An Overview of Recent Advances in Biological and Pharmaceutical Developments of Fluoro-containing Drugs

Nader G. Khaligh1*, Hanna Abbo2,3, Salam J.J. Titinchi3,2 and Mohd R. Johan1

1Nanotechnology and Catalysis Research Center, Institute of Postgraduate Studies, University of Malaya, 50603 Kuala Lumpur, Malaysia; 2Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq; 3Department of Chemistry, University of the Western Cape, Cape Town, South Africa

Abstract: This review article provides a brief assessment of the biological and pharmaceutical developments of fluorinated drugs. It also discusses possible impacts on the further development of new fluoro-containing pharmaceuticals. Structural aspects of new drug-candidates currently under development and their biological properties, therapeutic potential and syntheses are critically evaluated.

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1. INTRODUCTION

The importance of fluorine lies mostly in its numerous compounds having the ability to attract electrons and to the small size of its atom. Fluorine-containing compounds are found in many life science industries such as crop protection products and pharmaceutical drugs. In recent years, a steady increase in the number of fluorinated organic molecules reaching commercial availability as crop protection products and pharmaceutical drugs has become more evident. In the pharmaceutical area, several fluorine-containing compounds have also been successfully approved for commercialization.

Incorporation of fluorine into a biologically active compound can improve its potency dramatically due to alterations in several parameters viz., the electronic, lipophilic and steric parameters, which in turn, can critically increase its activity, chemical and metabolic stability and bioavailability.

The positive effects of fluorine on the biological efficiency may be illustrated through three examples: a) fluorine dramatically affects the biological activity of herbicidal thiaztirines; b) fluorine improves the metabolic stability and the pharmacokinetics of aminopyrazino none acetamide thrombin inhibitors and c) modification of the gem-difluorovinyl group in a novel class of insecticides/caricides. Organofluorine compounds find a wide range of applications in pharmaceuticals, catalysis and used in other industries such as oil and water repellents and refrigerants. However, some organofluorine compounds are considered pollutants because of their contributions to ozone depletion, global warming, bioaccumulation and toxicity. The area of organofluorine chemistry often requires special techniques associated with the handling of fluorinating agents.

Designing and synthesis of the fluorine-containing compounds for medicinal and biological applications are being successfully continued due to unique properties of the fluorine atom including possessing the highest electronegativity, smallest size next to hydrogen, special biomimetic effects, electrostatic interactions, low polarizability of the C-F bond, nuclear spin of ½, high thermal stability, amphiphobicity and lipophilicity which improve metabolic stability and enhance membrane permeation [1, 2]. Fluorine is the smallest halogen atom with a van der Waals radius of 1.47 Å. In covalent bonding, it is expected to cause minimal steric perturbations with respect to the compound's mode of binding to a receptor or enzyme [3]. Fluorine plays a crucial role in pharmaceutical and medicinal fields because fluorinated drug molecules exhibit an improvement in properties such as bioavailability, basicity, binding affinity and metabolism. Bioisoster substitution of hydrogen atoms by fluorine atoms was used to change electronic, lipophilic and sterically properties [4-6]. Therefore, such compounds should show essentially similar physical properties and thus, this type of modification can potentially induce altered biological responses of the molecule.

The fluorine as an interesting heteroatom and fluorinated compounds have received significant attention due to their diverse applications in agriculture, medicine, drug discovery and development and as reagents in catalysis [1, 7, 8].

Introducing fluorine atoms into medicinally active compounds could improve the pharmacokinetic and pharmacological properties including oral absorption [9] and its presence in key positions [10].