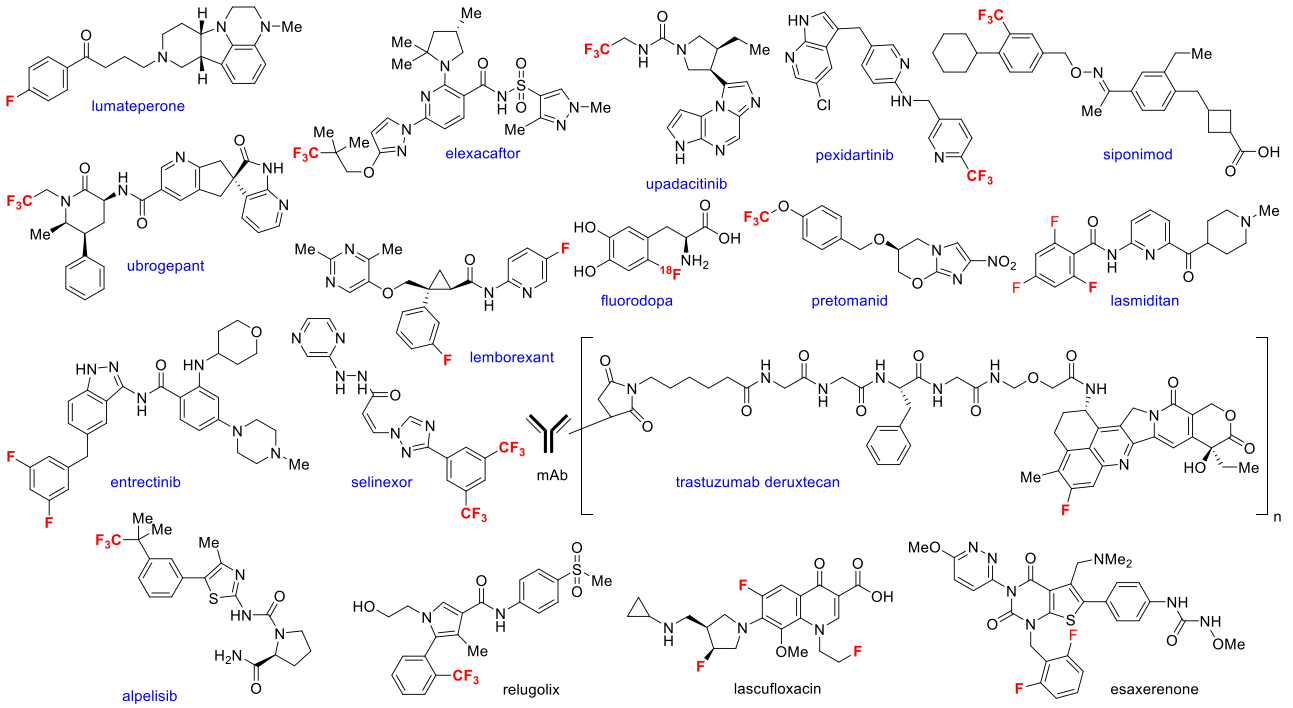

Figure 2. 17 fluoro-pharmaceuticals globally registered in 2019 including one fluorinated-biologic drug, trastuzumab deruxtecan. The 14 fluoro-pharmaceuticals indicated with blue color are approval by the FDA. Akynzeo was excluded since the active ingredient of akynzeo is fosnetupitant, which was approved in 2014 by the FDA. Elexacaftor is one of the active ingredients of trikafta, which contains another fluoro-pharmaceutical, tezacaftor.

this mechanism of action is fundamentally different from that of β-lactam antibiotics such as penicillin, cephalosporin, and antibacterial sulfur drugs.

Inspired by the success of fluorinated corticosteroids and fluoroquinolones, the number of fluoro-pharmaceuticals approved has steadily increased over the last 50 years. Globally, more than 300 fluoro-pharmaceuticals have been registered including the blockbuster drug Lipitor (Figure 1c).[4] Notably, in 2018, 38 small-molecule pharmaceuticals (64% in new molecular entities approved in 2018) were approved by the U.S. Food and Drug Administration (FDA), of which 17[5a−c] (45%) were fluoro-pharmaceuticals.[5] For comparison, 17[6b] new biologics were approved in 2018. Moreover, in 2019, 13 new fluoro-pharmaceuticals (small molecule) were approved by the FDA (Figure 2),[6a] accounting for 41% of all small-molecule drugs (32 total; three peptide pharmaceuticals, scenesse, vyleesi, and Ga-68-dotatoc, were excluded from newly approved small molecules of 32).[4,6] Twelve biologics[5b] were approved in 2019; in other words, the number of fluoro-pharmaceuticals approved in 2019 is comparable to the number of biologics, which are considered to be the "rising star" of the pharmaceutical industry.[2] More interestingly, one fluoro-pharmaceutical-conjugated antibody, trastuzumab deruxtecan, was included in the approved biologics. It should be mentioned that three more new fluoro-pharmaceuticals, relugolix, lascufloxacin, and esaxerenone, were additionally approved in Japan in 2019.[4a]

The continuous success of fluoro-pharmaceuticals[3] strongly suggests to medicinal chemists that choosing fluoro-organic molecules is a potential strategy to significantly minimize the risk of unsuccessful trial-and-error attempts during the drug-discovery process judging from the probability theory. Drug discovery is a challenging, risky, expensive, and time-consuming process, with an estimated success rate for small molecules of 1/20,000−30,000.[7] Although considerable progress has been made very recently using computer-aided methods such as molecular modeling in drug discovery,[8] these methods are still too immature for the successful design of drugs, as evident from unexpected failures in the subsequent clinical stages.

In this mini-review, we will attempt to analyze a database of fluoro-pharmaceuticals to extract robust insights for drug discovery. Our database of fluoro-pharmaceuticals registered between 1954 and 2019 contains 340 drugs, including fluoro-pharmaceuticals that have been withdrawn.[4,9] The chemical structures of the fluoro-pharmaceuticals registered in 2019 are shown in the main text (Figure 2), while the full list of fluoro-pharmaceuticals (340 drugs) and their chemical structures are provided in the Supporting Information (SI) (Table SI and Figure S1).

FLUORO-PHARMACEUTICALS IN THE PAST THREE DECADES

We first analyzed the pharmaceuticals registered globally in the past three decades (since 1991) by categorizing them into all drugs, synthetic drugs, and fluoro-pharmaceuticals (Figure 3).[4,9] The total number of fluoro-pharmaceuticals (191 drugs) accounted for 18% of the total pharmaceuticals (1072 drugs) and 22% of small-molecule drugs (839 drugs) (Table S2).[4b] The ∼20% share of fluoro-organic compounds among all pharmaceuticals is indeed notably high since (1) only a handful of organofluorine compounds have been found in nature[10] and (2) the structural constraints associated with the valency of fluorine predetermine relatively limited opportunities to diversify their chemical structures. As can be seen in the analyses in Figure 3, five to ten fluoro-pharmaceuticals have consistently been registered each year, and the relative number of fluoro-pharmaceuticals has increased in the past decade. Figure 3

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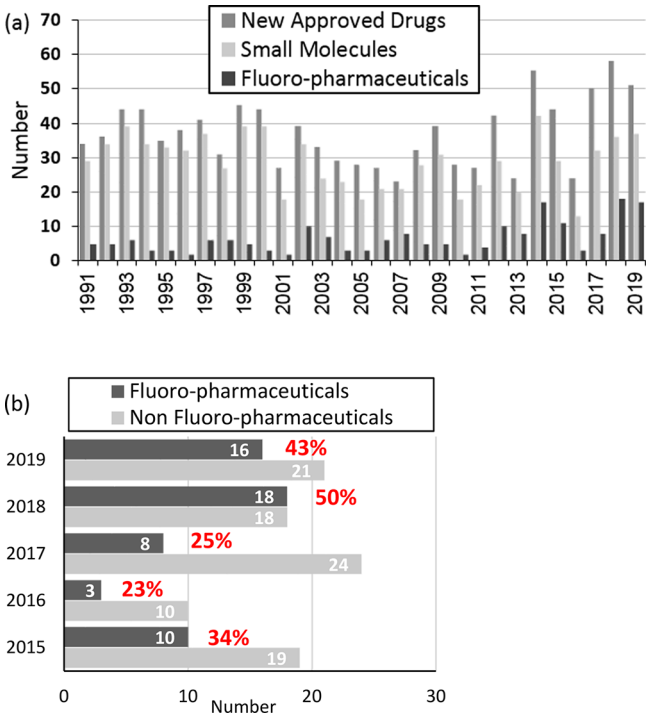

Figure 3. (a) Prevalence of fluoro-pharmaceuticals among globally registered drugs (1991−2019). The list of the all pharmaceuticals (1072 compounds), small-molecule drugs (839 compounds), and fluoro-pharmaceuticals (191 compounds) is provided (Table S2). (b) Data for small-molecule drugs over the past five years.

provides a closer look at the data for the past five years, which shows the significant medicinal impact of fluoro-pharmaceuticals. The percentages of fluoro-pharmaceuticals among the total number of registered synthetic drugs are extraordinary: 34% (2015), 23% (2016), 25% (2017), 51% (2018), and 43% (2019) (Figure 3). The data depicted in the graph strongly suggest a promising future for fluoro-pharmaceuticals.

The high prevalence of fluoro-organic compounds among pharmaceuticals can be explained by several factors.[3,11a] First, fluorine (F) is the second-smallest atom after hydrogen (H) in the periodic table of elements; thus, the replacement of an H atom in a drug candidate with F does not drastically change the parent structure. Second, the C−F bond is the strongest bond that carbon can form, which often increases the metabolic stability of fluoro-pharmaceuticals. Third, as the most electronegative element (3.98), F induces bond polarization, which may alter the lipophilicity/hydrophilicity balance of a compound. The pK_a values of the parent molecules are also affected. Fourthly, F acts as a weak hydrogen bond acceptor and can be used as a bioisostere of the hydroxyl group (OH). The hydrogen-bond-accepting analogy would suggest a carbonyl moiety, particularly relevant since the dipoles of the C−F and C═O are often viewed as similar. The combination of these unique properties of F presumably exerts subtle effects on the absorption, distribution, metabolism, and excretion (ADME) of drug candidates, although these effects can be expected to be very complex and would thus require further discussion.

CHEMOTYPES OF THE FLUORO-PHARMACEUTICALS ON THE MARKET

The database of 340 fluoro-pharmaceuticals (Figure S1)[4] was then broken down into several groups based on the chemotypes of their fluoro-functional motifs, which resulted in 369 compounds (Figure 4). Among 340 pharmaceuticals, 27

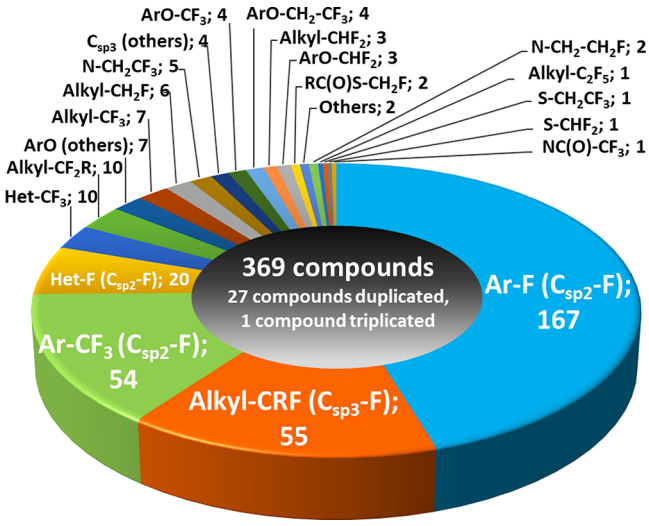

Figure 4. Chemotype distribution of fluoro-pharmaceuticals.

drugs, for example, lemborexant in Figure 2, are categorized into two groups, such as Ar−F drug and Het−F drug. One drug, lascufloxacin in Figure 9, is categorized into three groups (Ar−F, alkyl−CRF, and N−CH_2CH_2F). Thus, the number of compounds for this analysis is expanded into 369 compounds due to the duplicate and triplicate counting. The largest family of fluoro-pharmaceuticals is Ar−F-containing drugs (C_{sp2}-F, 167 compounds, 45.3%), followed by molecules with alkyl−CRF (C_{sp3}−F, 55 compounds, 14.9%), aryl−CF_3 (C_{sp2}−CF_3, 54 compounds, 14.6%), Het−F (C_{sp2}−F, 20 compounds, 5.4%), and Het-CF_3 (C_{sp2}−CF_3, 10 compounds, 2.7%) groups. The analysis also revealed that pharmaceuticals with monofluorinated moieties (Ar−F, alkyl−CRF, Het−F, alkyl−CH_2F, 67.2%) are most common, followed by drugs with trifluoromethyl groups (Ar−CF_3, Het−CF_3, alkyl−CF_3, 19.2%); these two categories comprise 86% of all fluoro-pharmaceuticals. None of the other fluoro-functional groups, including fluoroalkyl groups (CH_2F, CHF_2), fluorine-containing alkoxy groups (OCF_3, $OCHF_2$, OCH_2CF_3), fluorine-containing alkyl sulfides (SCH_2F, $SCHF_2$, SCH_2CF_3), and fluorine-containing alkylamino groups ($NC(O)CF_3$, NCH_2CH_2F, NCH_2CF_3), represent more than five compounds for each. However, it should be noted that the high prevalence of some fluoro-functional group chemotypes, such as "C_{sp2}−F" and "C_{sp3}−F", does not necessarily suggest that such moieties are more likely to produce successful pharmaceutical fragments than other fluoro-functional groups, such as OCF_3 or SCF_3.

The number of organofluorine compounds of a given chemotype that is investigated as potential drug candidates can be expected to depend strongly on the availability of synthetic methods to access the relevant moieties. For example, in 2019 (Figure 2),[4] the number of CF_3-containing drugs was eight (excluding the OCF_3 drug), while that of the C−F-bond(s)-containing drugs was seven. These numbers are in contrast to those presented in Figure 4 but may reflect the increasing diversity of the trifluoromethylation reactions. These facts indicate that synthetic methodology is providing access to new fluorinated motifs with unique physicochemical properties that medicinal chemists will take advantage of.[11] At the same

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time, more research is required in order to better understand the effect of fluorine and fluorinated functional groups on, e.g., target proteins and DNA.

CLASSIFICATION OF FLUORO-PHARMACEUTICALS BASED ON THEIR THERAPEUTIC PURPOSE

Subsequently, we were interested in classifying the fluoro-pharmaceuticals based on their medical purposes and uses. Thus, we categorized the fluoro-pharmaceuticals (Table S1, Figure S1) based on the *Anatomical Therapeutic Chemical Classification* of the WHO[12] (Anatomical Therapeutic Chemical Classification System, ATC, Figure 5). Fluoro-pharmaceuticals

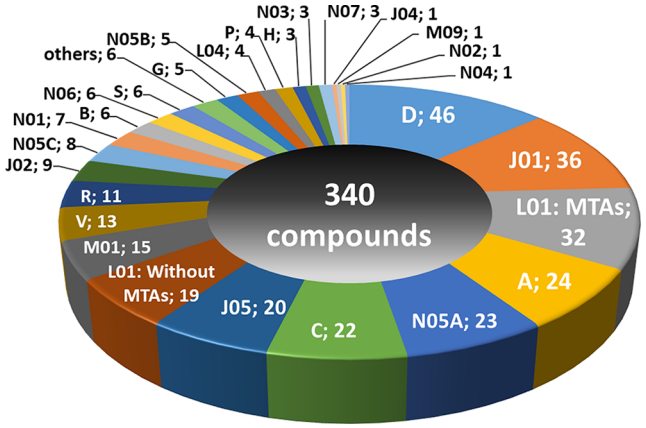

Figure 5. Disease-focused classification of fluoro-pharmaceuticals according to the *Anatomical Therapeutic Chemical Classification* (ATC) of the WHO. A: Gastrointestinal and metabolism action. B: Blood and hematopoietic organ. C: Circulatory system. D: Skin disease remedy. G: Urogenital system and sex hormone. H: General hormonal drug. J01: General antimicrobial. J02: General antifungal. J04: Antimycobacteria. J05: General antiviral. L01: Antitumor drug (molecularly targeted agents (MTAs)). L01: Antitumor drug (without MTAs). L04: Immunosuppressive agent. M01: Nonsteroidal anti-inflammatory drugs (NSAID). M09: Musculoskeletal system agents. N01: Anesthetics. N02: Antipyretic analgesics. N03: Antiepileptic drug. N04: Antiparkinson agent. N05A: Antipsychotic agent. N05B: Antianxiety agent. N05C: Hypnotic drug. N06: Antidepressant drug. N07: Nervous system agent. P: Anthelmintics. R: Respiratory disease agent. S: Sensory system disease agent. V: Others.

have been used for a broad range of therapeutic purposes, including antimicrobial, antitumor, and anti-inflammatory activity. While we could not identify any specific disease category to which fluorine-containing drugs contributed disproportionally, the top five medicinal uses were: skin disease remedies (46 compounds, 13.5%), general antifungal reagents (36 compounds, 10.6%), antitumor drugs (molecularly targeted agents (MTAs)) (32 compounds, 9.4%), gastrointestinal and metabolism agents (24 compounds, 7.0%), and antipsychotic agents (23 compounds, 6.7%).

FLUORO-PHARMACEUTICALS WITH HETEROCYCLES

Heterocyclic compounds, particularly nitrogen-containing heterocycles such as pyridine and piperidine, are frequently found in the structures of pharmaceuticals and biologically active natural products.[13] They are commonly used as privileged fragments for drug discovery. More than 85% of biologically active compounds contain one or more heterocyclic fragments in their structures.[14] These statistics suggest that fluoro-functionalized heterocyclic compounds should be promising candidates for drug discovery.[15] Therefore, we analyzed our list of fluoro-pharmaceuticals to identify those in which a heterocyclic fragment was directly functionalized with a fluorinated group (Figures 6, 7, and S2). Benzofused bi- or

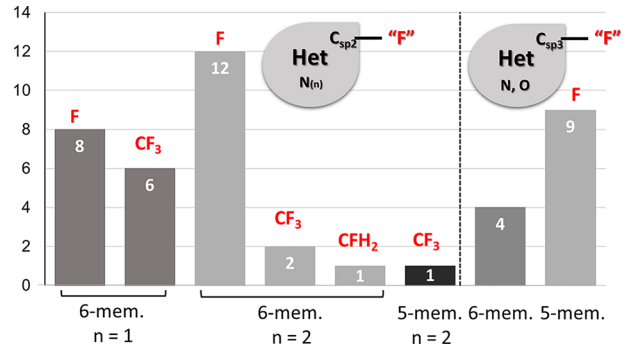

Figure 6. Fluoro-functionalized heterocycles in fluoro-pharmaceuticals (42 drugs with 43 chemo-type functional groups; gemigliptin contains two fluoro-functionalized heterocyclic fragments).

tricyclic heterocycles such as quinolines, indoles, and phenothiazines, where the fluoro-functional group is attached to the benzene part of a benzannulated heterocycle, but not a heterocyclic part, were removed from this category. Among these compounds, the most common heterocyclic groups were 6-membered heteroaromatics that contain two nitrogen atoms, including pyrimidine, pyrazine, and pyrimidone. The second-most-prevalent class was 6-membered heteroaromatics that contain one nitrogen atom, including pyridine, pyridine, quinolone, isoquinoline, cytosine, uracil, and adenosine. In terms of the fluoro-functional group, F-substituted compounds were most common, followed by CF_3-substituted drugs. 5-Membered C_{sp3} heterocycles that contain fluorine were also favored as pharmaceuticals. Contrary to our expectations, the number of drugs with fluoro-functionalized heterocyclic fragments was relatively low (42 drugs), and their structural diversity was also highly limited. Among these 42 drugs, the total number of fluoro-functionalized heterocyclic fragments was 43; i.e., gemigliptin contains two types of fluoro-functionalized heterocyclic moieties, piperidine (C_{sp3}–F) and pyrimidine (C_{sp2}–CF_3) (Figure 6).

C_{sp2}–F-functionalized 6-membered heterocycles with two nitrogen atoms were the most common motifs, i.e., derivatives of uracil and cytosine. Additionally, there were no examples of pharmaceuticals with pyrroles and indoles directly functionalized with fluorine, CF_3, or other fluorinated functional groups. This result was somewhat unexpected in light of the high prevalence of heterocycles in pharmaceuticals. This could possibly be attributed to the relatively small variety of fluoro-functionalized heterocyclic compounds available. In other words, novel fluoro-pharmaceuticals could potentially be developed by focusing on fluoro-functionalized heterocycles as possibly privileged motifs, which in turn would require advances in synthetic methodology, including methods for the fluorination and trifluoromethylation of a variety of heterocyclic compounds.[16]

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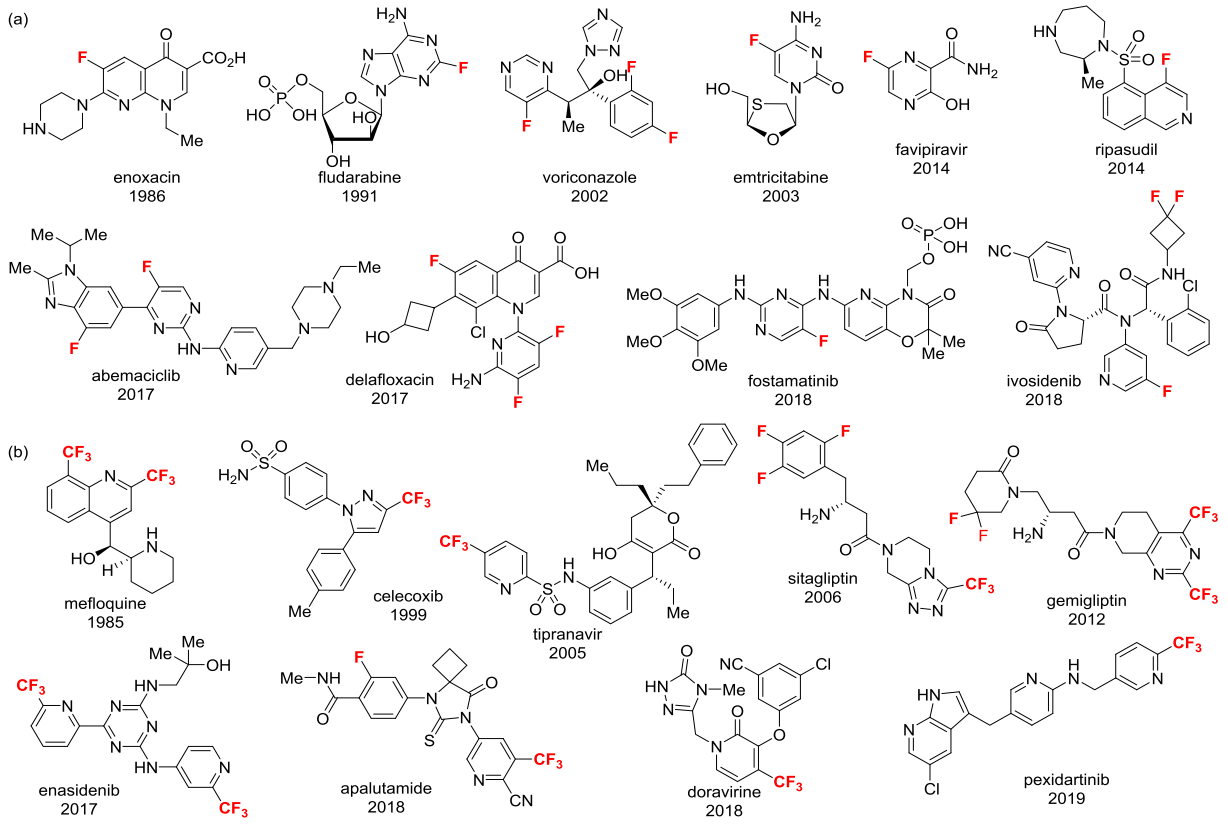

Figure 7. Selected examples of fluoro-functionalized heterocycles in fluoro-pharmaceuticals: (a) C_{Het}−F and (b) C_{Het}−CF_3. A full list of F-heterocycles is provided in Figure S2.

CHIRAL FLUORO-PHARMACEUTICALS

Chirality has gradually become a crucial factor in drug development.[17] The enantiomers of chiral drugs frequently exhibit diverging biological activity, as biological systems often recognize the two enantiomers as different compounds. The most notorious example in pharmaceutical history is arguably thalidomide.[18] Thalidomide contains a stereogenic carbon center that gives rise to two enantiomers, (*S*)- and (*R*)-thalidomide (Figure 8a). Racemic thalidomide was launched in the 1950s in West Germany and other first-world countries as a sedative, hypnotic, and later as a medicament to treat morning sickness. However, unexpected teratogenic congenital disabilities were reported for babies delivered from mothers who took thalidomide during their pregnancy, which led to a withdrawal of thalidomide from the market. Later, the (*S*)-enantiomer of thalidomide was found to be responsible for this tragic teratogenic side effect,[19] but avoiding the teratogenicity from thalidomide by administering only the (*R*)-enantiomer is impossible due to its racemization *in vivo*. Interestingly, despite its devastating side effects on unborn children, the racemic mixture of thalidomide is now back on the market as an effective drug for the treatment of leprosy and multiple myeloma. A potential strategy to overcome the unavoidable racemization of thalidomide *in vivo* that is currently examined is the use of chiral fluorinated thalidomide, given the enhanced metabolic stability of the carbon−fluorine (C−F) bond (Figure 8b).[20] While the (*S*)-fluorinated thalidomide showed to be two times more potent than the (*R*)-enantiomer in antitumor activity, the mechanism of teratogenic side effects of thalidomide is still obscure.

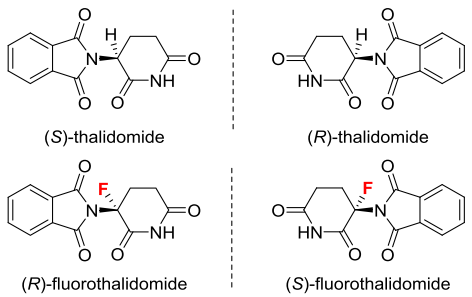

Figure 8. Chirality in fluoro-pharmaceuticals. (a) Enantiomers of thalidomide and (b) the fluorinated isosteres of fluorothalidomide.

Currently, more than 50% of the drugs marketed are chiral compounds.[21] In this context, we identified 62 fluoro-pharmaceuticals with a fluorine or fluoro-functional group directly connected to a stereogenic carbon center, including racemic compounds (Figures 9 and S3). The percentage of chiral fluoro-pharmaceuticals (18% of all fluoro-pharmaceuticals) is relatively low. The most common groups are synthetic fluoro-corticoids (46 compounds), followed by four fluoro-nucleosides. A clear majority of the molecules contains a stereogenic C_{sp3}−F unit (54 compounds containing fludeoxyglucose-^{18}F); the other fluoroalkyl groups, including C_{sp3}−CF_3, C_{sp3}−CHF_2, C_{sp3}−CH_2F, and C_{sp3}−CRF_2, contribute with one or two examples each. All the molecules with a stereogenic C_{sp3}−F bond are cyclic fluorinated compounds with limited structural variety. These analyses suggest that the present synthetic methodologies might be insufficient for the preparation of chiral fluorinated drug candidates, presumably due to the complexity

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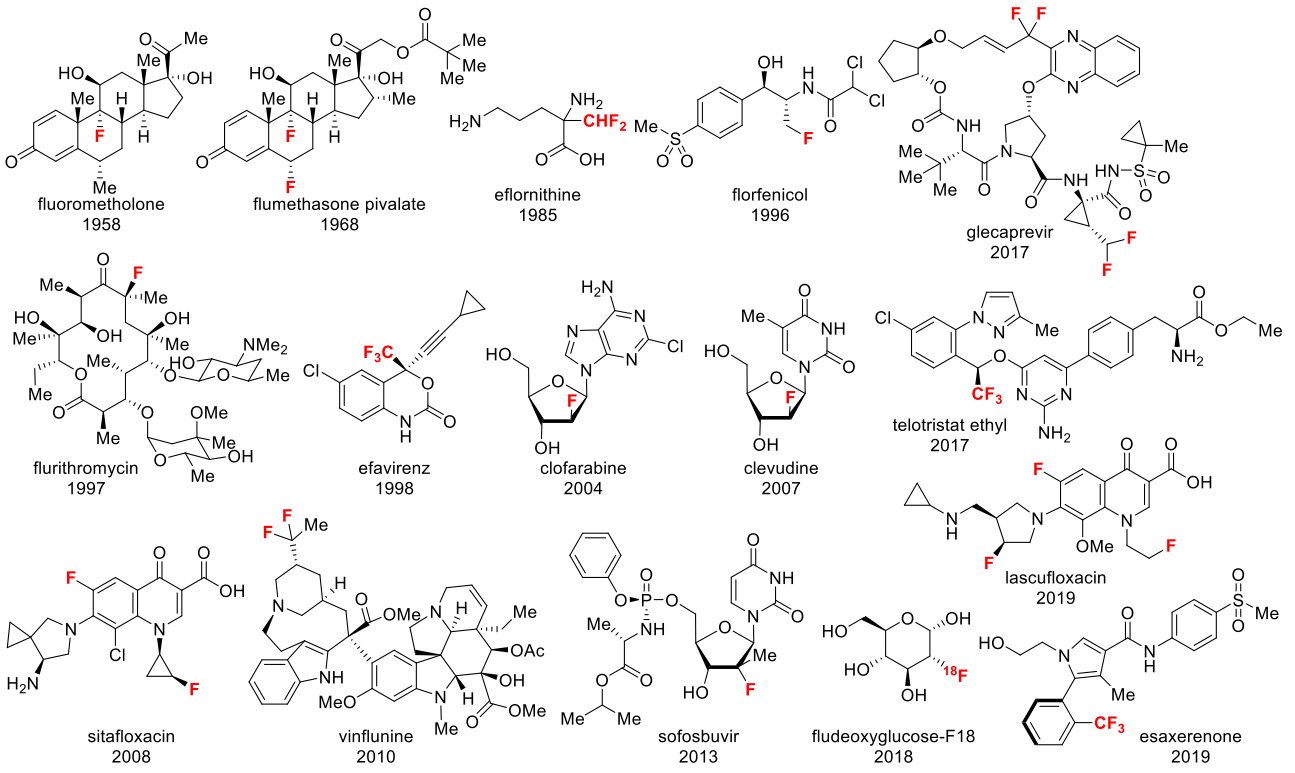

Figure 9. Selected fluoro-pharmaceuticals with a fluorine or fluoro-functional group at a stereogenic carbon center, including racemic compounds (see Figure S3 in the SI for the full list).

of the molecules, despite the relatively high number of reports on enantioselective fluorination and trifluoromethylation reactions.[22]

CONCLUSIONS

We have analyzed 340 fluoro-pharmaceuticals that have been registered since 1954 and categorized them into several groups based on the chemotype of their fluoro-functional substituents, therapeutic purpose, and the presence of heterocycles or chirality. While traditional small-molecule drugs have become a minority in recent years, this situation does not apply to fluoro-pharmaceuticals, which have maintained their place as attractive target molecules for drug candidates, along biologics. Additionally, the potential of fluoro-pharmaceuticals is expected to increase in the future in parallel to advancements in fluoro-functionalization methodologies. In recent years, a vast number of synthetic strategies have been reported for the synthesis of SCF_3,[23] OCF_3,[24] and even rare pentafluoro-λ^6-sulfanyl (SF_5)[25] -containing compounds, including SF_5−pyridines. Further progress in the development of synthetic methods for the formation of fluorinated heterocyclic compounds, including asymmetric reactions, could help to increase fluorine-based drug discovery in the future. To our knowledge, this mini-review treats the most substantial number of fluoro-pharmaceuticals registered globally.[3] The present manuscript will be renewed annually to provide a guide for medicinal chemists to develop novel fluoro-pharmaceuticals. We hope that synthetic fluorine chemists will more frequently approach the pharmaceutical industry to invigorate the fluoro-pharmaceutical area over the coming decades.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00830.

Lists of names, chemical structures, and ATC categories of 340 fluoropharmaceuticals (Tables S1−S2 and Figures S1−S3) (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

Biographies

Munenori Inoue is the vice president of Sagami Chemical Research Institute (SCRI). He received a Ph.D. (1999) in agricultural chemistry from the University of Tokyo (Professor T. Kitahara). After he worked as a postdoc at Yale University (Professor J. L. Wood), he joined SCRI as a researcher and was promoted to the group leader of the Fine Organic Chemistry Group in 2004. His research interests are the development of new organic reactions and fluorine chemistry.

Yuji Sumii is an Assistant Professor at the Nagoya Institute of Technology since 2015. He received a Ph.D. (2011) in pharmaceutical sciences from Osaka University (Professor M. Kobayashi). He worked as a postdoc at Osaka University (Professor M. Kobayashi) and California Institute of Technology (Professor B. M. Stoltz).

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