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EDITORIAL

Key developments in fluorinated heterocycles

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Since the beginning of pharmaceutical industry, synthetic drugs are often designed considering the presence of heterocyclic rings in natural products (alkaloids, vitamins, antibiotics, peptides, etc.) [1]. Therefore, heterocycles are considered fundamental platforms for the synthesis of future drugs, thus heterocyclic moieties are present in about 85% of bioactive compounds [2].

From the second half of the twentieth century, another fundamental tool for drug development was the introduction of fluorine atoms into molecular structures [3,4].

Fludrocortisone was the first fluorinated drug approved in 1954 representing the first fluorocorticosteroid [5]. Since this innovation, the presence for fluorinated drugs into the market growth exponentially, with more than 300 fluorinated drugs approved [3], reaching the 20% of drugs on the market with a considerable 30% of fluorinated blockbusters such as Lipitor, fluoxetine, linezolid, or fluticasone [4].

Introduction of the C–F bond into new drug gave the advantage of unique physicochemical properties like high bond strength and polarity with a minimal steric hindrance [6]. Furthermore, due the absence of this bond in nature, a good metabolic stability was obtained, thus improving drug's half-life [7].

Other common foreseen advantages are modulation of the acid/basic properties of neighboring functionalities, improving bioavailability and affinity, as well as, reduction of the lipophilicity, often associated to increased membrane's permeability [8,9].

The introduction of fluorinated groups into heterocycles represented a key step in modern medicinal chemistry, leading to the born of fluorinated heterocycles as important scaffolds able to combine and improve their properties.

This subclass of pharmaceuticals includes some of the FDA-approved drugs representing breakthrough innovations in recent decades, such as fluorouracil, the class of fluoroquinolones, sitagliptin, mefloquine, celecoxib, and fluorodeoxyglucose just to name few [10].

Considering those molecules where fluorinated group is directly linked to the heterocyclic ring, a total of 41 small molecules were approved by the FDA from 2016 to 2024. Notably, biological targets and therapeutic indications are widely covered, such as oncology, infectious diseases, rare diseases, and also diagnostics. This feature clearly demonstrates the versatility and general importance of such compounds.

Despite this tremendous importance and growing interest, the introduction of fluorinated moieties into organic compounds is perceived as challenging and requires further improvement to reach desired applicability [11]. Among all strategies, late-fluorination [12], catalyzed reactions [13], and the use of hypervalent iodine reagent [14] seem the most promising.

Despite late-fluorination is described as the most effective strategy for practical and industrial uses, the current main strategy is the use of fluorinated building blocks since the beginning of the synthetic plan, as outlined for the synthesis of many FDA-approved drugs [10].

Thus, this synthetic pathway requires the abundant use of fluorinated starting materials such as trifluoroacetic acid (TFA), trifluoroacetate, trifluoroacetic anhydride, trifluoroethylamine, and ethyl triflate, commonly employed for the introduction of the trifluoromethyl group. In addition, fluorinated (hetero)aromatic starting materials such as (poly)fluorobenzoic acid, fluoro-, or trifluoromethylpyridines are widely used.

Some of the main mechanisms used for the introduction of F atoms are the nucleophilic fluorination of electrophiles [11,15]. Fluorination of (hetero)arenes includes nucleophilic substitution and metal-catalyzed nucleophilic fluorination or deoxofluorination [11]. Trifluoromethylation occurs through electrophilic compounds such as Togni reagents [16] and S-(trifluoromethyl)dibenzothiophenium salts [17], or with cheaper derivatives such as CF_3I, preferred for industrial processes. The use of solid and stable reagents such as $NaSO_2CF_3$ in radical trifluoromethylations of electron-rich arenes is also increasing [11].

Despite the growing interest on fluorinated heterocycles, a great shadow is growing behind, due the raising concerns about "Forever Chemicals," such as perfluorinated alkylated substances (PFAS), that led to their partial ban in Europe and US.

The major concerns regard the use of long chain (especially alkyl chain $>C_8$) PFAS, but under the definition of Persistent Organic Pollutants (POPs) are also comprised smallest PFAS containing a single trifluoromethyl group such as TFA or many

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fluorinated pharmaceuticals. The presence of these compounds was recently monitored efficiently into municipal wastewater in US, revealing that the greater number of fluorinated pollutants in drinking water are prescribed drugs or their metabolites [18]. These finding rise many questions about the fate of fluorinated drugs into the environment and how these persistent compounds will affect the environment in the next years.

Under these circumstances, two essential needs seem proceeding into opposite directions, the need of effective drugs for different diseases, against the need of pure drinking water and a safe environment. Obviously these two universal rights must not be in conflict but should be pursued in a strictly connection. Thus, a full research focused on a comprehensive and deep knowledge of the potential fate of fluorinated drugs into the environment is needed, as well as the development of effective analytical methods and the optimization of fluorinated compounds removal from industrial water, preferably before they reach the environment.

All these issues could represent the key developments for the future sustainability of the industry of fluorinated heterocyclic drugs.

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Declaration of Interest

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