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Review

FDA-Approved Trifluoromethyl Group-Containing Drugs: A Review of 20 Years

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Abstract: As people around the world regard 2020 as the year of COVID-19, the medical community considers this year to be the second-best year, shared with the year 1996, with respect to the number of drug molecules approved by the US Food and Drug Administration (FDA). Both years, 2020 and 1996, had a record of 53 new drug molecules approved by the FDA. In the year 2020, 53 new chemical entities and 13 biological medicines were approved, including 10 monoclonal antibodies, 2 antibody-drug conjugates, 3 peptides, and 2 oligonucleotides. Among them, most of the compounds were found to have fluorine or fluorine-containing functional groups exhibiting numerous pharmacological activities. Herein, we summarized the trifluoromethyl (TFM, -CF_3)-group-containing FDA-approved drugs for the last 20 years. This article specially features and details the previous 20-year literature data, covering CF_3-incorporated potential drug molecules, including their syntheses and uses for various diseases and disorders. The review covers the detailed chemistry of 19 FDA-approved drugs in the past 20 years, which contains the TFM group as one of the pharmacophores.

Keywords: trifluoromethyl group; FDA-approved drugs; syntheses; uses

Citation: Nair, A.S.; Singh, A.K.; Kumar, A.; Kumar, S.; Sukumaran, S.; Koyiparambath, V.P.; Pappachen, L.K.; Rangarajan, T.M.; Kim, H.; Mathew, B. FDA-Approved Trifluoromethyl Group-Containing Drugs: A Review of 20 Years. *Processes* **2022**, *10*, 2054. https://doi.org/10.3390/pr10102054

Academic Editor: Alina Pyka-Pająk

Received: 2 September 2022
Accepted: 6 October 2022
Published: 11 October 2022

1. Introduction

Organo-fluorine chemistry is a unique branch of organic chemistry, as the fluorine incorporation in the organic molecules exhibits bizarre behaviors; hence, several applications are witnessed in medicines, electronics, agrochemicals, and catalysis [1]. Since fluorine-containing compounds significantly affect pharmaceutical growth, they make up more than 50 percent of the best-selling drug molecules approved by the US Food and Drug Administration (FDA) [2,3].

The fluorine's electronegativity, size, electrostatic interactions, and lipophilicity are widely recognized factors that significantly impact the chemical reactivity, physico-chemical behavior, and biological activity [4]. According to a recent study by Hagmann, about 15–20 percent of all licensed drugs introduced annually in the market contain fluorine/fluorine-containing functional groups [5]. Fluorine's role in medicinal chemistry and drug design has been extensively discussed recently. It is difficult to offer even a cursory description of the considerable progress that has been reported in organo-fluorine chemistry [6]. The influence of fluorine on a metabolic cascade of chemical events is greatly amplified; thus, even a single fluorine atom can fully transform the biological characteristics of a natural product. The first was published as a series of papers from a symposium titled "Fluorine in the Life Sciences" held in Switzerland in July 2003; the papers focused on the biological activities, compositions, and properties of organo-fluorine compounds [7]. Fluorine substitution has been studied widely in drug development to improve biological