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*NQPSUBODF PG 'MVPSJOF BOE 'MVPSPDBSCPO 0ODPMPHZ

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Abstract

Carbon-Fluorine (C-F) can serve as a molecular tag for many applications in medicinal chemistry and oncology VXFK DV LGHQWL¿FDWLRQ L H VFUHHQLQJ LPDJLQJ L H WUDFLQJ DQG DQDO D FKHPLFDO SURFHVV WR DGG D ÀXRULQH DWRP LQWR D VLQJOH PROHFXOH RU D LV ODUJHU\ XVHG LQ WKH SKDUPDFHXWLFDO ¿HOG WR FRQIHU VRPH LQWHUHVW enhancement of bioavailability). It is further more recently used for labelling some biological molecules of interest

Keywords: Fluorination; Carbone-Fluorine; Oncology; Nanomedicine; Pharmacy; Medicinal chemistry; Green chemistry; Green technology; Technological innovation; Carbon- uorine spectroscopy; Nuclear magnetic resonance; Magnetic resonance imaging; Positron emission tomography

Abbreviations: ADCs: Antibody-Drug Conjugates; C-F: Carbone-Fluorine; C-T: Computed Tomography; CFS: Carbone Fluorine Spectroscopy; dsRNA: Interference RiboNucleic Acid; miRNA: Micro iRNA; MRI: Magnetic Resonance Imaging; PCR: Polymerase Chain Reaction; ODN: Oligo Deoxy Nucleotide; PET: Positron Emission Tomography; NMR: Nuclear Magnetic Resonance; SiRNA: Small iRNA

Epistemology of Fluorine: From the Atom to Fluorocarbons

Fluorine (name derived from Latin eure, meaning to ow) is the lightest of the halogens, the most reactive of all the elements. In 1886, a French chemist, Ferdinand Frederic Henri Moissant (1852-1907), was the rst to isolate uorine [1]. He used platinum electrodes to produce uorine from the electrolysis of potassium uoride (KF), a hydro uoric acid. In 1872, Sir James Crighton-Browne postulated that a de ciency of uorine was responsible for higher incidency of dental carries [2]. In 1892, a Belgian chemist Frederic Jean Edmond Swarts discovered the Cl/F exchange chemistry of the inorganic antimony tri uoride (SbF_3), a hydro uoric acid (HF) widely used in dyeing and pottery [3]. e reaction, commonly called “Swarts reaction”, has since been improved to be an industrial process for the preparation of organo uorine compounds, such as for the synthesis of dimethyl and trimethyl chlorosilanes [4].

Although uorine is the thirteenth most abundant element in the earth’s crust, uoride concentrations in surface water are low and uorinated metabolites are extremely rare [5]. Indeed, up-to-date, only 13 naturally occurring uorinated organic compounds are known. Among them, we can cite the bacterial uorinating enzyme 5’- uoro-5’-deoxyadenosine synthase used by Streptomyces cattleya to naturally catalyze a uorination reaction [5]. is microorganism can form carbon- uorine (C-F) bonds using aqueous uoride through a nucleophilic substitution mechanism.

is particular rarity of natural uorination is of high industrial importance, with applications in pharmaceutical, biomedical, agrochemical and materials products.

Carbon-Fluorine Properties and E ects

e C-F bond is the most polar bond in organic chemistry, and thus the bond has a relatively large dipole moment with a signi cant -ve charge density on the uorine atom and correspondingly a +ve

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charge density on carbon [6]. Because the C-F bond has a much greater dipole moment than does the carbon-hydrogen (C-H) bond, a stronger binding with dipolar water might be expected [7]. e electrostatic nature of the C-F bond renders it the strongest one in organic chemistry [6]. Further, C-F displays isoelectronic e ects to oxygen (-O) atom and hydroxyl (-OH) group, and the high electronegativity of uorine (-F) frequently alerts chemical reactivity. However, the (-F) atom itself is almost non-polarizable, and thus, despite the charge localization on (-F), it is a poor hydrogen-bonding acceptor [6]. Although the polarizability of (-F) in the C-F bond is relatively low, considering its position in the periodic table, the dispersion interactions of C-F with water are reasonably expected to be more attractive than those of C-H with water [8]. erefore, a uorocarbon surface could be argued to be more hydrophilic than the corresponding hydrocarbon. A plausible resolution could be that the uorocarbon with a molecular cross-section of 28.3 Å^2

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^{19}F-MRI, which is tremendously useful for better understanding the general oncogenesis/carcinogenesis process (e.g. cancer staging, dynamism of tumor microenvironment). Moreover, the labeling of stem cells can be useful to control in situ tissue engineering and so, become very useful in regenerative medicine. For instance, a very recent study reports the good performance of ^{19}F-MRI to describe the association of the central zone with more aggressive prostate cancer [41]. Other studies used chemical-shi selective ^{19}F-MRI to directly detect a speci c intra-tumoral F-drug (e.g. 5-FU) trapping/retention (i.e. in solid tumors such hepatoma, in case of 5-FU), biodistribution (i.e. speci c tissue uptake such as liver and kidneys, in case of 5-FU) and catabolism (i.e. major catabolite such as - uoro- -alanine was detected in case of 5-FU) in tumor-bearing rats [42,43].

Besides, MRI can be coupled with other imaging technologies such as computed tomography (CT). As an example, 3D images and 2D models based on MRI/CT image fusion provided a powerful tool for the visualization of jaw tumors by de ning the relationship between tumors and adjacent structures, thereby assisting the subject-speci c preoperative planning, surgical simulation, and intraoperative guidance for tumors [44]. MRI/CT also obtained a better estimation of the organ tumor size than CT alone, which tends to overestimate it, and is then a quite useful combination in 'radiotherapy planning' for localized cancers (e.g. rectal carcinoma, prostate carcinoma can be treated by more adapted radio-therapeutic doses consequently decreasing organ complications) [45,46].

Positron Emission Tomography (PET)

PET is a common and powerful analytical method for medical diagnosis, particularly in oncologic sector v (19)Tj 1 it

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