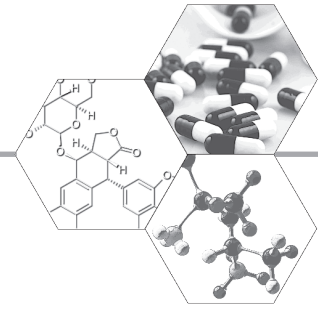



# Fluorine in medicinal chemistry: a century of progress and a 60-year retrospective of selected highlights

This perspective explores the origins of both fluorine and medicinal chemistry a century ago and traces the early history of the intersection of these areas and the subsequent roles that fluorine has played in advancing medicinal innovations and diagnoses during the past 60 years. The overview highlights remarkable breakthroughs in many diverse areas of medicinal chemistry, including inter alia, anesthetics, steroidal and nonsteroidal anti-inflammatory drugs, anticancer and antiviral agents, CNS medications, antibacterials and cholesterol biosynthesis inhibitors. The increasing use of fluorine-18-labeled radiotracers in PET for diagnostic imaging of the brain, heart and in oncology is briefly presented. The signature roles of fluorine in medicinal chemistry are now firmly established. The presence of fluorine in pharmaceuticals has had a major impact on a plethora of important medical applications, such as those cited above. Fluorine will very likely continue to contribute significantly by playing multifaceted roles in enhancing future medical advances.

Fluorine in medicinal chemistry has exploded during the past 20 years and especially in the last decade. In order to gain a better understanding and appreciation of the dynamic progress observed today, it seems desirable to reflect on the early days of this field from more than three generations ago. Our intent and main objective is to provide an historical narrative and overview of the birth of this field and to highlight those advances that have led to its ultimate emergence during a 60-year period to become a significant contributor in modern medical science.

The origins of organic fluorine chemistry date back to the 1890s when the Belgian chemist Frédéric Swarts launched a prolific 40-year career by almost singlehandedly creating a new subdiscipline in aliphatic fluorine chemistry [1]. He prepared many polyhalogen compounds containing fluorine and established the foundation for others to follow. The most notable example of this influence was the application of dichlorodifluoromethane and congeners as the next generation of refrigerants to replace toxic $NH_3$ and $SO_2$ [2]. These compounds were manufactured and marketed as Freons® in a joint venture of Frigidaire (General Motors) and DuPont. The serendipitous discovery of polytetrafluoroethylene (PTFE, Teflon®) by Plunkett at DuPont in 1938 has since provided a remarkable product used worldwide and also contributed to the fluoropolymer industry [3]. In contrast to fluoroaliphatics, the introduction of fluorine on the aromatic nucleus had an earlier and less eventful history. *p*-fluorobenzoic acid was prepared from its precursor diazonium salt and concentrated HF [4], and this was followed by other successes. However, the first practical method was developed by Balz and Schiemann in 1927 [5]. Isolated aryldiazonium tetrafluoroborate salts, dried and heated at 100°C or above, provided good yields of the fluoroaromatic compound. This major milestone has been the method of choice for the past 82 years, being of special importance for many new pharmaceuticals. Trifluoromethyl-substituted aromatics also play a major role as medicinals. Swarts once again led the way by converting benzotrichloride to benzotrifluoride using only $SbF_3$, the Swarts reagent [6]. The top secret Manhattan Project during World War II involved research into fluorine compounds compatible with $UF_6$. The results of this massive effort were not cleared for release until 1946, with the first public disclosure of 200 pages of significant results and experimental details in an early 1947 issue of *Industrial and Engineering Chemistry* [7]. During that period, the issue was often referred to as the 'bible'.

It has been little noted that organofluorine chemistry and medicinal chemistry developed during a similar period, but with distinctly different growth patterns. The genesis of medicinal chemistry stems from the prodigious research of Paul Ehrlich who, after 606 experiments, identified in 1910 a chemical entity for treatment

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Future science part of fsg

of disease. Salvarsan, an arsenic compound, became a cure for syphilis, which ran rampant in the Western world. A 1908 Nobelist, Ehrlich, has been recognized as the 'father of chemotherapy'. After his death in 1915, there was a hiatus of 20 years until the introduction in the mid-1930s of sulfanilamide and the other 'miracle' sulfa drugs. The availability of these outstanding synthetic antibacterials to fight infections gained widespread support and ushered in a new era in therapeutics. Several years later, during World War II, an antimalarial drug program was activated in response to the high incidence of malaria among servicemen in the South Pacific. Finally, the advent of the 'wonder-drug' antibiotics penicillin and streptomycin changed the landscape and opened the door to great medical advances.

It was now the late 1940s and medicinal chemistry, still in its infancy, was poised to cross paths with fluorine. The idea was to incorporate fluorine into compounds of medicinal interest, very early examples of molecular modification in drug design. Just as the stage was set, came word that a separate but closely related subdiscipline was emerging: the biochemistry of the C-F bond. From the start, it was apparent that the biochemical and medicinal aspects were frequently intertwined and that clear separation was not always possible. However, the biochemistry is beyond the scope of this perspective, whose focus is primarily on the synthesis of fluorine-containing pharmaceuticals, their effects on disease and their ultimate marketability as approved drugs for the public. These biochemical developments have had a brilliant history and merit their own retrospective. It will suffice to mention here the pioneer studies of Sir Rudolph Peters, who elucidated the mechanism of toxic action of fluoroacetate during the Krebs cycle by invoking the concept of 'lethal synthesis' [8]. Subsequent studies by Peter Goldman [9], Charles Heidelberger, Ernest Kun and others built a firm foundation of C-F biochemistry. Two books in the 1970s provide excellent contributions to the science [10,11]. The two volumes by Kenneth Kirk in 1991 are a tour-de-force and are highly recommended [12,13]. A special issue of the *Journal of Fluorine Chemistry*, edited by Kirk, brings this subject up to date [14].

## Discussion

During the decade beginning in the late 1940s and particularly between 1952 and 1957, the spotlight shone on fluorinated compounds in at least four unrelated areas of great medical interest. The developments featured practical applications in inhalation anesthesia, steroids (especially anti-inflammatory agents), CNS medications and anticancer drugs. The combination of these milestones and the changing dynamics of pharmacology, which led to structure–activity relationships (SARs), 'molecular modification' in drug design [15] and discovery programs and subsequent studies of drug–receptor interactions, provided a powerful impetus for the advances that lay ahead. Adding to these impending breakthroughs were:

- The availability of new fluorochemicals with functional groups via the Simons' hafnium-based electrochemical fluorination (ECF) process [16];
- Improvements in the handling of fluorine and HF;
- The developing arsenal of new reagents for the site-selective introduction of fluorine in organic molecules (*vide infra*);
- The further advances involving trifluoromethyl-substituted aromatics in medicinal applications [17].

### ■ Volatile anesthetics (previously known as inhalation anesthetics)

**Volatile anesthetics**

These compounds were previously known as inhalation anesthetics. The search for a safer, better tolerated and nonflammable replacement for diethyl ether has resulted in several highly fluorinated compounds most commonly used today

The need to replace flammable diethyl ether, the dominant general anesthetic for 100 years, became urgent because of growing incidents of fires caused by the increasing use of electrical devices in surgery as well as the patient's slow recovery and unfavorable side effects, which motivated the search for a volatile, fast-acting and potent material that was nontoxic and nonflammable. In 1946, Robbins evaluated a host of Swarts–Henne fluorohalocarbons, with less than satisfactory results [18]. Others joined the fray, including McBee and Filler, who prepared two potential candidates, which, unfortunately, failed the critical soda–lime stability test [19]. Soon thereafter, Suckling and Raventós prepared and evaluated halothane **(1)**, a nonflammable, volatile (boiling point of 50°C) compound with properties far superior to anesthetics then in use [20,21]. The fluorovinyl ether, fluroxene **(2)**, less flammable than ether or cyclopropane, was introduced in 1951, but never gained a foothold. In the subsequent quest for even more effective candidates, many fluoroethers were synthesized and evaluated over the next 40 years. Three compounds,

isoflurane **(3)**, desflurane **(4)** and sevoflurane **(5)**, have survived the rigorous testing and are now in use, although halothane continues to be the leader. An updated detailed review [22] and a mini-review [23] are strongly recommended.

## ■ Fluorinated steroids

The development and remarkable success of fluorinated steroids represents one of the most significant advances in chemotherapeutics. The incorporation of one or two fluorine atoms into the steroid nucleus has been invaluable as adrenocortical and progestational agents and in androgenic hormone therapy. However, the greatest practical impact has been as anti-inflammatory (AI) drugs. The opening gambit was the pioneer studies of Fried and Sabo [24,25], who prepared and evaluated 9α-fluoro-11-β-hydroxy corticoids, obtained by *trans*-diaxial opening of epoxides by hydrogen fluoride **(Figure 1)**.

A variety of 9α- and 6α-fluorosteroids, as well as 9α- and 6α-difluoro compounds, were subsequently prepared. Indeed, activated olefins (enol ethers and esters and enamines) reacted with electrophilic fluorinating agents, such as $ClO_3F$ and $CF_3OF$, to yield steroids with fluorine at the 2-, 4-, 6-, 10-, 16- and 21-positions, as well as 9α- and 6α-difluoro compounds. Many of these have exhibited far greater anti-inflammatory activity than cortisone and cortisol, often with much lower sodium retention. They have proven to be especially effective in the treatment of rheumatoid arthritis. Two examples are triamcinolone **(6)** and dexamethasone **(7)**. The topical potencies of corticosteroids are magnified when the lipoid–water ratio increases. The presence of fluorine enhances the ratio. Thus, fluprednisolone **(8)** is a valuable topical anti-inflammatory agent. Although progress has slowed in recent years, fluticasone propionate (Flonase®) **(9)**, a glucocorticosteroid introduced in 1990, has emerged as a very effective and widely used anti-inflammatory for the treatment of allergic rhinitis and asthma. Its structure is unusual, with fluorine in the 9α- and 6α-positions and in a 17-substituted *S*-fluoromethyl carbothiate group. An excellent review covering fluorosteroids through the 1970s is recommended [26].

## ■ Nonsteroidal anti-inflammatory agents

Adrenocortical steroids are among the most powerful prescribed drugs and must be monitored carefully. They are contraindicated or used with caution with patients suffering from peptic ulcer, heart disease, infections, psychoses, diabetes and glaucoma. In order to obviate these limitations, a major effort was launched in the early 1960s to find nonsteroidal anti-inflammatory drugs (NSAIDs) that would surpass the effectiveness of salicylates, especially aspirin. A number of fluorine-containing NSAIDs have been identified, although aspirin, ibuprofen and naproxen lead the current market. These fluoro compounds, some structurally resembling aspirin and ibuprofen, while more costly, often provide special advantages, with greater activity, longer analgesic effects and reduced gastrointestinal irritation. Several examples include flufenisal **(10)**, which is four- to five-times more active than aspirin. Diflunisal (Dolobid®) **(11)** is effective in the treatment of osteoarthritis and flurbiprofen (Froben®) **(12)**, an analog of ibuprofen, relieves symptoms in degenerative and inflammatory arthritis. Both **11** and **12** inhibit the synthesis of prostaglandins.

**Fluorosteroids**

The incorporation of fluorine in natural and synthetic steroids has greatly enhanced the effectiveness of these powerful drugs, especially in the treatment of inflammatory diseases such as rheumatoid arthritis

## ■ CNS medications

For those old enough to recall the abysmal handling of mental illness before the 1950s, the dramatic transformation since then has been astonishing. In what has been called 'biochemical psychiatry', the increasing knowledge

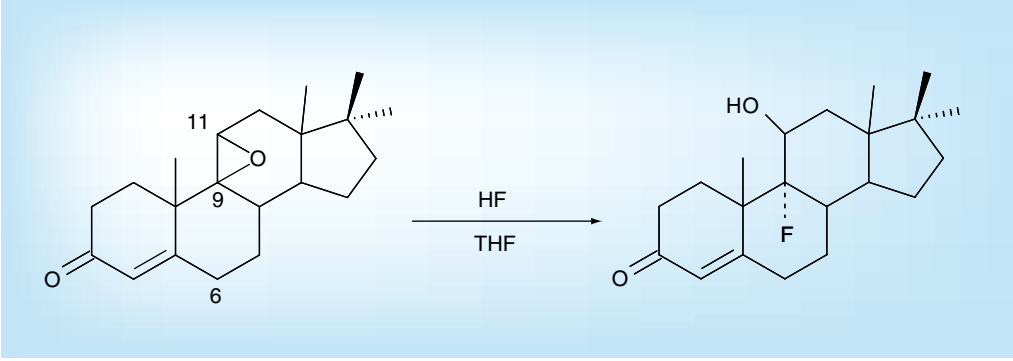


**Figure 1. Preparation of a 9-α-fluorosteroid by epoxide ring opening.**

about brain chemistry and the introduction of a wide range of drugs have completely altered the therapeutic management of CNS diseases, including psychoses, anxiety, depression and obsessive–compulsive disorder. Fluorine has played a pivotal role in the evolution of more potent and selective CNS agents. The chief advantage of fluorine, as trifluoromethyl- or fluoro-substituted aryl compounds, is the ability to increase lipid solubility and thereby enhance the rate of absorption and transport of the drug across the blood–brain barrier. Most of these agents are available as prescription drugs. An outstanding detailed review of this subject, with special emphasis from 1980 to 1993, has been presented by AJ Elliott [27]. It will suffice here to mention a few important pharmaceuticals. Neuroleptics (antipsychotic) drugs: the tricyclic phenothiazine, fluphenazine **(13)**, the butyrophenone haloperidol **(14)** and the diarylbutylamine penfluridol **(15)**. Anxiolytics (1,4-benzodiazepines): flurazepam **(16)**. Antidepressants: especially fluoxetine (Prozac®) **(17)**, a serotonin-reuptake inhibitor and one of the most prescribed drugs in the USA. Since all of these compounds are F- or $CF_3$-substituted aryls, there is no need or advantage in using special fluorinating agents.

## ■ 5-fluorouracil: a watershed on the road to anticancer & antiviral therapy

In 1957, Heidelberger and co-workers prepared 5-fluorouracil (5-FU) **(18)** and demonstrated its significant tumor-inhibiting activity [28,29]. This landmark contribution heralded a new era for future developments in fluoronucleoside chemistry, especially those involving anticancer and antiviral agents. The replacement of hydrogen in uracil (found in RNA) by unreactive fluorine (a 'deceptor' group) is pivotal, since 5-FU is anabolized to 5-fluoro-2-α-deoxyuridylate **(19)**, a potent competitive inhibitor of thymidylate synthetase. The resulting enzymatic blockade inhibits tumor growth, since 5-FU and its anabolites concentrate in these cells. However, toxic side effects led to structural variations of 5-FU, such as ftorafur (Futraful®) **(20)**, a masked compound that slowly releases 5-FU *in vivo*. The tedious, multistep procedure of the original synthesis of 5-FU limited its availability and kept the cost high until direct fluorination markedly reduced the price **(Figure 2)** [101]. This is one of the few examples of the use of fluorine gas in a successful commercial process.

**5-fluorouracil**

The introduction of 5-fluorouracil as a tumor-inhibiting drug for the treatment of breast cancer, leukemia and Hodgkin's disease was a landmark that heralded a major push in cancer chemotherapy

## ■ What advantages does fluorine impart to bioactive molecules?

After the developments of the 1950s, advances in all these areas continued apace and provided increasing evidence that the incorporation of fluorine imparts special characteristics that enhance therapeutic efficacy and improved pharmacological properties in bioactive molecules. An early listing of these advantages was presented in a broad review of the field [30] and subsequently refined after additional research and new data became available. At least five important features include:

- As the second smallest substituent, fluorine closely mimics hydrogen with respect to steric requirements at enzyme receptor sites. It is also an effective replacement for isosteric oxygen, as in the -OH group. The trifluoromethyl group, however, is not only substantially larger than methyl, but occupies more space than isopropyl;
- The presence of fluorine often leads to increased lipid solubility, thereby enhancing rates of absorption and transport of drugs *in vivo*. While fluoro is only slightly more lipophilic than hydrogen, trifluoromethyl is much more lipophilic than methyl or chloro, which are frequently replaced by $CF_3$. This factor is often the most significant in improving pharmacological activity;

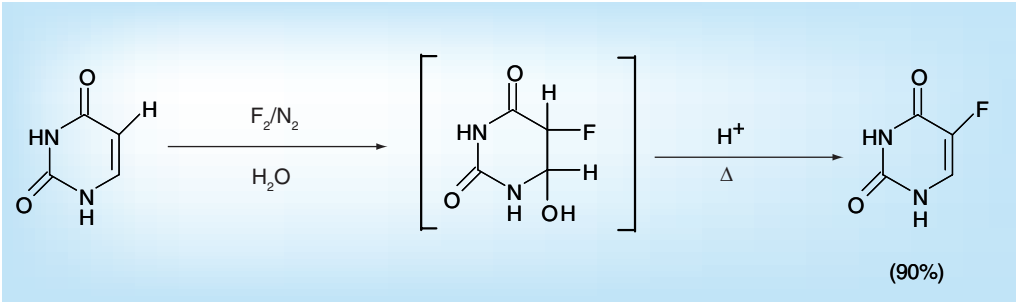


**Figure 2. Commercial synthesis of 5-fluorouracil.**

- The high electronegativity of fluorine alters electronic effects and, thereby, chemical reactivity and physical properties;
- Fluorine imparts increased oxidative and thermal stability because the C-F bond is much stronger than the C-H bond. However, improved stability may have a downside, as in the 'lethal synthesis' associated with fluoroacetate;
- In special cases, such as 5-FU, the specific location of 'deceptor' fluorine instead of hydrogen blocks an essential biochemical reaction and leads to its tumor inhibitory-behavior.

A hallmark contribution by Edwards has provided a long-needed, in-depth look at the principles behind the use of fluorine in drugs and biochemical applications [31]. For the first time, the subject was approached from a mechanistic physicochemical viewpoint. On the basis of the energies of OH and CO bonds, relative to the OF bond that would be formed by oxidative attack on the C-F bond, Edwards concludes that the strength of the C-F bond is unimportant. In a very recent elegant perspective, Hagmann elaborates on the many roles of fluorine in medicinal chemistry [32].

## Fluoronucleosides & nucleic acids as anticancer & antiviral drugs

The toxicity of 5-FU limits its use in treating skin, breast, gastrointestinal and colorectal cancers, except in conjunction with nonfluorinated agents, such as methotrexate and cisplatin, or in combination therapy with 5-FU prodrugs, such as ftorafur **(20)** and galocitabine **(21)**. In the decades since the introduction of 5-FU, there has been a very intense competitive quest to identify more effective and less toxic pyrimidine and purine **fluoronucleosides and nucleic acids**. The scope of this avalanche of studies is so broad that only a few examples since about 1980 will be cited. Readers can glean detailed information from at least four thorough reviews [33–36].

## Anticancer agents

Fludarabine **(22)**, a purine antimetabolite, has been effective in treating B-cell chronic lymphocytic leukemia [37] and certain mammary carcinomas [38]. Gemcitabine (Gemzar®) **(23)**, a *gem*-difluorodeoxynucleoside containing a cytosine moiety, was first prepared as a potential antiviral agent. It has proven to be much more effective as an antimetabolite for the treatment of solid tumors such as non-small-cell lung cancer and, especially, pancreatic cancer [39], for which it is currently used in clinical therapy.

## Antiviral drugs

In recent years, up to the present, much emphasis has been placed on nucleosides with fluorine located on the sugar moiety, which have played a prominent role in antiviral therapeutics [34]. An early candidate was 3α-fluorothymidine **(24)**, which showed promising *in vivo* activity against hepatitis B virus (HBV), HIV-1 and murine leukemia. Many other fluoro compounds have subsequently been synthesized and evaluated. Notably, the presence of a single fluorine at C-2α confers hydrolytic and enzymatic stability to the glycosyl linkage. For example, 2α-fluoro,2α,3α-dideoxyadenosine **(25)** is effective against HIV strains resistant to other dideoxynucleosides. A host of 2α-$CF_3$, $CF_2H$ and $CH_2F$ compounds, as well as monofluorinated methylenecyclopropane nucleosides, have been prepared and assessed. The L-isomer of a 2α-fluoro-carbocyclic nucleoside **(26)** showed potent activity against HIV-1 in human peripheral mononuclear cells [35]. Compound **27** is very active against herpes simplex viruses (HSVs), HSV-1 and HSV-2. Efavirenz (Sustiva®) **(28)**, containing a tertiary $CF_3$ group, is a non-nucleoside reverse transcriptase inhibitor, which, in combination with two nucleoside inhibitors, is very effective in the treatment of HIV-1 [41]. Finally, clevudine (Levovir®) **(29)**, a fluorinated β-L-nucleoside analog for oral treatment of chronic Hepatitis B infection, was marketed in 2007. Meng and Qing provide an excellent up-to-date overview of this area [35].

## Other anticancer agents

Beyond the nucleosides, several structurally diverse fluoro compounds have drawn major attention for anti-tumor activity. These include flutamide **(30)**, an anti-androgen, which was launched in 1983 for the treatment of prostate cancer, anthracycline antibiotics, steroids, vitamin D3 analogs such as **(31)** [41] and, most importantly, fluorine-containing taxoids, led by the prodigious and stellar research of Ojima [42,43]. Thus, naturally occurring paclitaxel (Taxol®) **(32)** and the semisynthetic docetaxel (Taxotere®) are widely used to treat advanced ovarian cancer, metastatic breast cancer and non-small-cell lung cancer. Fluorine was introduced into these complex structures to assess its effect on cytotoxicity. It was also hoped that replacing phenyl by

**FLUORONUCLEOSIDES AND NUCLEIC ACIDS**

These synthetic fluorine-containing analogs of DNA- and RNA-related compounds have found expression as very effective anticancer and antiviral agents

the more lipophilic 4-fluorophenyl at the C-3α position **(33)** would accelerate the formation of the desired 'hydrophobic cluster' conformation in aqueous media. Indeed, the presence of fluorine at the active site blocks undesirable enzymatic hydroxylation, resulting in more potent activity than the parent compounds. Providing details of Ojima's contributions and those of others to this exciting and promising field is beyond the scope of this article. However, a very recent paper reports the increased efficacy of 3α-difluoromethyl and 3α-trifluoromethyl second-generation taxoids [44].

**FLUOROQUINOLONES**

The members of this major class of compounds, many now in clinical use, have brought the greatest advances in antibacterial drugs since the sulfa drugs of the 1930s. The presence of fluorine is pivotal

## ■ Fluoroamino acids & peptides

In 1932, Balz and Schiemann prepared *p*-fluorophenylalanine (FPA), which behaved as a metabolic antagonist to phenylalanine in microorganisms. FPA is incorporated into proteins to inhibit growth. It also interferes with viral replication. The first aliphatic fluoroamino acids were reported by Lontz and Raasch in 1953 [102] and Walborsky and Baum in 1956 [45]. These included 5-fluoronorvaline **(34)**, 6-fluoronorleucine **(35)** and 2-amino-2-methyl-3,3,3-trifluoropropionic acid **(36)**. Many contributions by prominent researchers followed during the 1950s and 1960s, including studies by Heidelberger, Bergmann and Knunyants. These advances are described elsewhere [46]. In a remarkable exposition, Ojima summarized his signature research between 1982 and 1992 on the synthesis and medicinal applications of fluoro α- and β-amino acids [47]. A novel approach and more efficient reactions led to a range of alkyl fluoro analogs and 4,5,6,7-tetrafluorotryptophan **(37)**. **FIGURES 3 & 4 (38 & 39)** [48,49] illustrate the process. In some cases, optically active amino acids were obtained. Medical applications include a major discussion of new $CF_3$ analogs of the ACE inhibitor captopril. Subsequent studies, including enantiopure fluoroamino acids [50], fluoromethano amino acids [51], fluorinated amino acids in nerve systems [52] and molecular design of fluorine-containing peptide mimetics [53], have been presented.

## ■ Antibiotics

### Antibacterials

#### *Fluoroquinolones*

Nalidixic acid **(40)**, a synthetic antibacterial, introduced in the 1960s, is the prototype of the 4-quinolone class. Molecular modification led to the **fluoroquinolones** in the early 1980s and the greatest advances in antibacterials since the sulfa drugs of the 1930s. These compounds possess potent broad-spectrum activity against a wide range of Gram-positive and Gram-negative aerobes, with several active against anaerobic organisms. Over the past 25 years, a veritable cornucopia of new fluoroquinolones has been prepared (a totally synthetic enterprise), evaluated and marketed. The key structural feature of these molecules is the presence of a fluorine at the C-6 position and a nitrogen heterocyclic structure at C-7. Many are now in clinical use, with great success. Two examples are ciprofloxacin ('cipro') **(41)** and temafloxacin **(42)**. This area is one of the leading success stories in fluoropharmaceutical chemistry. An excellent review by Chu provides the reader with a strong b-ackground on this subject [54].

#### *Antiprotozoal drugs*

Malaria, one of the world's greatest scourges, is preventable and curable. Despite victorious battles during the past 70 years, the war has not yet been won. The disease, most prevalent in sub-Sahara Africa and South East Asia, claims over 1 million lives each year, substantially more than deaths from HIV–AIDS. The US antimalarial program, launched during World War II, dictated by the unavailability of quinine, produced several useful drugs for both the prevention and amelioration of existing infections. Of these, chloroquine emerged

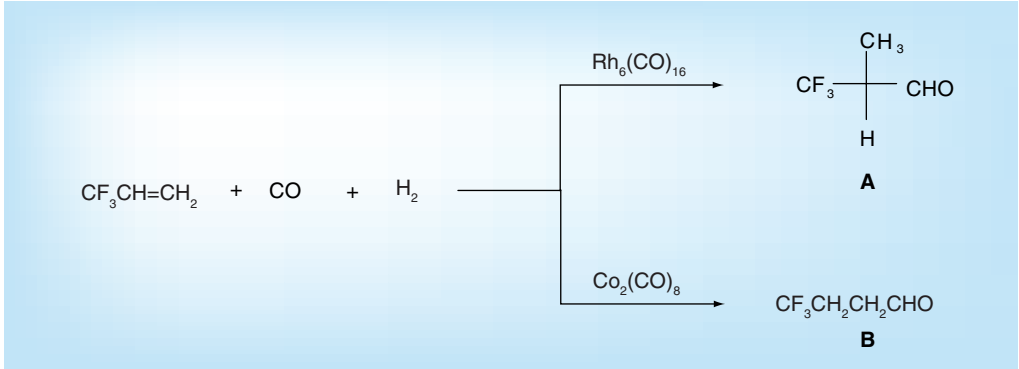


**Figure 3. Hydrocarbonylation of 3,3,3-trifluoropropene.**

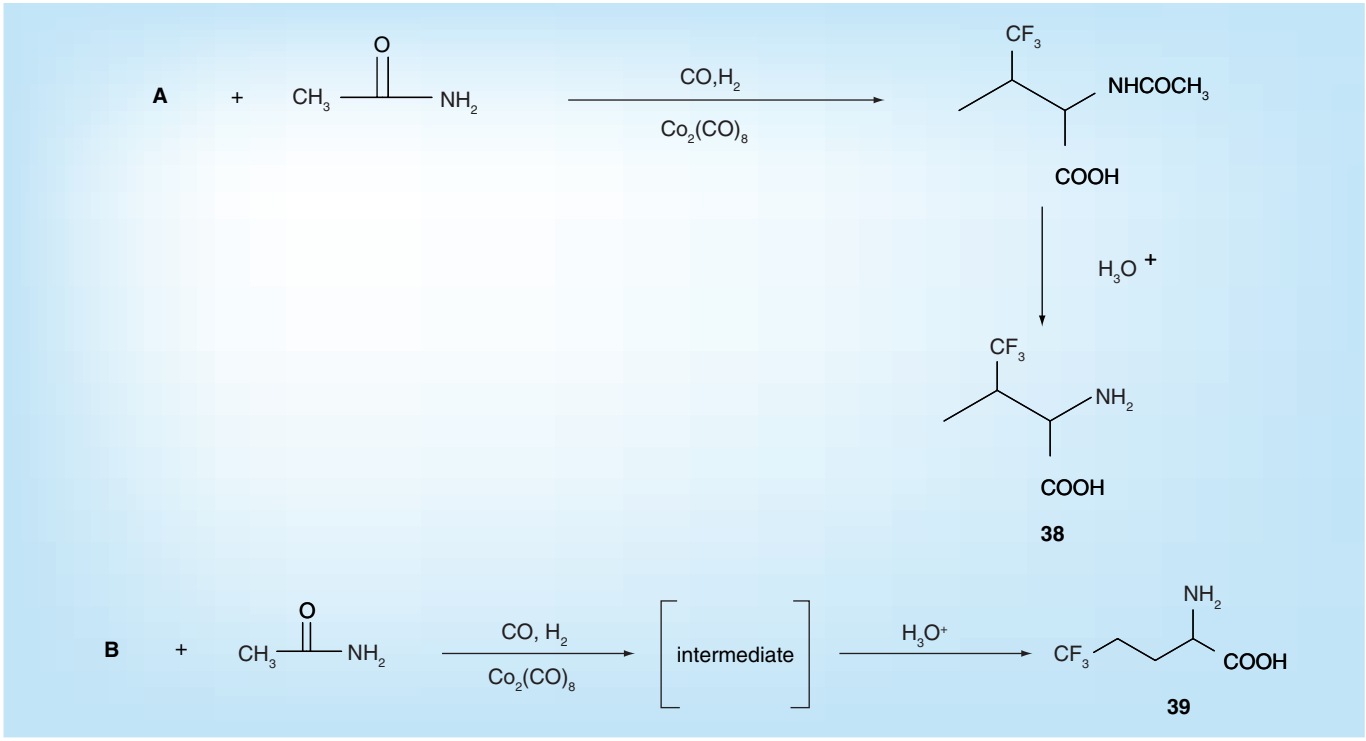


**Figure 4. Synthesis of trifluoro α-amino acids from precursor aldehydes.**

as the leading pharmaceutical. Mefloquine **(43)**, later introduced to counter chloroquine-resistant organisms, is used in combination with other agents, including chloroquine. However, drug resistance remains a recurring problem. More recently, artemisinin, isolated from a plant, and its derivatives have proven to be quite effective, but undergo rapid *in vivo* biotransformation, resulting in a limited duration of protection. New fluoro-substituted analogs are currently being designed, with the hope of increasing metabolic stability [55].

*Antifungal agents*

Fluorine-substituted compounds are important antifungal agents. Fluconazole (Diflucan®) **(44)**, introduced in 1988, was the first member of a new generation of stable oral drugs – the azoles. It is effective in the treatment of dermal and vaginal fungal infections. Subsequently, voriconazole **(45)**, licensed in 2002, exhibits significantly greater activity than fluconazole. A stable of new fluorine-bearing azole antifungals are now in clinical development.

## ■ Cholesterol biosynthesis inhibitors as hypolipidemic agents

Hypercholesterolemia (HC) involves disorders in lipid metabolism characterized by elevated levels of plasma total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). The latter is recognized as a significant factor in coronary heart disease. Only two sources of cholesterol enter the body pool – absorption from diet or endogenous synthesis. Dietary changes may be useful, but inhibition of the synthesis is more effective in lowering TC and LDL-C. The biosynthetic pathway to TC involves many enzymes. The rate-limiting step is regulated by the enzyme HMG-CoA reductase (HMGR). Many studies of HMGR inhibitors have resulted in several orally active agents, members of a class called statins, such as lovastatin sodium **(46)** and, especially, atorvastatin calcium (Lipitor®) **(47)**, introduced in 1997. The pivotal structural feature is the presence of a *p*-fluorophenyl group. Atorvastatin calcium, a type 2 statin, is a liver-selective reversible competitor of HMGR and leads to major reduction of LDL-C. Its superior properties are attributed to its greater intake and longer duration of action in the liver. Greater affinity to HMGR may also be important. X-ray analysis suggests that tighter binding is related to favorable stacking of the *p*-fluorophenyl group [56]. Atorvastatin calcium, also effective in lowering the level of triglycerides [57], achieved phenomenal market share and was the first pharmaceutical ever to attain over US$1 billion in sales in its first year.

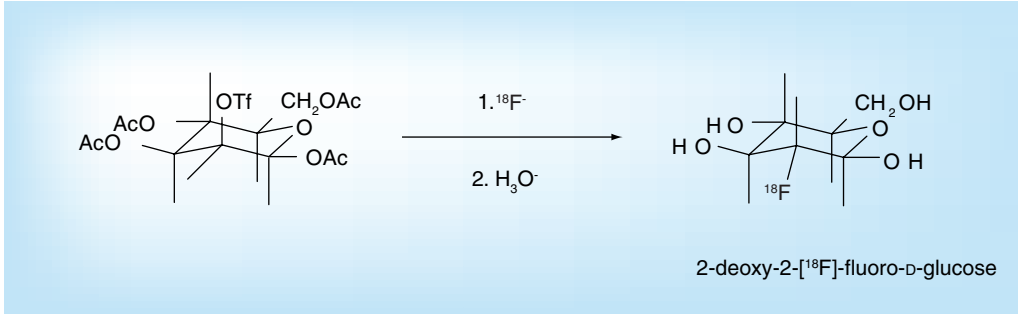


**Figure 5. Synthesis of 2-deoxy-2-[$^{18}$F]-fluoro-D-glucose.**

**Fluorine-18**

The radioisotope of fluorine, incorporated in selected compounds, serves as a leading vehicle in PET, a noninvasive medical imaging tool, especially in studies of the brain, heart and cancer

## ■ The sibling diagnostics: $^{18}$F (PET) & $^{19}$F NMR imaging

The fluorine family has brought noninvasive medical imaging to a new level. Fluorine-18 positron emission tomography (PET) continues to make great strides, not only in research, but as an important clinical diagnostic tool. More recently, fluorine-19 NMR is also providing useful applications in medical diagnosis.

### $^{18}$F (PET)

Fowler, a pioneer in this field, has presented exceptional critical reviews, from which much of the following précis is derived [58–62]. $^{18}$F, a positron-emitting isotope, with a half-life of 110 min, is produced in a cyclotron by two methods. The preferred route, $^{18}$O(p,n)$^{18}$F, using $H_2{}^{18}O$-enriched water, yields $^{18}$F as the fluoride ion. The other method is by bombarding neon gas with deuterons: $^{20}$Ne(d,α)$^{18}$F, using neon containing 0.1% $F_2$. The major challenges are to incorporate $^{18}$F at high-specific activity into biologically important compounds, where it can be used as a PET tracer in probing metabolic functions. During the past decade, there have been several brief updates by others [63–66]. It will suffice to provide here a brief overview. Two good examples are the syntheses of 2-deoxy-2-[$^{18}$F]-fluoro-D-glucose (FDG), the most widely used PET tracer **(Figure 5)** [58], and compounds prepared by nucleophilic aromatic substitution **(Figure 6)** [60,61].

Practical applications include CNS drugs for studies of the human brain, such as blood flow and metabolism, neurotransmitter properties, dopamine reuptake sites and serotonin receptors. $^{18}$F PET studies of the heart and in cancer research have been advancing rapidly, especially in the detection of malignant tumors, such as use of 5-[$^{18}$F]fluorouridine **(48)** and $^{18}$F-labeled steroid hormones.

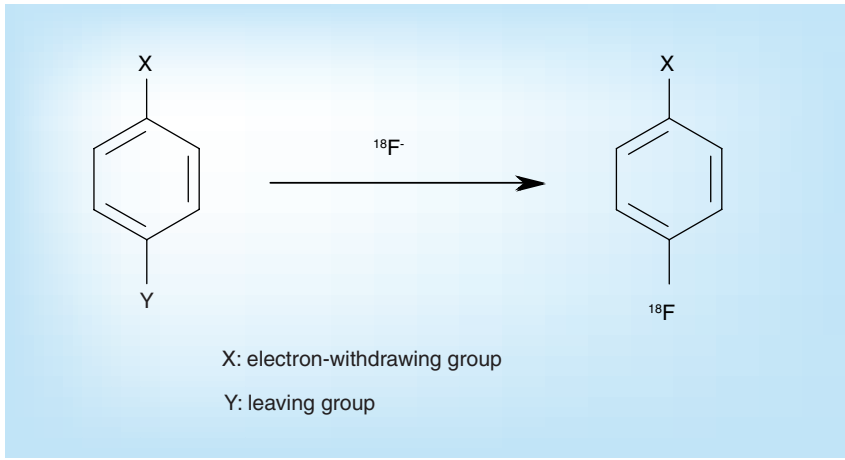


**Figure 6. Nucleophilic aromatic substitution with $^{18}$F fluoride.**

### $^{19}$F NMR

MRI using 100% isotopic natural abundance $^{19}$F is feasible because, with no endogenous fluoro compounds, background noise is very low [59]. For noninvasive monitoring of therapeutic agents, $^{19}$F NMR possesses excellent potential and opportunities once imaging technology becomes more sophisticated. An example of recent advances is the use of 4-fluoro-2-nitrophenyl-β-D-galactopyranoside (PFONPG) **(49)** and its isomer **(50)**, identified as novel prototype NMR-sensitive reporter molecules, for the treatment of prostate cancer [63]. A very recent review cites studies that demonstrate the usefulness of $^{19}$F NMR in tracing the catabolic fate of some fluorinated drugs, such as 5-FU, which eventually forms fluoroacetate and 2-fluoro-3-hydroxypropionic acid [67]. A fascinating discussion outlines the application of fluorinated aliphatic and aromatic amino acids as probes in binding and conformational studies.

## ■ Chiral fluoromedicinals

The worldwide market for single enantiomers of chiral drugs has developed rapidly since the early 1990s. A good, relatively nontechnical report on

this topic appeared in 1995 [68]. Fluoromedicinals have joined the fray and are making significant contributions. While resolution is still the leading technology, methods involving asymmetric synthesis, such as aldol and alkylation reactions, enantioselective fluorinating agents and enzymatically controlled processes using microorganisms, have gained increasing popularity. In some cases, one enantiomer is considerably more bioactive than its partner or the racemate. Several aspects of these advances are presented in a splendid book [69]. It will suffice to cite a few representative highlights, such as:

- Synthesis of enantiopure fluoro amino acids by asymmetric aldol reactions [70,71];
- Enantiopure fluorine-containing taxoids [72];
- Enantiomers of chiral fluorinated catecholamines and amino acids [73];
- Chiral fluorinated anesthetics [74];
- A broad overview of fluorine-containing compounds of biomedical interest [75].

## ■ A brief listing of second-generation fluorinating agents (1960–2000)

As previously mentioned, progress in fluoropharmaceutical research would have been severely hampered without the remarkable competitive race by fluorine chemists to identify and prepare novel reagents for selective introduction of fluorine, especially at bioactive sites. Hydrogen fluoride was not sufficiently specific and too dangerous to handle in quantity. As discussed in previous papers, such as by Hagmann [32], these reagents may be placed into one of four categories, excluding the less-used fluorine radical:

- Nucleophilic sources of fluorine;
- 'Electrophilic' fluorine;
- Nucleophilic $CF_3$;
- 'Electrophilic' perfluoroalkylating agents;
- The 'taming' of anhydrous HF: pyridinium poly(hydrogen fluoride) (30% $C_5H_5N$, 70% HF (w/w), Olah's reagent) [76,77];
- 'Naked' $F^-$:KF/Crown ether;
- $SF_4$ [78], a gas, and its easier-to-handle descendant diethylamino sulfur trifluoride ($Et_2NSF_3$; DAST) for conversion of > CHOH → > CHF and > C=O → > $CF_2$ and similar reagents, $Et_2NCF_2CHFCl$ (FAR, Yarovenko's reagent) and $Et_2NCF_2CHFCF_3$ (PPDA, Ishakawa's reagent);
- 'Electrophilic' fluorine;
- Perchloryl fluoride, $ClO_3F$;
- Xenon difluoride, $XeF_2$ [79];
- Reagents containing the OF group, such as $CF_3OF$ [80];

Electrophilic NF agents [81], $(CF_3SO_2)_2NF$ for fluorination of enolates [103] and aromatics [82] **(Figure 7)**. Another popular NF reagent is the doubly quaternized quinuclidinium salt (F-TEDA)$BF_4$ (Selectfluor®) **(51)**;

- Nucleophilic trifluoromethylation using the Ruppert–Prakash reagent [83,84] $Me_3SiCF_3$ plus tetrabutylammonium fluoride (TBAF) to generate a trifluoromethide ($CF_3^-$) equivalent. This reagent reacts with a host of substrates, as exemplified in **Figure 8**.

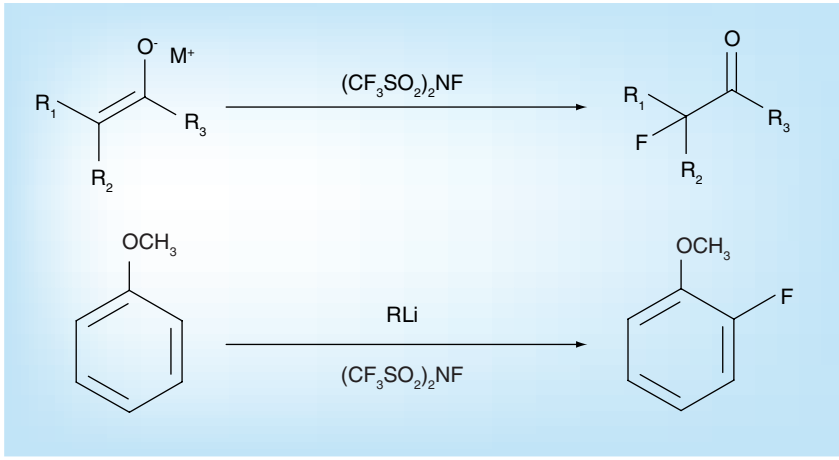


**Figure 7. Electrophilic fluorination reactions with NF reagents.**

**Fluoromedicinals**

The element fluorine imparts unique properties to organic compounds and, in many cases, significantly enhances the therapeutic activity of important medications

## ■ 'Electrophilic' perfluoroalkylating agents

These novel compounds generate $CF_3^+$ and other $Rf^+$ equivalents. Yagupolskii was the first to prepare such a precursor, but it has been the

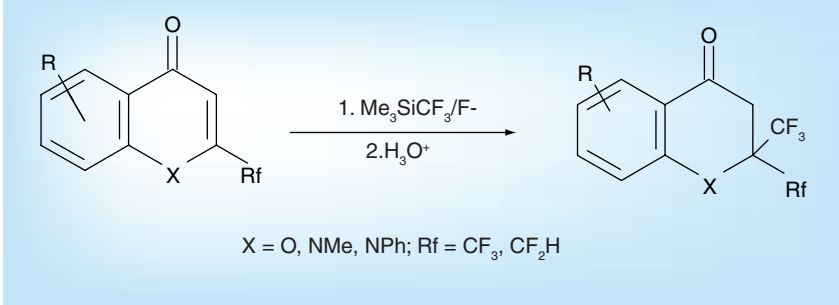


**Figure 8. Trifluoromethylation via a $CF_3^-$ equivalent.**

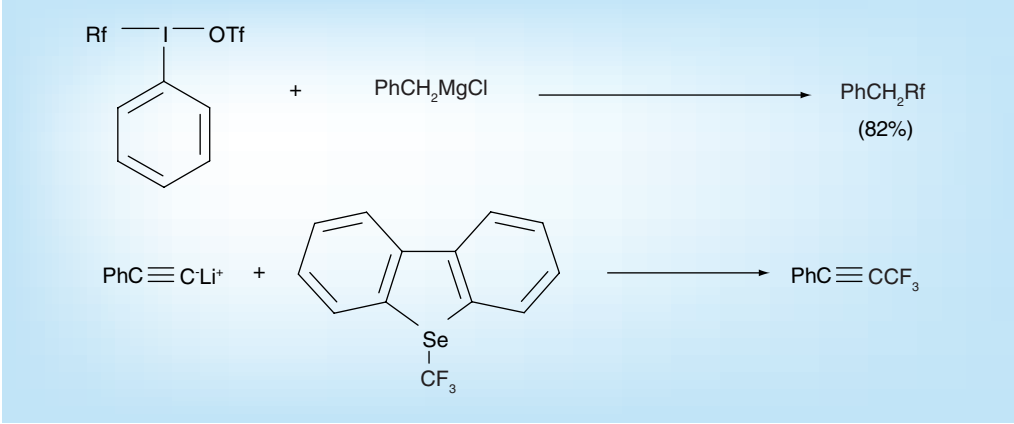


**Figure 9. Examples of electrophilic perfluoroalkylation of carbanions.**

magnificent work of Umemoto that has created the excitement about these reagents [85]. Umemoto has prepared two distinct classes of compounds – perfluoroalkyl phenyliodonium triflates (FITS reagents) and a host of 'power variable' S, Se, Te and O salts with an unusual structure. Some reactions of these reagents are shown in **Figure. 9**.

## Then & now

This 60-year retrospective has focused on the roles that fluorine has played in the growth and development of medicinal chemistry. What started as a trickle in the 1950s became a torrent between 1970 and 2000 and, since then, a tidal wave of publications. No fluoropharmaceuticals had been approved for clinical use in 1950. A total of 20 years later, the incorporation of fluorine had gained enormous momentum and many compounds were approved and brought to market. These advances led to a proliferation of studies, articles, reviews and books, which culminated in a cascade during the past decade. Since 2004, at least 25 reviews and special issues have appeared on many aspects of this subject.

It has been estimated that, by 2002, over one hundred fluoromedicinals had been brought to market or were in Phase II or III trials. Although there has been a major decline in the introduction of new drugs, including those with fluorine, during the past decade, it is of interest that, in 2007, of the 19 approved by the US FDA, nine contained fluorine. On a personal note, I (Robert Filler) recall a conversation in 1963 with the late Bill Sheppard of DuPont and his skepticism of my prediction that fluorine would play an important role in future advances in medicinal and biochemistry. I wish Bill could be here today.

## Future perspective

Where to begin? So much has happened in recent years. Several hot areas will continue to be pursued. These include:

- A greater emphasis on chiral fluoro compounds;
- Further advances in $^{18}F$ (PET) and especially $^{19}F$ NMR as diagnostic imaging tools;
- Maintaining a high level of activity on fluoronucleosides;
- Intense research to identify improved anticancer agents;
- Active pursuit of better antimalarials;
- Increased efforts to address other diseases, such as diabetes and cardiovascular disease;
- A new area just being launched – the degradation of fluorinated materials by bacterial strains [86].

## Conclusion

In selecting the topics to be covered in this retrospective, it was inevitable that significant studies in some key research areas would not be cited. The authors regret these omissions, for they do not diminish their importance. Finally, kudos to all those, young and old, cited or not, whose creative ideas and efforts have contributed to the broad tapestry that fluorine has woven.

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*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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## Executive summary

- This article describes the remarkable transformation of fluorine, that brash, undisciplined element, into a mature and highly valued participant in the growth and development of medicinal chemistry during the past 60 years.
- The presence of fluorine in selected molecules has contributed to the great advances in anesthesia.
- Fluorinated steroids have changed the therapeutics toward inflammatory diseases.
- Incorporation of fluorine has dramatically advanced the treatment of cancers and viral diseases and further research is essential.
- Fluorine has helped to revolutionize the therapeutic management of mental illness by providing key agents to treat psychoses, anxiety and depression. More work needs to be done in this area.
- The antibacterial fluoroquinolones have provided the greatest advances since the sulfa drugs of the 1930s. Research should continue in this field.
- A fluorine-containing antimalarial has aided in the battle against this pervasive illness that kills more than 1 million people each year. However, increasing drug resistance now requires a continuing effort to meet the enormous challenges. Perhaps fluorine compounds can play an important role in the future.
- Fluoro statins are important agents to control cholesterol (total and low-density lipoprotein cholesterol) at healthy levels.
- Fluorine has played a pivotal role a diagnostic tool in noninvasive medical imaging. Further advances should be anticipated.
- Novel fluorinating agents have helped to accelerate the advances in medicinal chemistry.

## Bibliography

1 Banks RE, Tatlow JC. In: *Fluorine: The First Hundred Years (1886–1986)*. Banks RE, Sharp DWA, Tatlow JC (Eds). Elsevier Science Publishing Co., Inc., NY, USA, 93–97 (1986).

2 Midgley T, Henne AL. Organic fluorides as refrigerants. *Ind. Eng. Chem*. 22, 542 (1930).

3 Banks RE, Tatlow JC. In: *Fluorine: The First Hundred Years (1886–1986)*. Banks RE, Sharp DWA, Tatlow JC (Eds). Elsevier Science Publishing Co., Inc., NY, USA, 101–103 (1986).

4 Schmitt R, von Gehren H. *J. Prakt. Chem*. 1, 394 (1870).

5 Balz G, Schiemann G. Über aromatische fluorverbindungen, I: ein neues verfahren zu ihrer darstellung. *Chem. Ber*. 1186 (1927).

6 Swarts F. Fluorine derivatives of toluene. *Bull. Acad. Roy. Belg*. 35, 375 (1898).

7 McBee ET. Fluorine chemistry. *Ind. Eng. Chem*. 39, 236–237__ (1947).

8 Peters RA. Croonian lecture: lethal synthesis. *Proc. Roy. Soc. Series B* 139, 143 (1952).

9 Goldman P. The carbon-fluorine bond in compounds of biological interest. *Science* 164, 1123–1130 (1969).

10 Smith F. *Carbon-Fluorine Compounds. Chemistry, Biochemistry and Biological Activities*. A Ciba Foundation Symposium, Elsevier, London, UK (1972).

11 *Biochemistry Involving Carbon-Fluorine Bonds*. ACS Symposium Series 28, Filler R (Ed.) 1976.

12 *Biochemistry of the Elemental Halogens and Inorganic Halides*. Kirk KL, Plenum Press, NY, USA (1991).

13 *Biochemistry of Halogenated Organic Compounds*. Kirk KL, Plenum Press, NY, USA (1991).

14 Kirk KL. Fluorine in biomedicinal chemistry. *J. Fluorine Chem.* 129 (9), 725–887 (2008).

15 *Molecular Modification in Drug Design: Advances in Chemistry Series 45*, American Chemical Society (1964).

16 Simons JH. Production of fluorocarbons. *J. Electrochem. Soc.*, 95, 47 (1949).

17 Yale HL. The trifluoromethyl group in medicinal chemistry. *J. Med. Pharm. Chem.* 1(2), 121–133 (1959).

18 Robbins BH. Preliminary studies of the anesthetic activity of fluorinated hydrocarbons. *J. Pharmacol. Exptl Therapeutics* 86, 197–204 (1946).

19 McBee ET, Filler R. The reaction of 1,2-dichloro-1,1,3,3,3-pentafluoropropane with ethanolic alkali. *J. Org. Chem.* 21(3), 370–371 (1956).

20 Suckling CW. Some chemical and physical factors in the development of fluothane. *Brit. J. Anesthesia* 29, 466 (1957).

21 Raventós J. The action of fluothane; a new volatile anaesthetic. *Brit. J. Pharmacol.* 11, 394 –410(1956).

22 Halpern DF. Recent developments in fluorine substituted volatile anesthetics. In: *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*. Filler R, Kobayashi Y, Yagupolskii LM (Eds). Elsevier, Amsterdam, The Netherlands, 101–133 (1993).

23 Ferstandig LL. Fluorinated anesthetics. *Chemistry of Organic Fluorine Compounds II. A Critical Review*. Hudlicky M, Pavlath AE (Eds). American Chemical Society Monograph 187, American Chemical Society, Washington DC, USA, 1133–1137 (1995).

24 Fried J, Sabo EF. Synthesis of 17α -hydroxycorticosterone and its 9α-halo derivatives from 11-epi-17α – hydroxycorticosterone. *J. Am. Chem. Soc*. 75, 2273–2274 (1953).

25 Fried J, Sabo EF. 9α-fluoro derivatives of cortisone and hydrocortisone. *J. Am. Chem. Soc*. 76, 1455–1456 (1954).

26 Wettstein A. Chemistry of fluorosteroids and their hormonal properties. *Reference* 10, 281–301 (1972).

27 Elliott AJ. The role of fluorine in the chemistry of central nervous system agents. *Reference* 22, 209–239 (1993).

28 Duschinsky R, Pleven E, Heidelberger C. The synthesis of 5-fluoropyrimidines. *J. Am. Chem. Soc.* 79, 4559 (1957).

29 Heidelberger C, Chaudhuri NK, Danneberg P *et al*. Fluorinated pyrimidines, a new class of tumour-inhibitory compounds. *Nature* 179, 663–666 (1957).

30 Filler R. Fluorinated compounds of medicinal interest. *Chem. Tech.* 4, 752–757 (1974).

31 Edwards PN. Uses of fluorine in chemotherapy. In: *Organofluorine Chemistry, Principles and Commercial Applications*. Banks RE, Smart BE, Tatlow JC (Eds). Plenum Press, NY, USA, 501–541 (1994).

32 Hagmann WK. The many roles for fluorine in medicinal chemistry. *J. Med. Chem.* 51(15), 4359–4369 (2008).

33 Bergstrom DE, Swartling DJ. Fluorine substituted analogs of nucleic acid components. In: *Fluorine-Containing Molecules, Structure, Reactivity, Synthesis, and Applications*. Liebman JF, Greenberg A, Dolbier WR Jr (Eds). VCH Publishers, Inc. NY, USA, 259–308 (1988).

34 Hertel LW, Ternansky RJ. Fluorine-containing antiviral and anticancer compounds. *Reference* 22, 23–71 (1993).

35 Meng W-D, Qing F-L. fluorinated nucleosides as antiviral and anti-tumor agents. *Curr. Top. Med. Chem.* 6, 1499–1528 (2006).

36 Isanbor C, O'Hagan D. Fluorine in medicinal chemistry: a review of anticancer agents. *J. Fluorine Chem.* 127, 303–319 (2006).

37 Grever MR *et al.* Long-term results of the CHOP regimen in stage C chronic lymphocytic leukaemia. *Nouv. Rev. Fr. Hematol*. 30, 457 (1988).

38 Montgomery JA. Has the well gone dry? The first Cain memorial award lecture. *Cancer Res.* 42, 3911 (1982).

39 Grindey GB, Boder GB, Hertel LW *et al.* Antitumor activity of 2′,2′-difluorodeoxycytidine (LY188011). Presented at: *American Assn. Cancer. Res.* 27, Los Angeles, CA, USA, 7–10 May 1986.

40 Purser S, Moore PR, Swallow S, Gouverneur V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* 37, 320–330 (2008).

41 Iseki K, Kobayashi Y. Fluorinated vitamin D3 analog with *in vivo* anticancer activity. In: *Biomedical Frontiers of Fluorine Chemistry*, Ojima I, McCarthy JR, Welch JT (Eds.). ACS Symposium Series 639, 214–227 (1996).

42 Ojima I *et al.* Synthesis, biological activity and conformational analysis of fluorine-containing taxoids. *Reference* 42, 228–243 (1996).

43 Ojima I, Kuduk SD, Slater JC *et al*. Use of fluorine in medicinal chemistry and chemical biology of bioactive compounds – a case study on fluorinated taxane anticancer agents. *ChemBioChem*, Wiley–VCH Verlag, Weinheim, Germany, 5, 628–635 (2004).

44 Kuznetsova L, Pepe A, Ungureanu IM, Pera P, Bernacki RJ, Ojima I. Synthesis and structure–activity relationships of novel 3′-difluoromethyl and 3′-trifluoromethyl-taxoids. *J. Fluorine Chem.* 129, 817–828 (2008).

45 Walborsky HM, Baum ME. Chemical effects of the trifluoromethyl group: III. Synthesis of 2-amino-4,4,4-trifluorobutyric acid. *J. Org. Chem.* 21, 538 (1956).

46 Loncrini DF, Filler R. *Aliphatic Fluoro Amino Acids. Advances in Fluorine Chemistry*. Tatlow JC, Peacock RD, Hyman HH, Stacey M (Eds). Butterworths, London, UK, 6, 43–67 (1970).

47 Ojima I. New developments in the synthesis and medicinal applications of fluoroamino acids and peptides. *Reference* 22, 241–273 (1993).

48 Ojima I, Kato K, Okabe M, Fuchikami T. Hydroformylation of fluoro olefins, $^{R}_{F}CH{:}CH_2$, catalyzed by group VIII transition-metal catalysts. Crucial factors for extremely high regioselectivity. *J. Am. Chem. Soc.* 109, 7714 (1987).

49 Ojima I, Hirai K, Fujita M, Fuchikami T. New synthetic route to *N*-acyl-α-amino acids via amidocarbonylation by means of homogeneous binary catalyst systems. *J. Organometal. Chem.* 279, 203 (1985).

50 Soloshonok VA. Practical synthesis of enantiopure fluoramino acids of biological interest by asymmetric aldol reactions. *Reference* 42, 26–41 (1996).

51 Taguchi T, Shibuya A, Morikawa T. Asymmetric synthesis of functionalized fluorinated cyclopropanes and its application to fluoromethano amino acids. *Reference* 42, 73–82 (1996).

52 Kirk KL, Nie J-Y. Fluorinated amino acids in nerve systems. *Reference* 42, 312–327 (1996).

53 Cieplak P, Kollman PA, Radomski JP. Molecular design of fluorine-containing peptide mimetics. *Reference* 42, 143–156 (1996).

54 Chu DTW. Fluoroquinolone carboxylic acids as antibacterial drugs. *Reference* 22, 165–207 (1993).

55 Bonnet-Delpon D. Artemisinin, a target for fluorine chemists: challenging molecule, efficient antimalarial drug. Presented at: *Abstracts, Division of Medicinal Chemistry, ACS National Meeting*. Boston, MA, USA, 19–23 August 2007.

56 István ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* 292, 1160–1164 (2001).

57 *Annual Reports in Medicinal Chemistry, 33*. Bristol JA (Ed.). 328 (1998).

58 Fowler JS. The synthesis and application of F-18 compounds in positron emission tomography. *Reference* 22, 309–338 (1993).

59 Hamacher K, Coenen HH, Stocklin G. Efficient stereospecific synthesis of no-carrier-added 2-[$^{18}$F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *J. Nucl. Med.* 27, 235 (1986).

60 Arnett CD, Shiue C-Y, Wolf AP. Improved delineation of human dopamine receptors using [18F]-*N*-methylspiroperidol and PET. *J. Neurochem.* 44, 835 (1985).

61 Shiue C-Y, Fowler JS, Wolf AP *et al.* No-carrier-added fluorine-18-labeled *N*-methylspiroperidol: synthesis and biodistribution in mice. *J. Nucl. Med.* 27, 226 (1986).

62 Ding Y-S, Fowler JS. $^{18}$F labeled tracers for positron emission studies in the neurosciences. *Reference* 42, 328–343 (1996).

63 Isanbor CI, O'Hagan D. Fluorine in medicinal chemistry: a review of anti-cancer agents. *Reference* 37, 315–316 (2006).

64 Sun S, Adejare A. Fluorinated molecules as drugs and imaging agents in the CNS. *Curr. Top. Med. Chem.* 6, 1457–1464 (2006).

65 Shah P, Westwell AD. The role of fluorine in medicinal chemistry. *J. Enzyme Inhib. Med. Chem.* 22(5), 536–538 (2007).

66 Purser S, Moore PR, Swallow S *et al.* Fluorine in medicinal chemistry. *Chem. Soc. Rev.* 37, 328–329 (2008).

67 Cobb SL, Murphy CD. $^{19}$F NMR applications in chemical biology. *J. Fluorine Chem.* 130, 132–143 (2009).

68 Stinson SC. Chiral drugs. *Chem. Eng. News*, 44, October 9, 1995.

69 Ramachandran PV. *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions. ACS Symposium Series 746.* American Chemical Society (2000).

70 Soloshonok VA. Biomimetic reductive amination of fluoro aldehydes and ketones via [1,3]-proton shift reaction. *Reference* 71, 26–41 (1996).

71 Soloshonok VA. Biominetic, redundancy agent – free reductions amination of fluorocarbonyl compounds: practical asymmetric synthesis of enantiopure fluoroamines and amino acids. *Reference* 71, 74–83 (2000).

72 Ojima I, Inoue T, Chakravarty S. Synthesis of enantiopure fluorine-containing taxoids and their use as anticancer agents as well as probes for biomedical problems. *Reference* 71, 158–181 (2000).

73 Kirk KL, Herbert B, Lu SF, Jayachandran B *et al.* Chemical and biochemical approaches to the enantiomers of chiral fluorinated catecholamines and amino acids. *Reference* 71, 194–209 (2000).

74 Ramig K. Chiral fluorinated anesthetics. *Reference* 71, 282–292 (2000).

75 Filler R. Fluorine-containing chiral compounds of biomedical interest. *Reference* 71, 1–20 (2000).

76 Olah GA, Nojima M, Kerekes I. Synthetic methods and reactions III. Halofluorination of alkenes in poly-hydrogen fluoride/pyridine solution. *Synthesis* 12, 780–783 (1973).

77 Olah GA, Shih JG, Prakash GKS in. *Reference* 1, 377–380 (1986).

78 Boswell GA Jr, Ripka WC, Scribner RM, Tullock CW. Fluorination by sulfur tetrafluoride. *Organic Reactions* 21, 1–124 (1974).

79 Filler R. Reactions of organic compounds with xenon fluorides. *Israel J. Chem.* 17, 71–79 (1978).

80 Rozen S. Selective fluorinations by reagents containing the OF group. *Chem. Rev.* 96, 1717–1736 (1996).

81 Lal GS, Pez GP, Syvret RG. Electrophilic NF fluorinating agents. *Chem. Rev.* 96, 1737–1755 (1996).

82 Resnati G, DesMarteau DD. *N*-fluorobis[(trifluoromethyl)sulfonyl]imide: an efficient reagent for the α-fluorination of functionalized carbonyl compounds. *J. Org. Chem.* 56, 4925–4929 (1991).

83 Prakash GKS, Krishnamurti R, Olah GA. Synthetic methods and reactions. 141. Fluoride-induced trifluoromethylation of carbonyl compounds with trifluoromethyltrimethylsilane (TMS-$CF_3$). A trifluoromethide equivalent. *J. Am. Chem. Soc.* 111, 393–395 (1989).

84 Ma J-A, Cahard D. Strategies for nucleophilic, electrophilic and radical trifluoromethylations. *J. Fluorine Chem.* 128, 975–996 (2007).

85 Umemoto T. Electrophilic perfluoroalkylating agents. *Chem. Rev.* 96, 1757–1777 (1996).

86 Iwai N, Sakái R, Tsuchida S, Kitazume M, Kitazume T. Screening of fluorinated materials degrading microbes. *J. Fluorine Chem.* 130, 434–437 (2009).

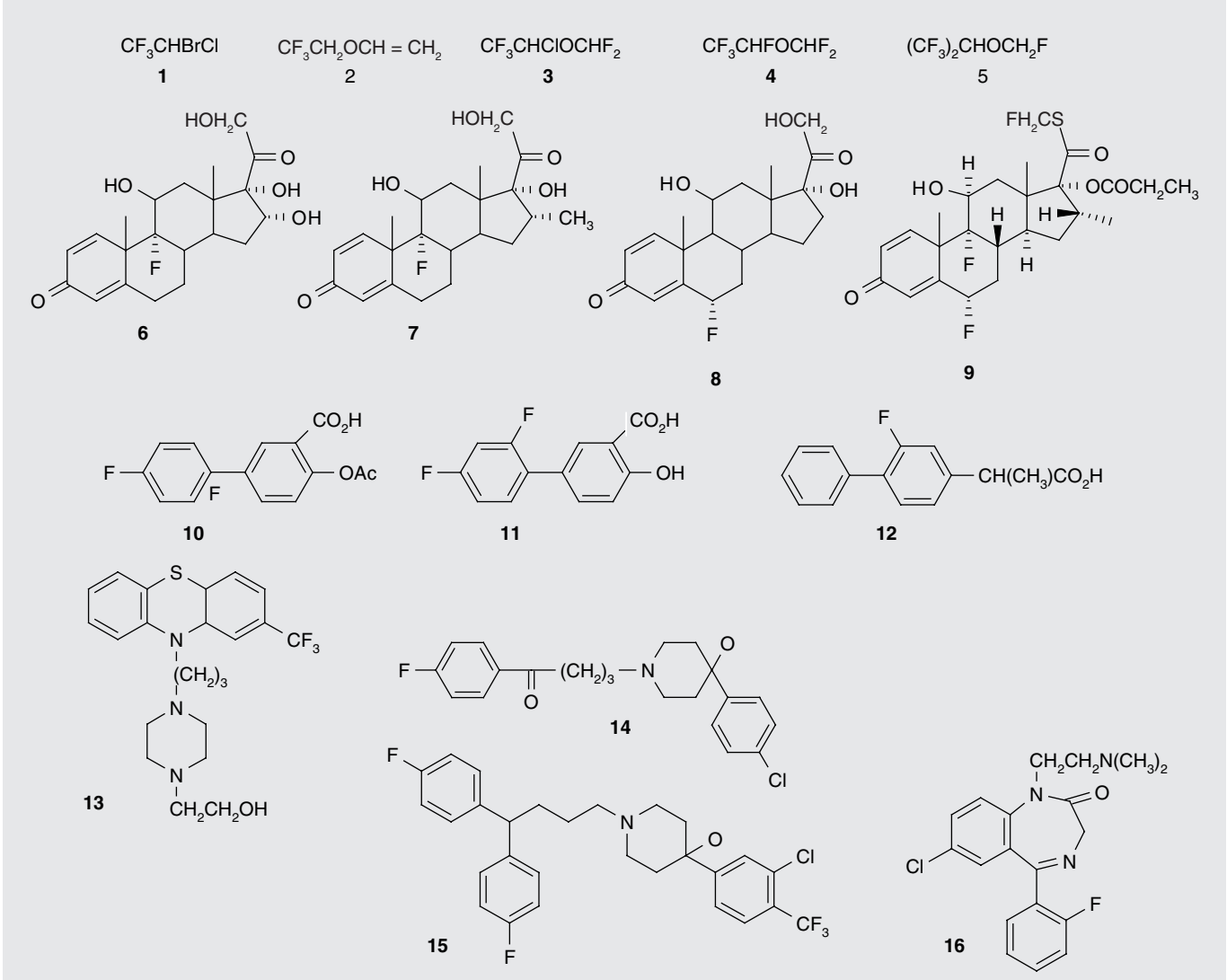

## ■ Patents

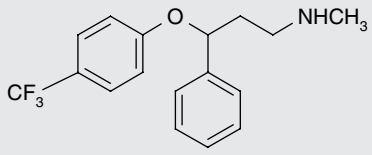

101 Schuman PD, Tarrant P, Warner DA, Westmoreland G. Process for fluorinating uracil and derivatives thereof. *US Patent* 3954758 (1976).

102 Lontz JF, Raasch MS. α-amino acids containing α-fluorinated-alkyl or cycloalkyl groups. *US Patent 2,662,915* (1953).

103 Lal GS. Process for selectively ortho-fluorinating substituted aromatic compounds. *US Patent* 5,233,074 (1993).


## Appendix 1.





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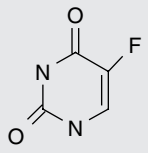

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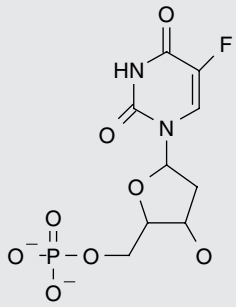

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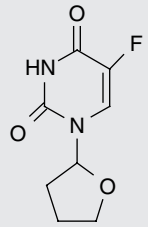

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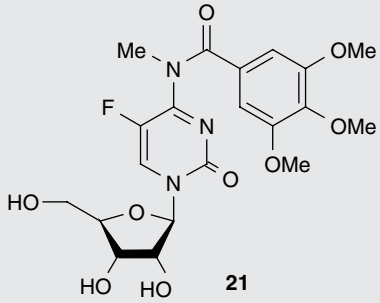

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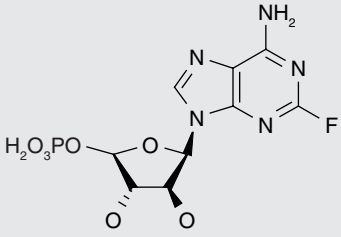

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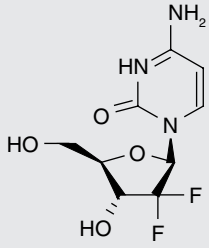

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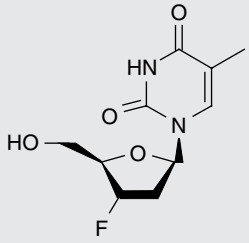

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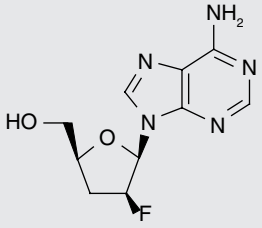

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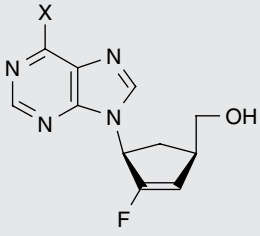

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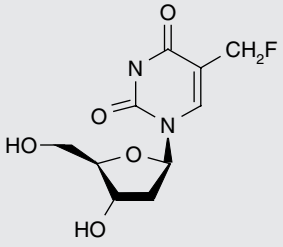

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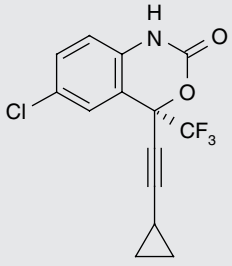

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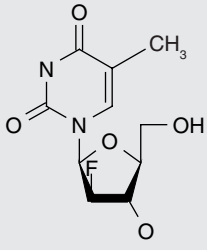

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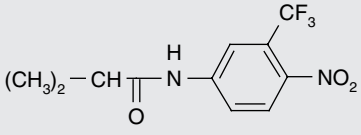

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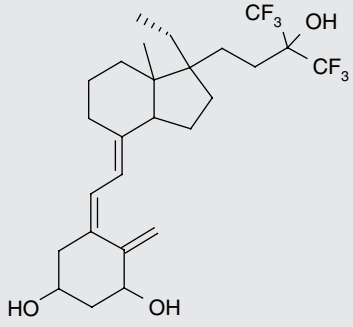

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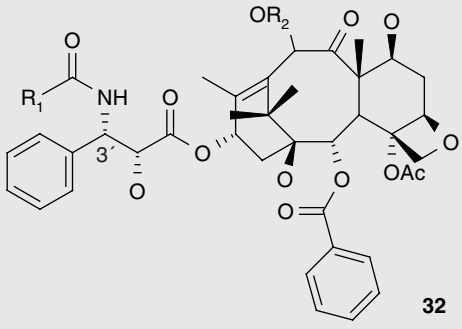
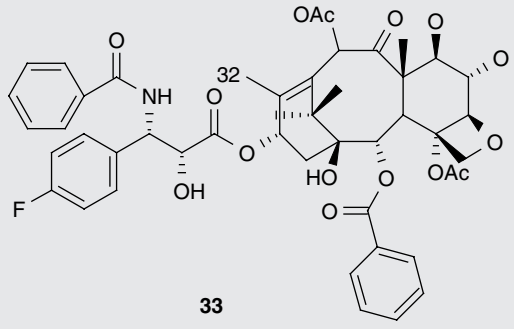


Paclitaxel: $R_1$ = Ph, R2 = Ac
Docetaxel: $R_2$ = tBuO, R2 = H

32



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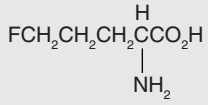

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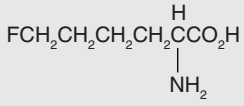

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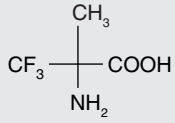

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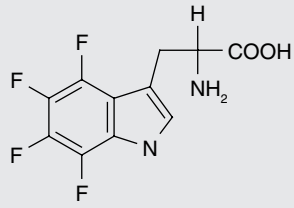

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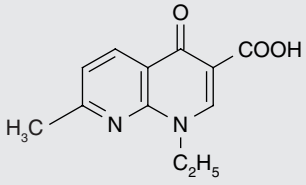

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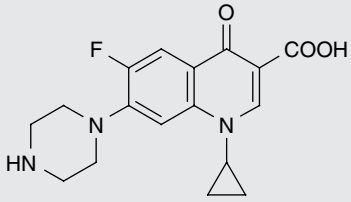

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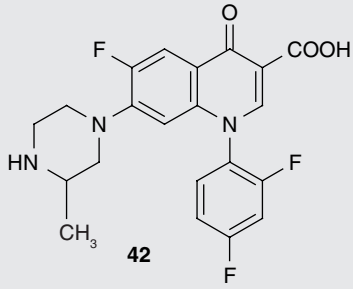

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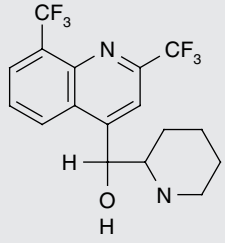

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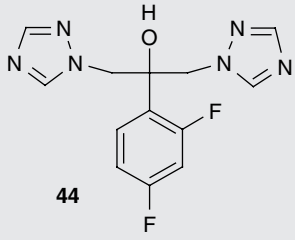

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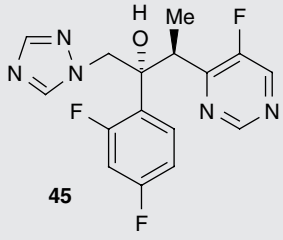

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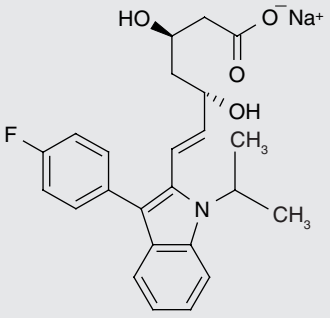

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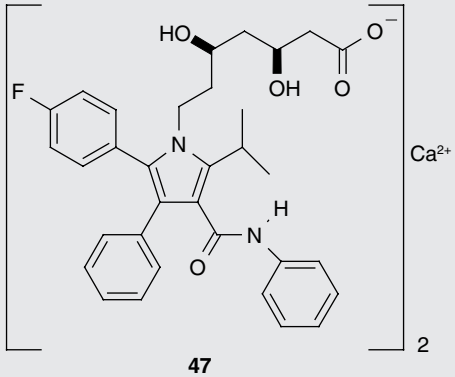

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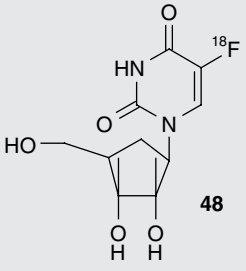

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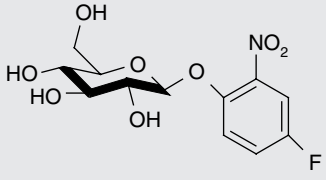

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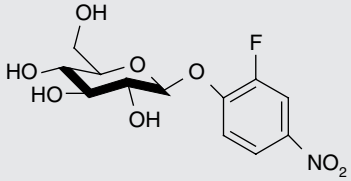

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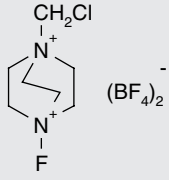

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