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Fluorine Function in Medicinal Chemistry

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Abstract
The small, electronegative fluorine atom may have a huge influence on medicinal chemistry. Fluorine preferentially improves metabolic stability and membrane permeability in medicinal or diagnostic small molecule candidates. Many fluorinated medicine candidates have improved target protein binding affinity. Using a few carefully chosen examples from a wide range of therapeutic and diagnostic contexts, this brief introduction unifies these many fluorine applications in medicinal chemistry. Fluorine is often used in medicinal prospects, indicating a bright future in medication research and development. Installing fluorine rationally to optimize molecular properties will be a major issue.

Keywords: Medicinal chemistry; Metabolic stability; Antibiotics; Pharmaceutical

Introduction

With a van der Waals radius of about 1.47 A, fluorine is the most electronegative and tiniest element in the Periodic Table (3.98 Pauling scale).Hence, fluorine has particular effects when coupled with carbon in small organic molecules. Fluorine's role in medicinal chemistry suggests that adding even one fluorine atom or trifluoromethyl group to an organic compound at a crucial location on a biologically active molecule may have substantial pharmacological effects. In the 1970s, fluorinated compounds were uncommon because traditional medical chemistry relied on natural chemicals or their derivatives that contained few fluorine molecules. The early work of Fried on 9a-fluorohydrocortisone acetate demonstrated the beneficial effects of fluorine on physiologically active compounds [1]. Current pharmaceutical research synthesizes several fluorinated compounds for disease therapy. Recent reviews of fluorine-containing anti-cancer, antidepressant, and anti-inflammatory, an aesthetic, and central nervous system drugs have been published [2–6]. There has been research on the possibility of using fluorine substitution to improve a drug's biological activity and chemical or metabolic stability. For synthesizing compounds using fluorine, its small size (van der Waals radius of 1.47 A is equivalent to hydrogen's 1.20 A) and powerful electron withdrawing capability are essential. Lipophilicity of fluorine is higher than that of hydrogen. A C-F bond is far more stable than a C-H one. Despite its bigger size compared to hydrogen, fluorine is an effective hydrogen mimic and should not interfere with the compound's ability to attach to enzymes or receptors [7].Fluorine's high electronegativity also modifies the compound's physical properties. This may modify the molecule's biological behavior. Current fluorine atom introduction methods concentrate on:

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Metabolic Stability

As the C-F bond is stronger than the C-H bond, substituting fluorine at the metabolic attack site may slow oxidative metabolism. Bioavailability is influenced by metabolic stability. Drug metabolism may be affected by inductive/resonance, conformational, and electrostatic effects regardless of where substitution occurs [7].

Physicochemical changes

Fluorine, the most electronegative element, may shift the electron distribution in a molecule, which can affect the pKa, dipole moment, and chemical reactivity and stability of surrounding functional groups. Fluorine lowers a compound's basicity, making it more membrane-permeable and bioavailable.

Enhanced binding

Fluorine substitution to boost target protein binding affinity is rising. Fluorine's interaction with the protein or the compound's other groups' capacity to change protein-interacting group polarity may cause this.

Metabolic stability

Drug research must overcome metabolic instability. Cytochrome P450 may oxidase lipophilic compounds. Make the molecule more polar or add a fluorine atom to affect drug metabolism speed, mechanism, or extent. As long as fluorine substitution doesn't interfere with target protein interaction, it may be done at the metabolically labile location or close or distant from it. Based on (a) whether the metabolic assault is electrophilic or nucleophile and (b) if the inductive or resonance effects of fluorine predominate, substitution at neighboring sites may either speed up or slow down biotransformation.

Antitumor fluorinated benzothiazoles

Two-(4-aminophenyl)-benzothiazoles, a class of fluorinated anticancer benzothiazoles, feature a simple structure with remarkable antitumor characteristics. As absorption and biotransformation have been documented in sensitive cell lines like breast MCF-7 and MDA 468 cells but not in insensitive cell lines like prostate PC 3 cells [8], metabolism is expected to play a substantial role in the mechanism of action of these medications. Cell death occurs at low nanomolar concentrations and proliferative response at low micromolar concentrations, known as the second growth phase [9]. However, the first lead chemical (DF 203) displayed a biphasic dose-response relationship in sensitive breast cancer lines. This might be due to the inactivation of cytochrome P4501A1 in sensitive cell types by metabolic metabolites [10]. In sensitive cell lines, 6OH 203 was the predominant metabolite [11]. The biphasic dose-response relationship of DF 230 was lost during the process of synthesizing multiple fluorine replacements to avoid deactivation metabolism. There was no biphasic dose-response relationship seen for the growth-inhibiting effects of 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5F 203) on MCF-7 cells [12, 13]. Since 5-fluorination inhibits 6-position oxidative metabolism, 5F 203 was metabolically stable and produced no exportable metabolites in sensitive MCF-7 cells. The pro drug form of L-lysine, 5F 203, is now in phase 1 clinical trials [14]. The preclinical lead chemical 5, 40-diamino-6, 8, 30-trifluoroflavone (Figure 1) was found by using a rational fluorination method [15]. Another anticancer benzothiazoles with structural similarities to 5F 203, 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (GW 610, Figure 1), has been shown to have a potent and selective

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antitumor profile [16]. Fluorine's fundamental role in this series' cellular anticancer effect is fascinating.

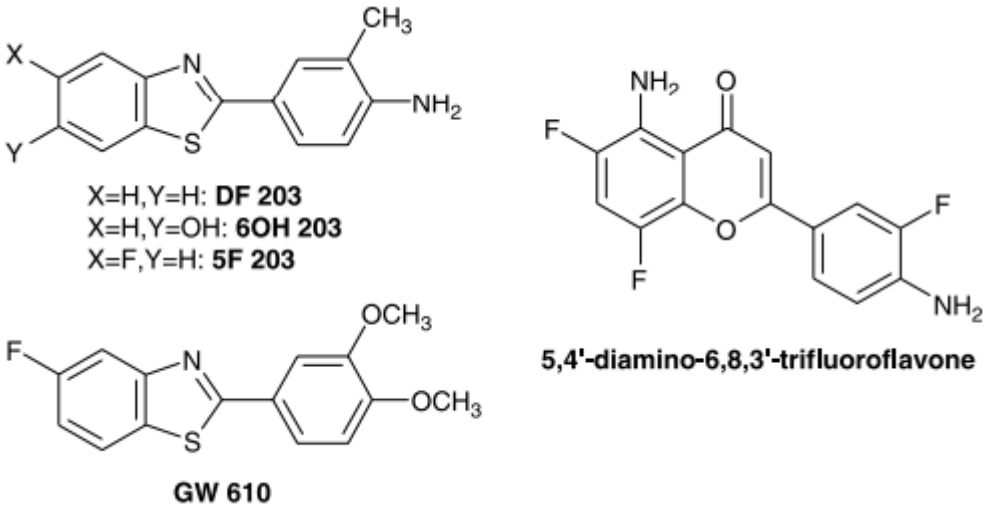

Fig:1 The composition of anticancer agents to name a few, we have 2-(4-amino-3-methylphenyl) benzothiazole (DF 203), 6-hydroxy-6OH 203, 5,40-diamino-6,8,30-trifluoroflavone, 5-fluorobenzothiazole (5F203), and 2-(4-amino-3-methylphenyl) benzothiazole (5F203) (3,4-dimethoxyphenyl) -5-fluorobenzothiazole (GW 610) (GW 610)

Fluorine removal for celecoxib

The COX-2 inhibitor celecoxib proves fluorine's role in metabolic stability. Penning et al. [16] synthesized 1,5-diarylpyrazole compounds and performed SAR studies to discover high-powered COX-2 selective inhibitors. As a result of the unsatisfactory half-life of the original fluorinated structural lead, in vivo research into pyrazole analogues with metabolic sites has been conducted. The half-life in rats was reduced from 220 hours to 3.5 hours when the fluorine on the benzene ring was replaced with a metabolically labile methyl group to create celecoxib. The trifluoromethyl and difluoromethyl groups showed the maximum efficacy and selectivity [17], and the fluorine atom is crucial because the 3-position of the pyrazole is malleable.

Replacement of fluorine lengthens the biological half-life

Half-lives of prostaglandins in living organisms are just approximately 5 minutes. The platelet-clumping thromboxane A2 (TxA2) has a unique oxetane acetal structure that hydrolyzes at pH 7.4 and has a half-life of 30 seconds. Hydrolysis is slowed by fluorine in the oxetane ring; 7,7-difluoro-TxA2 hydrolyzes at a rate 108 times slower than TxA2 [18].Prostacyclin's acid-labile enol-ether group shortens its half-life. The addition of a fluorine atom boosts the molecule's stability against acid hydrolysis by inductively decreasing electron density on the enol-ether group. It is clear from Figure 4 that the 10,10-difluoro-13-dehydro-prostacyclin produced by Fried et al. retains the same qualitative and quantitative biological potency as natural prostacyclin. This analogue mimics PGI2 except for its 150-fold longer half-life and inactivation by 15-hydroxyprostaglandin dehydrogenase.

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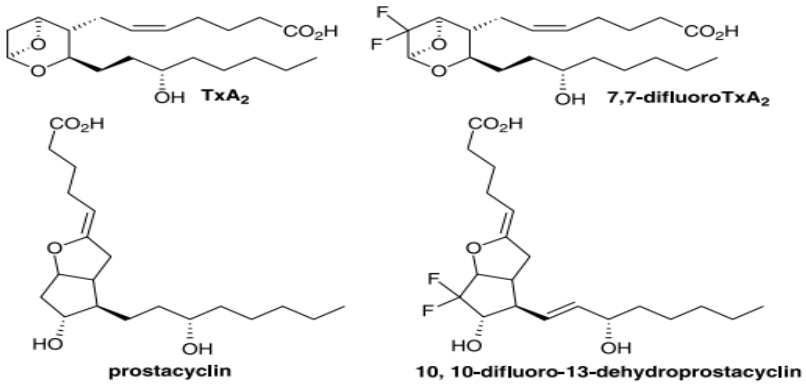

Fig:2 shows how fluorine substitution may prolong biological half-lives in thromboxane A2, which induces platelets to aggregate, and its 7,7-difluoro derivative, as well as 10(10)-difluoro-13-dehydro-prostacyclin and endogenous prostacyclin.

Fluorine substitution's physicochemical effects

The most electronegative element, fluorine, may shift the pH of nearby functional groups towards more acidic or basic conditions. A highly basic group may be required for binding, yet this may reduce the drug's bioavailability because of its reduced membrane permeability. High lipophilicity is required for strong binding affinity but may reduce solubility and cause other un favorable qualities, therefore there has to be a compromise between the two [19].

Force of the C-F bond

Certain fluorine-containing compounds are metabolically inactive because the energy required to break the C-F bond is higher than that required to break the C-H bond (116 kcal/mol vs. 99 kcal/mol) [4]. The anticancer medicine 5-fluorouracil is metabolized into an active metabolite that inhibits thymidylate synthase, which in turn decreases thymidine and DNA synthesis. The C-5 fluorine is unreactive; therefore the molecule may enter the enzyme active site without triggering any metabolic reactions [7].

Inhibition of an enzyme in an irreversible manner

It is possible to remove fluoride, a useful leaving group, when fluorine is attached to a reactive center. Covalent attachment of electrophilic species to the enzyme may cause irreversible impairment of enzymatic function [20, 21]. Quickly removing glycosylic fluoride, 2-deoxy-2-fluoro-b-D-glucosyl fluoride creates an oxocarbonium ion that may react with the enzyme. The 2-deoxy-2-fluoro-glycosyl-enzyme complex is stabilized by the fluorine substitute at carbon-2 (Fig 3). The final transformation is halted when a more stable intermediate binds to the enzyme and renders it inactive. Type 2 diabetes may be treated by inhibiting gut aglucosidases, enzymes responsible for the absorption of glucose from the gastrointestinal tract. An inert fluoride species is produced as a byproduct, and it has more therapeutic potential than comparable compounds [22].

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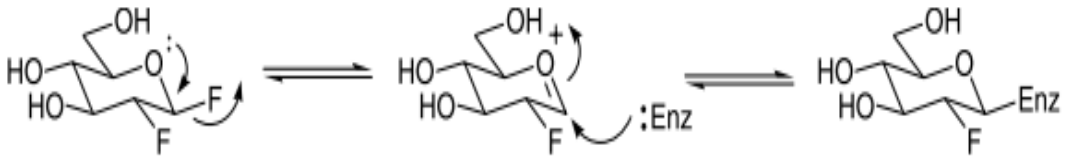

Fig: 3 An oxocarbonium ion is formed when the glycosidic fluorine in 2-deoxy-2-fluoro-w-D-glucosyl fluoride is eliminated. This ion then reacts with the enzyme to create a complex.

Fluorine in Medicine

Fluoride and Tooth Caries Prevention

This mottling of tooth enamel due to fluoride in drinking water was first observed in 1931. (dental fluorosis). As a result of early studies showing decreased tooth decay in children with dental fluorosis, there was worry that fluoride may preserve teeth even without causing fluorosis [23]. Between 30 and 50 percent of children living in fluoridated areas have dental fluorosis, and it's not always mild, as shown by the biggest US research and a worldwide assessment (www.fluoridealert.org). More than three to five times as many kids as expected have dental fluorosis. The practice of fluoridating water is very contentious. While the World Health Organization has deemed water fluoridation to be "one of the top 10 public health triumphs of the twentieth century," and has ignored health concerns, some experts are worried about the health impacts of the increasing fluoride addition. There are a number of variables that make them doubt that the health advantages of widespread dental care would exceed the hazards. Concerned about the effects of high fluoride levels on newborn infants' developing brains [24], Nobel Prize in medicine winner Dr. Arvid Carlsson spearheaded Sweden's successful campaign against water fluoridation. Carlson's worries about fluoride's dangers have been rekindled by the available information [25].

In order to cure osteoporosis, fluoride is often utilized to stimulate the formation of osteoblasts [26]. In calcified tissues like teeth and bone, fluoride rapidly swaps with the hydroxide ion on calcium hydroxy apatite crystals to generate calcium fluorapatite: Ca10 (PO4)6(OH)2+2F-=Ca10(PO4)6(F)2+2OH. It has been suggested [27] that bones exposed to fluoride lose their mechanical strength. The balance between fluoride's beneficial and negative effects on bone quality seems to depend on daily doses, treatment time, and bone fluoride concentration. When you examine fluoride's effects on bone, the problem worsens. Fluoride affects several bone regions differently. The exterior layer of bone responsible for resisting torsional and shear stress (cortical bone) loses density, whereas the inner trabecular bone gains density (the mesh-like core of the bone that is vital for weight bearing).

Antibiotics

Artificial fluorine substitution alters physiologically active molecules. Fluorine replaces hydrogen and hydroxyl groups in drug development [28]. Fluorine substitution in a pharmacological molecule may impact pharmacodynamics, toxicity, absorption, tissue distribution, secretion, and biotransformation [29]. Almost 200 fluorinated drugs are available, and more are being developed. Fluorinated drugs provide benefits for human medicine, but their health dangers are unknown. Fluorine's role in numerous harmful effects is unclear. The amino group in lysine, the sulphydryl group in cysteine, and the hydroxyl

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group in serine are all examples of nucleophilic groups that may catalyze the defluorination of fluorinated medicines [30,31,32].5-fluoro-amodiaquine and 2-fluoroethynilestradiol are defluorinated examples. Even trifluoromethyl may defluorinate [33].

Fluorine antibiotics and antivirals

High antiviral activity is seen in several recently synthesized 3-thioxo-1, 2, 4-triazin-5-ones with fluorine-containing substitutions [34]. Certain nucleosides and fluorinated purine nucleotides may inhibit the replication of HIV, another virus (Marquez et al. 1990). Fluorine may be found in the sugary residue and the base. Zidovudine's direct fluorine counterpart, alovudine, is one example of a potential new class of anti-HIV medications known as fluorine-containing antimetabolites (3-azidothymidine, AZT). Inhibitor of reverse transcriptase (RT) linked with HIV is alovudine, which is phosphorylated inside cells to become alovudine 5-triphosphate (Matthes et al. 1988). [(-)-beta-L-2',3'-dideoxy-5'-fluoro-3'-thiacytidine] (emtricitabine) is an HIV drug that has been authorised by the FDA [35].

5-fluorouracil is used to combat malignant solid tumours. One of the building blocks of DNA is called thymidine, and its production may be inhibited by the pharmacologically active metabolite 5-fluoro-deoxyuridine monophosphate [36].As cancer cells concentrate 5-fluorouracil and its byproducts, enzymatic blockade limits tumour growth [37]. Fluoroacetate poisons humans when it enters the tricarboxylic acid cycle and creates fluorocitric acid [38]. A 5-fluorouracil catabolite from fluorinated pyrimidine breakdown promotes tumour cytotoxicity [39]. Contemporary oncology uses fluorine-containing anthracycline derivatives.

Fluorine-based anti-inflammatories

Anti-inflammatory drugs treat both pain and swelling. There are several fluorinated forms of medicines in this class. Different drugs have different effects and strengths. Other side effects depend on the drug and the person. Fluorine-based anti-inflammatory drugs that are defluorinated make the toxic and stable fluoride ion [40]. Fluorinated niflumic acid, which is used to treat inflammation, is dangerous in France. A 86-year-old man with severe osteofluorosis and renal failure took 500 mg of niflumic acid every day for many years [41]. A 61-year-old man who drank 2.5 litres of Vichy St-Yorre water every day for 11 years (mineral water with 8 mg of fluoride ions per litre) had similar health problems. These results show how important it is to be careful when giving fluorine-based medicines and fluorine salts to treat osteoporosis.

Fluorine pharmaceutical use

Fluorine is used in pharmaceuticals to help the central nervous system get through cell membranes better. For drugs to work, they must get through the blood-brain barrier in high concentrations. Butyrophenones, diaylbutylamines, and tricyclics that block dopamine receptors in the central nervous system (CNS) have fluorophenyl or trifluoromethyl groups to help them get into the CNS. Haloperidol makes up most of butyrophenone. On the lookout for stronger drugs, fluorophenyl-containing compounds have longer half-lives than haloperidol [42]. Fluphenazine, trifluoropromazine, and trifluperazine are stronger than chlorpromazine [43]. Most psycho pharmaceuticals containing fluorine are antipsychotics and antidepressants. Citalopram and fluoxetine are popular (Prozac). Prozac treats depression, bulimia, and OCD. Fluoxetine with citalopram may cause drowsiness, nausea, headaches, anxiety, insomnia, and appetite loss [44].

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Conclusion and outlook

This study discusses the many medicinal chemistry and drug development applications of strategically positioned fluorine groups. Fluorine is added to things to improve their stability in the body, their physicochemical properties, or their ability to stick together. These are the ways that medicinal chemists use to make new drugs. Fluorine is often added to molecules on the spot, but it could also be used in a more scientific way to make drugs by using more than one method to figure out where to swap fluorine atoms to make them work better. Fluorinating medications increase human overexposure to fluoride from the environment [45]. Fluoride is most dangerous for babies and kids, people who drink a lot of water, people over 65, people who are very sensitive to fluoride, people who are sick, and people with kidney disease. Fluoride may activate G proteins and cause degenerative changes when tiny amounts of aluminium are present. Aluminofluoride compounds may aggravate preclinical pathophysiological alterations. Fluorinated hormones may cause major health problems. Fluorinated chemicals' effects on humans are unknown. Pharmacological and clinical research targets infants, babies, children, and ill people. In his Nobel Prize address, Albert Gilman stated the objective is to develop drugs that inhibit abnormal G protein activation. î Aluminum and fluoride disrupt G proteins. How many persons are needed for applied biomedicine to accept this information? Due to improved awareness of fluoride and aluminium ion health risks, many significant ailments would decline in the 21st century.

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