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Therapeutic and Diagnostic Value of Fluorine

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Abstract

Fluorine has a useful positron transmitting isotope and it enjoys broad application in the medical field. It is utilized in fluorinated agents, therapeutic sciences and steroid field. Fluorine incorporation via fluoroalkylation is a useful approach in the development of new functional materials and in drug design. Fluorine also plays its role as an anticancer agent and is a successful chemotherapeutic agent for certain sorts of malignant growth. 5-fluorouracil plays a vital role in the treatment of cancer. ^{18}F acts as a radiolabel tracer atom in PET imaging. ^{19}F has the second most sensitive and stable NMR-active nucleus.

Keywords: anticancer, fluorine, medical, positron, radiolabel

1. Introduction

Fluorine has been widely investigated due to its therapeutic and diagnostic potential [1]. There are unique properties associated with this unusual element and its role in drug development / design has been increasing rapidly. Fluorine substitution into a molecule can affect its pharmacokinetic properties, metabolic pathways, membrane permeability, intrinsic potency, pKa and conformation. ^{18}F is a useful positron emitting isotope that finds considerable utility in the clinical field [2]. In 1950s, fluorine was used for the first time in the steroid field. The utilization of fluorinated agents in therapeutic science is common and the electronegative fluorine particle also finds applications in pharmacokinetics, power and physical science [3]. In 1970s, fluorine substituent was expanded from 2% to 18% in pharmaceutical industries [4]. ^{19}F is a 100% naturally abundant isotope

and the second most sensitive and stable NMR-active nucleus. Its absence in almost all of the biological systems makes it unique among them and it is commonly used in NMR studies of proteins [5]. Till now, only about a dozen of naturally fluorinated products have been isolated. The biosynthesis pathway of 4-fluorothreonine and fluoroacetate in the bacterium *Streptomyces cattleya* has been significantly investigated and well understood [6]. There have been extensive investigations on fluorine substitution for the purpose of increasing metabolic or chemical stability. It can enhance membrane permeation and various physicochemical and pharmacokinetic properties. While synthesizing fluorine containing compounds, it is important to consider high electron withdrawing ability of fluorine, its high lipophilicity and relatively small size (van der Waals radius = 1.47Å) as compared to hydrogen (van der Waals radius = 1.20Å). Fluorinated drugs also demonstrate an improved binding affinity with target proteins [7]. Fluorine finds many uses in medicinal chemistry, such as fluorinated taxane has been investigated as an anticancer agent [8]. Similarly, some fluorinated thiourea derivatives carrying sulfonamide moieties have been investigated as anticancer and antimicrobial agents [9]. Figure 1 displays a fluorinated pyridine derivative which showed the strongest antimicrobial activity; it showed IC50 value of 4.8µg/mL with HepG2.

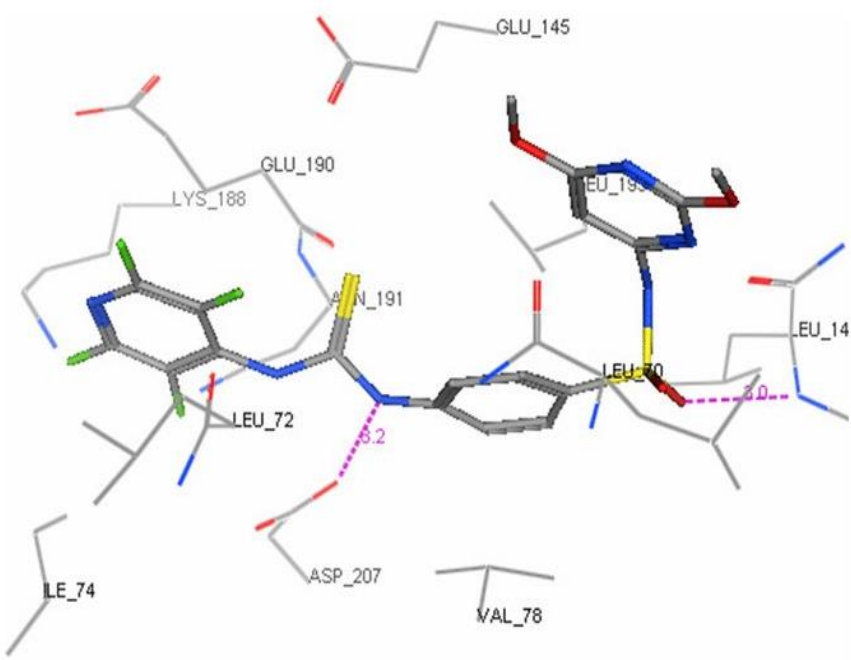

Figure 1. Fluorinated pyridine derivative [9]

Currently, there are a large number of compounds which are under investigation for their medicinal and biological applications [10, 11, 12, 13]. The current study was conducted to review the therapeutic and diagnostic value of fluorine.

2. Biologically Active Fluorochemicals

The incorporation of fluorine into organic compounds has a significant impact on medicinal chemistry. When fluorine is incorporated into biologically active compounds, their steric, lipophilic and electronic parameters are altered which results in their increased bioavailability, chemical metabolic and chemical stability as well as their intrinsic activity. Uracil is a compound containing nitrogen, oxygen, carbon, and hydrogen. It is one of the essential segments of RNA. It is particularly dangerous and is responsible for the development of malignant growth cells. Fluorouracil is a successful chemotherapeutic agent used for the treatment of certain sorts of malignant growth. Another important role of fluorochemicals in improving the quality of human life is the formation of compounds which exhibit anesthetic properties. Fluorine chemistry governs the formation of all modern inhalation anesthetics [14]. Indeed, very potent and selective antitumor activity is exhibited by 2-(4-aminophenyl) benzothiazoles against colon, ovarian, inter alia, breast and renal cell lines. There are reports about the modification of the antitumor activity of such compounds by acetylation with trifluoroacetic anhydride [15]. A similar compound 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole also has very selective and potent antitumor characteristics [16]. A variety of medicinal applications including analytical characterization, imaging and identification are attributed to the carbon-fluorine bond. Many important characteristics (such as the enhancement of bioavailability) in cancer drug compounds are developed through fluorination. Moreover, it is also used to label some important nanomaterials or biomoelcules (such as peptides, nucleic acids) which are important in tumor / cancer imaging and cancer chemo- and biotherapy. Furthermore, additional advantages are associated with the fact that C-F bond is easily soluble, efficient, cheaper and easy-to-handle; it is less harmful than radio waves, less toxic than fluorine radioisotopes and more stable than fluorescent dye [17].

3. Fluorine Utilization in Positron Emission Tomography Imaging (PET)

Fluorine-18 is a major isotope used in positron emission tomography (PET). A disadvantage of fluorine-18 is that it cannot act as a true isotopic tracer because in human body, no fluorine containing compound is present. Otherwise, among radio pharmaceuticals ^{18}F is widely used; it is a major radiopharmaceutical which acts as a glucose transporter in various cells. It is used to indicate various diseases including Alzheimer's disease and epilepsy through FDG-PET. For the treatment of cancer, two major types of radio pharmaceuticals are used. The first type is used to check the growth activity of tumors, that is, what is the rate of growth and how fast the tumor spreads. The second type is used to check the tumor's biological characteristics including the type of receptors present in it [7]. Fluorine-19 finds applications in MRI and NMR spectroscopy [18]. PET is an atomic medication imaging instrument which permits three dimensional quantitative assurance of conveyance with radioactivity inside the body. It is ending up as progressively imperative for the estimation of biochemical processes, as well as physiological and pharmacological capacity [19].

4. Fluorinating Agents and C-F Bond Forming Reactions

After the first report of asymmetric fluorination reagents in 1988, a lot of focus has been given to enantio selective introduction of a C-F bond at a stereogenic center in the field of organic chemistry. Fluorine has a unique importance in organofluorine science. It shows some important properties, such as exceedingly high reactivity as fluorine gas (F2), low nucleophilicity as fluoride and generally lower accessibility of "F+" sources (select fluor which is an important F+ species), among others [20]. Fluorinating reagents are widely employed in transitional metal catalyzed transformations used to prepare synthetically valuable fluorinated targets. The procedure finds application in chemical synthesis of fluorine containing agrochemicals and pharmaceuticals [21].

5. Non-invasive Physiology and Pharmacology Using ^{19}F Magnetic Resonance

Magnetic resonance imaging (MRI) is very important in the detection of various diseases in the field of radiology. ^{19}F has become important

in MRI and in spectroscopic (NMR) investigations. ^{19}F does not send any background signal in the body but it has high NMR sensitivity. There are numerous reports available on the syntheses of molecules which employ the sensitivity of F atom to its microenvironment; it also involves other important aspects such as volume, vascular flow, hypoxia reporters, gene reporter molecules, metal ion concentrations (such as calcium and magnesium), pH, and pO_2 [22].

6. Fluorine Containing Taxoids as Anticancer Operators

Paclitaxel (taxol) and docetaxel (a "taxoid") are two of the most broadly utilized chemotherapeutic specialists. Another taxoid cabazitaxel was affirmed by FDA for hormone-hard-headed prostate malignancy after mixing with prednisone. Currently, various novel taxoids are in different phases of clinical and preclinical advancement [23]. Figure 2 depicts the structures of paclitaxel and docetaxel.

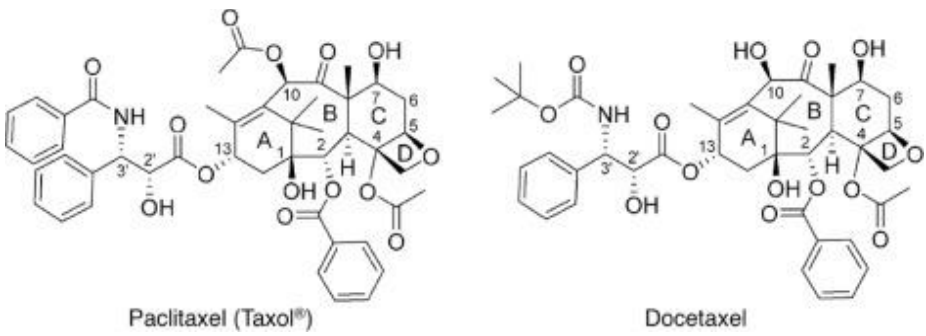

Figure 2. Structures of palitaxel and docetaxel [23]

In spite of ongoing advances in symptomatic and remedial modalities (otherwise known as theranostics modalities), malignancy remains a noteworthy wellspring of misery and mortality all over the world. The nearness of fluorine among pharmaceuticals (including radiopharmaceuticals, F-drugs) has greatly affected a number of essential restorative applications (such as treatment and imaging) [17].

Fluorine incorporation *via* fluoroalkylation is a useful approach in new functional material development and drug design. The substitution of fluorine can dramatically influence the chemical outcome in fluoroalkylation reactions [24]. ^{18}F atoms are used to examine a broad range of frameworks inside the body. Using CT and PET, a diversified sat of data can be generated about the tumor and wide information can be collected [25].

7. Role of ^{18}F in Breast Cancer

Analytic imaging in breast diseases is utilized for screening, recognizing different sores, assessing treatment reaction and for other purposes. Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emanation tomography / registered tomography (PET / CT) was created to recognize hyper-glucometabolism in malignant tissues and its utilization in clinical administration [26]. In breast malignant growth, entire body (WB) PET / CT is utilized for useful imaging since it is valuable for arranging lymph hubs and inaccessible metastasis [27].

8. Better Drug Metabolic Stability

Cytochrome P450 (liver enzyme) is responsible for the oxidation of lipophilic compounds which are easily oxidized by liver enzymes. So, due to low drug metabolic stability, a big challenge is posed in drug discovery. This problem may be resolved if a fluorine atom is introduced into the compound or by enhancing the polarity of that compound for the purpose of altering the route, rate, or level of drug metabolism. It can be done by substituting fluorine at a metabolically labile site. Fluorine substitution at the adjacent position results in either the decrease or increase of biotransformation which depends upon the following,

1. Whether the metabolic attachment is nucleophilic or electrophilic.
2. Whether resonance or inductive effect of fluorine predominates the process.

The inductive effect of fluorine may be produced in a saturated system due to the lowering of the susceptibility of near groups to a metabolic attack by cytochrome P450. On the other hand, studies have proved that the fluorine atom positioned at *ortho* to a phenolic moiety is able to enhance its reactivity as a nucleophile during glucuronidation and methylation [28]. Ezetimibe compound is a drug that has the ability to inhibit the absorption of cholesterol in intestine and it was recommended by FDA in 2002 to decrease the cholesterol level in patients with hypercholesterolemia. It helps in low rational drug design and has led to the introduction of fluorine into the target compound in order to enhance its in vivo potency and to improve the metabolic stability [29].

9. Anticancer Fluorinated Drugs

An initially marketed drug for cancer treatment is 5-fluorouracil (5FU) which is an antimetabolite. This drug enters into the cells through the uracil transporter and undergoes biotransformation into a variety of metabolites including fluorodeoxyuridine monophosphate. Due to the high redox potential and small size of fluorine, this metabolite reacts with co-substrates 5,10-methylene tetrahydrofolate and thymidylate synthase (an enzyme) to produce a stable ternary complex, thus preventing the methylation of deoxyuridine monophosphate (native substrate) [30]. As a result, the synthesis of deoxythymidine monophosphate is stopped. Cancer cells which increase in number rapidly as compared to healthy normal cells are excessively affected by the drug. A cardiotoxic drug such as 5FU is responsible for the metabolism of drug to lethal metabolite [31].

10. Fluorinated Drug Molecules and Imaging Agents in CNS

The utilization of drugs targeted towards the central nervous system (CNS) has been very useful in the case of many peripherally acting drugs. Fluorine containing CNS drugs such as sevoflurane, trifluprom azine, and fluconazole are most important in this regard [32].

11. Antitubercular Activity of Fluorinated Drugs

A novel active fluorinated drug consisting of quinoline-pyrazole hybrid analogs was developed and tested for its antibacterial potential against pathogenic bacteria and antitubercular activity against MTB [33].

12- Fluorine Containing Anesthetics

Fluorine containing compounds such as desflurane, enflurane, sevoflurane, isoflurane and halothane were investigated and it was found that they are bio-transformed into toxic metabolites, which is the reason of the toxicity of these medicines. Human liver is responsible for the metabolism of fluorine anesthetics into inorganic fluoride and hexa-fluoro-isopropanol. At saturating substrate concentrations, the order of anesthetic metabolism (as shown by the production of fluoride) was
methoxyflurane>sevoflurane>enflurane>isoflurane>desflurane>0. Till now, inorganic fluoride has been considered as the main etiological specie for fluorinated anesthetic nephrotoxicity [34].

13. Steroidal Inflammatory and Proton Pump Inhibitor Fluorinated Drugs

Fluticasone propionate is an anti-inflammatory agent of steroidal origin; it is used for the treatment of inflammation associated with psoriasis and dermatoses [35]. In combination with salmaterol, it is used for the treatment of asthma. Lansoprazole is the most successful commercial drug regulating the gastric acid secretion [36]. Other important drugs such as omeprazole, pantoprazole, rabeprazole and pantoprazole contain difluoromethoxyl moiety. They are advised to treat esophagal inflammation, peptic ulcers and heartburn. For the substitution of protons (H^+) by potassium ions (K^+) in stomach lumen, lansoprazole acts as an important 'proton pump inhibitor' (PPI); it involves a metabolic process which is driven by adenosine triphosphate [37].

14. Future Prospects

Fluorinated pharmaceutical drugs have a major impact in the field of medicinal chemistry including cholesterol biosynthesis inhibitors, antibacterial, CNS medications, antiviral agents, anticancer, non-steroidal and steroidal anti-inflammatory drugs and anesthetics [38]. Fluorine will significantly contribute in future medical advancements.

15. Conclusion

In medicine, fluorine has various applications such as it is used in the development of various drugs and drug discovery. It is used to cure cancer and also for its detection. Labeled ^{18}F is widely used for cancer treatment and for its diagnosis. ^{18}F plays a vital role in diagnosing tumors. In the major technique of PET imaging, fluorine-18 and also fluorine-19 act as radiolabel tracer atoms. As fluorine has various applications in the medical field, so it may be used in drug discovery and also for its development. Hence, it is concluded that fluorine and its derivatives play a vital role in human life and are used to cure and detect different types of diseases.

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