Fluorine is Flourishing in Pharmaceuticals
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Editorial

Since Moissan isolated elemental fluorine in 1886, fluorine has always been an element of surprise. Its small size, high electron negativity and high C-F bond dissociation energy make fluorinated compounds fit perfectly in a variety of application. In the field of pharmaceuticals, introducing a fluorine atom or fluorinated group into drugs or drug leads is often accompanied with higher binding affinity, enhanced metabolic stability, improved bioavailability, and sometimes, increased selective activity. Additionally, the development and therapeutic monitoring of fluorinated drugs can be facilitated by additional techniques, such as 19F positron emission tomography (PET), 19F magnetic resonance imaging/spectroscopy (MRI/S) and fluoruous technology, to name a few. To date, there are over 150 fluorinated drugs on the market which account for about 20% of all FDA approved drugs. Three out of the top 10 best selling drugs, Lipitor, Advair and Crestor, contain fluorine, and seven out of 35 newly approved drugs contain fluorine in 2011.

With recent development in novel fluorination strategies [1-8], 19F PET, 19F MRI/S and fluoruous technology [9-12], fluorine is playing an ever more important role in pharmaceuticals. First, fluorination has become an established strategy to modify physical properties, binding characteristics and metabolic disposition during drug leads development. Traditionally, selective fluorination, i.e., introducing fluorine or fluorinated group at specific positions with preferred configuration, could be very challenging. Direct fluorination with fluorine gas or Diethyl Amino Sulfur Trifluoride (DAST) usually suffers low selectivity, disappointing yield, poor functional group compatibility and severe side reactions. In recent years, fluorine chemistry has become a hot spot in chemical research due to its extensive application in pharmaceuticals. Breakthroughs in this field bring about several commercially available selective fluorination reagents, such as bis(2-methoxyethyl) aminosulfur trifluoride (Deoxofluor) [1], 1-chloromethyl-4-fluorodiazoniabicyclo [2,2,2] octane bis(tetrafluoroborate). Acc Chem Res 37: 31-44.

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Since nearly 70 years ago when Fried replaced 9α-hydrogen in cortisone with fluorine and unexpectedly found single fluorine can improve bioactivity by 11 times [14], fluorine has been playing a multifaceted role in pharmaceuticals. Although fluorine was used to be regarded as an element of magic and used with intuition [15], fluorine is now used in pharmaceuticals with confidence after more details about fluorination effect on small molecule and the interaction with biological system have been revealed. medicinal chemists are happy to see selective and efficient synthetic methods keep adding to their tool box. 19F PET, 19F MRI/S and fluoruous technology give pharmacologists precious insights into drugs’ in vivo behaviors and help doctors design personalized therapy. Fluorine is certain to keep surprising the pharmaceutical community.

References

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